

# **Addressing the Complexity of Medication Use in Older People with Intellectual Disability**

A thesis submitted to the University of Dublin, Trinity College,  
for the Degree of Doctor of Philosophy

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## Declaration

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Date

## Summary

**Background:** People with intellectual disabilities (ID) experience high levels of polypharmacy and medication burden. Many of the most commonly occurring medical conditions in older adults with ID are treated with medications that have anticholinergic and/or sedative activity. The Drug Burden Index (DBI), Anticholinergic Cognitive Burden (ACB) Scale and Sedative Load Model are three tools which evaluate the burden of these types of medications on an individual. These measures have been found to be associated with poorer cognitive and physical performance in older adults without ID. However, little research has been carried out to date assessing these measures of drug burden in older adults with ID.

**Objectives:** The thesis aimed to assess the complexity of medication burden among older adults with ID, and the associations of anticholinergic and sedative medication burden with potential adverse effects, functional limitations, physical function, and frailty. Three primary aims were: (i) to investigate anticholinergic and sedative exposure using the DBI tool in a cohort of older adults with ID, and to evaluate its association with demographic characteristics, dependency and potential adverse effects; (ii) to examine the association between DBI and performance in two physical function measures, grip strength and timed up and go (TUG), and a measure of dependency, Barthel Index activities of daily living (ADLs), in a cohort of older adults with ID at a cross-sectional level to establish if exposure in people with ID leads to the same functional effects as has been reported in the general population; and (iii) to describe frailty and examine the cross-sectional association between medication exposure using four tools (polypharmacy, DBI, ACB and Sedative Load) with frailty in a cohort of older adults with ID.

**Methods:** Data for this study is drawn from Wave 2 (2013/2014) of the Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing (IDS-TILDA), a representative population of people with ID aged 40 years and over in Ireland. Medication data was available for 677 (95.6%) of participants who completed Wave 2.

Three inventories of medications were compiled and the DBI score, ACB score and Sedative Load score for each individual was calculated and analysed for associations using self- and objectively-reported data on medication use and physical health, including health conditions. Physical function measures were Barthel Index ADLs, grip strength and TUG. Frailty was measured using

a modified version of Fried's Frailty Phenotype. Multinomial logistic regression was used to evaluate the association between DBI score and potential adverse effects. Analysis of Covariance (ANCOVA) was used to evaluate the association between DBI score and physical function measures. Multinomial logistic regression was used to assess the association between polypharmacy, DBI, ACB and Sedative Load exposure and frailty using modified Fried's Frailty Phenotype.

**Results:** DBI exposure was found to be higher than that observed among older adults without ID. Multivariate regression found no statistically significant association between DBI and three potential adverse effects – daytime dozing, chronic constipation or fall in the previous 12 months. ANCOVA found a significant association between DBI exposure and Barthel Index ADLs. No significant association was found between DBI score and performance in two objective measures of physical function, grip strength and TUG, using ANCOVA analysis. Excessive polypharmacy was found to be significantly associated with frailty in multivariate regression analysis. However, DBI, ACB and Sedative Load were not significantly associated with frailty.

**Conclusions:** This is the first time DBI has been described in older adults with ID. Scores were much higher than those observed in the general population and higher scores were associated with higher dependence in Barthel Index ADLs. Grip strength and TUG scores were not significantly associated with DBI. Frailty was significantly associated with excessive polypharmacy, but not with DBI, ACB or Sedative Load. Future work will focus on other measures of drug burden and their association with functional decline in this population.

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## Table of Abbreviations

| Abbreviation           | Term                                                                        |
|------------------------|-----------------------------------------------------------------------------|
| <b>AAIDD</b>           | American Association on Intellectual and Developmental Disabilities         |
| <b>ACB</b>             | Anticholinergic Cognitive Burden                                            |
| <b>ADE</b>             | Adverse Drug Event                                                          |
| <b>ANCOVA</b>          | Analysis of Covariance                                                      |
| <b>ANS</b>             | Autonomic Nervous System                                                    |
| <b>ARDS</b>            | Acute Respiratory Distress Syndrome                                         |
| <b>ATC</b>             | Anatomical Therapeutic Classification                                       |
| <b>B<sub>AC</sub></b>  | Anticholinergic Burden                                                      |
| <b>BI</b>              | Barthel Index                                                               |
| <b>BMI</b>             | Body Mass Index                                                             |
| <b>BNF</b>             | British National Formulary                                                  |
| <b>B<sub>s</sub></b>   | Sedative Burden                                                             |
| <b>BWC</b>             | Behaviours Which Challenge                                                  |
| <b>CAPI</b>            | Computer-Assisted Personal Interview                                        |
| <b>CCI</b>             | Charlson Comorbidity Index                                                  |
| <b>CHAMP</b>           | Concord Health and Ageing in Men Project                                    |
| <b>CI</b>              | Confidence Interval                                                         |
| <b>CNS</b>             | Central Nervous System                                                      |
| <b>COPD</b>            | Chronic Obstructive Pulmonary Disease                                       |
| <b>DBA</b>             | Drug Burden Index (anticholinergic-only medications)                        |
| <b>DBI</b>             | Drug Burden Index                                                           |
| <b>DBS</b>             | Drug Burden Index (sedative-only medications)                               |
| <b>DDD</b>             | Defined Daily Dose                                                          |
| <b>DR<sub>50</sub></b> | Dose required to achieve 50% of maximal contributory effect at steady state |
| <b>DSM-V</b>           | Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition)       |
| <b>ESRI</b>            | Economic and Social Research Institute                                      |
| <b>FCI</b>             | Functional Comorbidity Index                                                |
| <b>GABA</b>            | Gamma (γ)-Aminobutyric Acid                                                 |
| <b>GI</b>              | Gastrointestinal                                                            |



|                  |                                                                                               |
|------------------|-----------------------------------------------------------------------------------------------|
| <b>GDPR</b>      | General Data Protection Regulation                                                            |
| <b>GMS</b>       | General Medical Service                                                                       |
| <b>GP</b>        | General Practitioner                                                                          |
| <b>HA-ID</b>     | Healthy Ageing and Intellectual Disability                                                    |
| <b>HPRA</b>      | Health Products Regulatory Authority                                                          |
| <b>HRCDC</b>     | Health Research Consent Declaration Committee                                                 |
| <b>HRR</b>       | Health Research Regulations                                                                   |
| <b>HSE</b>       | Health Service Executive                                                                      |
| <b>(I)ADL</b>    | (Instrumental) Activities of Daily Living                                                     |
| <b>ICD-11</b>    | International Statistical Classification of Diseases and Related Health Problems (Version 11) |
| <b>ID</b>        | Intellectual Disability                                                                       |
| <b>IDS-TILDA</b> | Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing                  |
| <b>INN</b>       | International Non-Proprietary Name                                                            |
| <b>IPAQ</b>      | International Physical Activity Questionnaires                                                |
| <b>IQ</b>        | Intelligence Quotient                                                                         |
| <b>IQR</b>       | Interquartile Range                                                                           |
| <b>LTI</b>       | Long Term Illness                                                                             |
| <b>MAR</b>       | Medicine Administration Record                                                                |
| <b>Mcg</b>       | Micrograms                                                                                    |
| <b>MDD</b>       | Minimum Effective Daily Dose                                                                  |
| <b>Mg</b>        | Milligrams                                                                                    |
| <b>MI</b>        | Myocardial Infarction                                                                         |
| <b>MS</b>        | Multiple Sclerosis                                                                            |
| <b>NIDD</b>      | National Intellectual Disability Database                                                     |
| <b>OR</b>        | Odds Ratio                                                                                    |
| <b>OTC</b>       | Over-The-Counter                                                                              |
| <b>PCRS</b>      | Primary Care Reimbursement Service                                                            |
| <b>PIN</b>       | Personal Identification Number                                                                |
| <b>PIQ</b>       | Pre-Interview Questionnaire                                                                   |
| <b>PKU</b>       | Phenylketonuria                                                                               |
| <b>PRN</b>       | Pro Re Nata (As Required)                                                                     |
| <b>QoL</b>       | Quality of Life                                                                               |

|               |                                                                      |
|---------------|----------------------------------------------------------------------|
| <b>QUS</b>    | Quantitative Ultrasound                                              |
| <b>RANSAM</b> | Random Sample Design for Ireland                                     |
| <b>RNID</b>   | Registered Nurse in Intellectual Disability                          |
| <b>RDDA</b>   | Regional Disability Database Administrator                           |
| <b>SAA</b>    | Serum Anticholinergic Activity                                       |
| <b>SAM</b>    | Safe Administration of Medicines                                     |
| <b>SD</b>     | Standard Deviation                                                   |
| <b>SmPC</b>   | Summary of Product Characteristics                                   |
| <b>SPPB</b>   | Short Physical Performance Battery                                   |
| <b>SPSS</b>   | Statistical Package for Social Sciences                              |
| <b>STOPP</b>  | Screening Tool of Older People's Prescriptions                       |
| <b>STROBE</b> | Strengthening the Reporting of Observational Studies in Epidemiology |
| <b>TIA</b>    | Transient Ischaemic Attack                                           |
| <b>TILDA</b>  | The Irish Longitudinal Study on Ageing                               |
| <b>TUG</b>    | Timed up and go                                                      |
| <b>UK</b>     | United Kingdom                                                       |
| <b>VIF</b>    | Variance Inflation Factor                                            |
| <b>WHO</b>    | World Health Organisation                                            |

## Presentations and Publications

### Oral presentations at national and international conferences:

- 47th ESCP (European Society of Clinical Pharmacy) Symposium, Belfast, Northern Ireland, October 2018  
“Drug Burden Measures and Physical Function in Older Adults with Intellectual Disabilities”  
Juliette O'Connell, Éilish Burke, Máire O'Dwyer, Philip McCallion, Mary McCarron, Martin C Henman.  
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“Use of the Sedative Load Model in Older Adults with Intellectual Disabilities”  
Juliette O'Connell, Éilish Burke, Máire O'Dwyer, Philip McCallion, Mary McCarron, Martin C Henman.  
(also published abstract) *Age and Ageing*. 2018; 47(suppl 5): v13-v60.
- 5th International IASSIDD (International Association for the Scientific Study of Intellectual and Developmental Disabilities) Europe Congress, July 2018, Athens, Greece.  
“A comparison of drug burden measures on physical function scores in a cohort of older adults with intellectual disabilities”  
Juliette O'Connell, Éilish Burke, Martin C Henman, Philip McCallion, Mary McCarron, Máire O'Dwyer.  
(also published abstract) *Journal of Applied Research in Intellectual Disabilities*. 2018; 31(4): 553
- Celebrating Excellence in Research, Innovation & Impact: 10 Years of IDS-TILDA, School of Nursing & Midwifery, Trinity College Dublin, December 2017  
“Associations between Drug Burden Index and Physical Function in Older Adults with Intellectual Disabilities.”  
Juliette O'Connell, Máire O'Dwyer, Eilish Burke, Martin C Henman, Mary McCarron, Philip McCallion.
- 46th ESCP (European Society of Clinical Pharmacy) Symposium, Heidelberg, Germany, October 2017  
“Drug Burden Index and Physical Function Measures in Older Adults with Intellectual Disabilities”

Juliette O'Connell, Máire O'Dwyer, Eilish Burke, Martin C Henman, Mary McCarron, Philip McCallion.

(also published abstract) *International Journal of Clinical Pharmacy*. 2018. 40(1); pp 209

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- Irish Gerontological Society, Postgraduate Study Day in Ageing Research, Dublin, April 2017  
“Addressing the complexity of medication use in people with Intellectual Disability”  
Juliette O'Connell.
- 39th All Ireland Schools of Pharmacy Conference, University College Cork, April 2017.  
“Factors Associated with Drug Burden Index in Irish Older Adults with Intellectual Disabilities: An Observational Cross-Sectional Study”  
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#### **Poster presentations at national and international conferences:**

- Irish Gerontological Society, 65th Annual and Scientific Meeting, Wexford, September 2017  
“Association of Drug Burden Index with Physical Function in Irish Older Adults with Intellectual Disability”  
Juliette O'Connell, Máire O'Dwyer, Eilish Burke, Martin C Henman, Clare Donegan, Mary McCarron, Philip McCallion, Niamh Mulryan.  
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- IASSIDD (International Association for the Scientific Study of Intellectual and Developmental Disabilities) Health Special Interest Research Group Conference, Belfast, Northern Ireland, June 2017.  
“Drug Burden Index and Physical Function in Older Adults with Intellectual Disabilities: An Observational Cross-Sectional Study”  
Juliette O'Connell, Martin C Henman, Mary McCarron, Philip McCallion, Eilish Burke, Claire O'Dwyer, Niamh Mulryan, Clare Donegan, Máire O'Dwyer.
- Irish Gerontological Society, 64th Annual and Scientific Meeting, Killarney, September/October 2016  
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“Development of the Drug Burden Index Tool for use in an Irish Population with Intellectual Disabilities”

Máire O'Dwyer, Juliette O'Connell, Philip McCallion, Mary McCarron, Martin C Henman.  
(also published abstract) *Age and Ageing*. 2016; 45(suppl 2): ii13-ii56.

- 45th ESCP (European Society of Clinical Pharmacy) Symposium, Oslo, Norway, October 2016  
“Development of the Drug Burden Index tool for use in an Irish population of older people with intellectual disability”  
Juliette O'Connell, Máire O'Dwyer, Clare Donegan, Martin C Henman, Mary McCarron, Philip McCallion.  
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- 45th ESCP (European Society of Clinical Pharmacy) Symposium, Oslo, Norway, October 2016  
“Drug burden index to define functional and cognitive effects in older adults with intellectual disabilities: an observational cross-sectional study”  
Máire O'Dwyer, Juliette O'Connell, Clare Donegan, Eilish Burke, Mary McCarron, Philip McCallion, Martin C Henman  
(also published abstract) *International Journal of Clinical Pharmacy*. 2017. 39(1); pp 312

### Published Abstracts

- O'Dwyer M, O'Connell J, O'Dwyer C, Burke É, McCarron M, McCallion P, Henman M C.  
Patterns of antipsychotic utilisation and associations with Behaviours Which Challenge in older adults with intellectual disability: a cross sectional study. *Journal of Applied Research in Intellectual Disabilities*, IASSIDD European Congress, Athens. 2018. 31(4); pp544.
- O'Dwyer M, Galvin N, McCallion P, McCarron M, Henman M C, O'Connell J.  
Use of High-Risk Medicines in Older Adults with Intellectual Disabilities: A cross-sectional study. *Journal of Applied Research in Intellectual Disabilities*, IASSIDD European Congress, Athens. 2018. 31(4); pp544.
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# Chapter 1

## Introduction

## 1.1 Intellectual Disability

Intellectual disability (ID) is a neurodevelopmental disorder which manifests early in life and is characterised by impairments of general mental abilities that affect adaptive functioning. Three domains of function are primarily affected: conceptual skills (language, reading, writing, mathematics, knowledge and memory); social skills (communication, social judgement, forming and maintaining relationships) and practical skills (self-management in personal care, money management etc) (1). A number of terms have been used to describe ID, with “intellectual disability”, “mental retardation” and “learning disabilities” among the most common descriptors used since the early 1990s. “Mental retardation” is considered an outdated term, and the terms “intellectual disability”, “learning disability” or “developmental cognitive impairment” are now preferred. Rather than defining ID as a disease or disability, it has been proposed that the more correct term is that it is a meta-syndrome characterised by deficits in cognitive functioning prior to acquisition of skills through learning (2, 3).

Historically, the most frequently used criteria for diagnosis of ID were Intelligence Quotient (IQ) below approximately 70, impaired social skills and onset before age 18. However, the reliance on IQ tests alone for diagnosis of ID has been superseded by the use of metrics for level of adaptive behaviour deficits (4). Deficits in intellectual functioning include deficits in reasoning, problem solving, planning, abstract thinking, judgment, academic learning, and learning from experience, while deficits in adaptive functioning are those which significantly hinder conforming to developmental and sociocultural standards (5). The Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-V), American Association on Intellectual and Developmental Disabilities (AAIDD – formerly American Association on Mental Retardation), and International Statistical Classification of Diseases and Related Health Problems Version 11 (ICD-11) provide similar categorisation of ID, though the ICD-11 and AAIDD provide further statements around diagnosis which support the concept of dual-diagnosis with physical and/or mental health conditions (ICD-11) and encourage diagnosis with due consideration of the cultural and linguistic context and community environment of the individual (AAIDD) (2).

According to statistics from the National Intellectual Disability Database (NIDD; described in more detail in *Section 1.1.3* and *Chapter 2*), the prevalence rate of ID in Ireland has been reported as 5.96 per 1,000 population based on 2016 Census of Population figures (6). The prevalence rate for mild ID was 1.92 per 1,000 and moderate, severe or profound ID was 3.49 per 1,000 (6). The number of people with ID registered with NIDD in older age groups has increased in recent years. In 2002, 6,500 people aged 35 and older with ID were registered with

the NIDD (7). Most recent data from the NIDD in 2017 revealed 8,200 people aged 35 and older with ID (6, 7). This represents a 25% increase in the population of adults with ID over 35 in Ireland over a 15-year period. This ageing population has implications for future service provision needs, and the NIDD have identified that an extra 2,200 people over 35 with ID will require residential service or residential support services by 2022 (7).

### **1.1.1 Aetiology of Intellectual Disability**

A number of aetiologies have been identified for ID. These are categorised as genetic factors, hereditary factors and acquired factors (8, 9). *Figure 1.1* presents a flow chart of aetiologies of ID.

Genetic factors include chromosomal disorders, including Down syndrome (the most common identified cause of ID (10)), Cornelia de Lange syndrome, fragile X chromosomal syndrome, Prader-Willi syndrome, Angelman syndrome, Turner syndrome, Rett syndrome, neurofibromatosis, tubular sclerosis and adrenoleukodystrophy, among others (8).

Hereditary factors include phenylketonuria (PKU), galactosaemia, Tay-Sachs disease and Lesch-Nyhan syndrome. These are typically diagnosed neonatally through metabolic screening (8).

PKU is an autosomal recessive inborn error of metabolism caused by variants on the gene for phenylalanine hydroxylase, with a resulting accumulation of phenylalanine to neurotoxic levels. Long-term, PKU can cause ID, motor dysfunction, dysphagia, seizures, dystonia, and spasticity. Management requires following a diet free from phenylalanine, typically by using specialised medical foods designed to be free from or with very low phenylalanine content (11). Similarly, galactosaemia, another autosomal recessive condition, restricts the individual to a galactose-free diet as they lack the enzyme required to metabolise galactose, a naturally occurring sugar. Despite following this diet, patients develop long-term complications which include ID, verbal dyspraxia, motor dysfunction and hypogonadism (12). Tay-Sachs disease, also autosomal recessive, is caused by an enzyme deficiency leading to accumulation of GM2 ganglioside in nerve cells (13). It causes ID, gait disturbance, speech problems and behavioural symptoms (14). Lesch-Nyhan syndrome is an X-linked recessive disorder caused by deficiency of the purine salvage enzyme hypoxanthine-guanine phosphoribosyltransferase which causes self-injurious behaviour, extrapyramidal syndrome (especially dystonia) and respiratory abnormalities (15, 16).

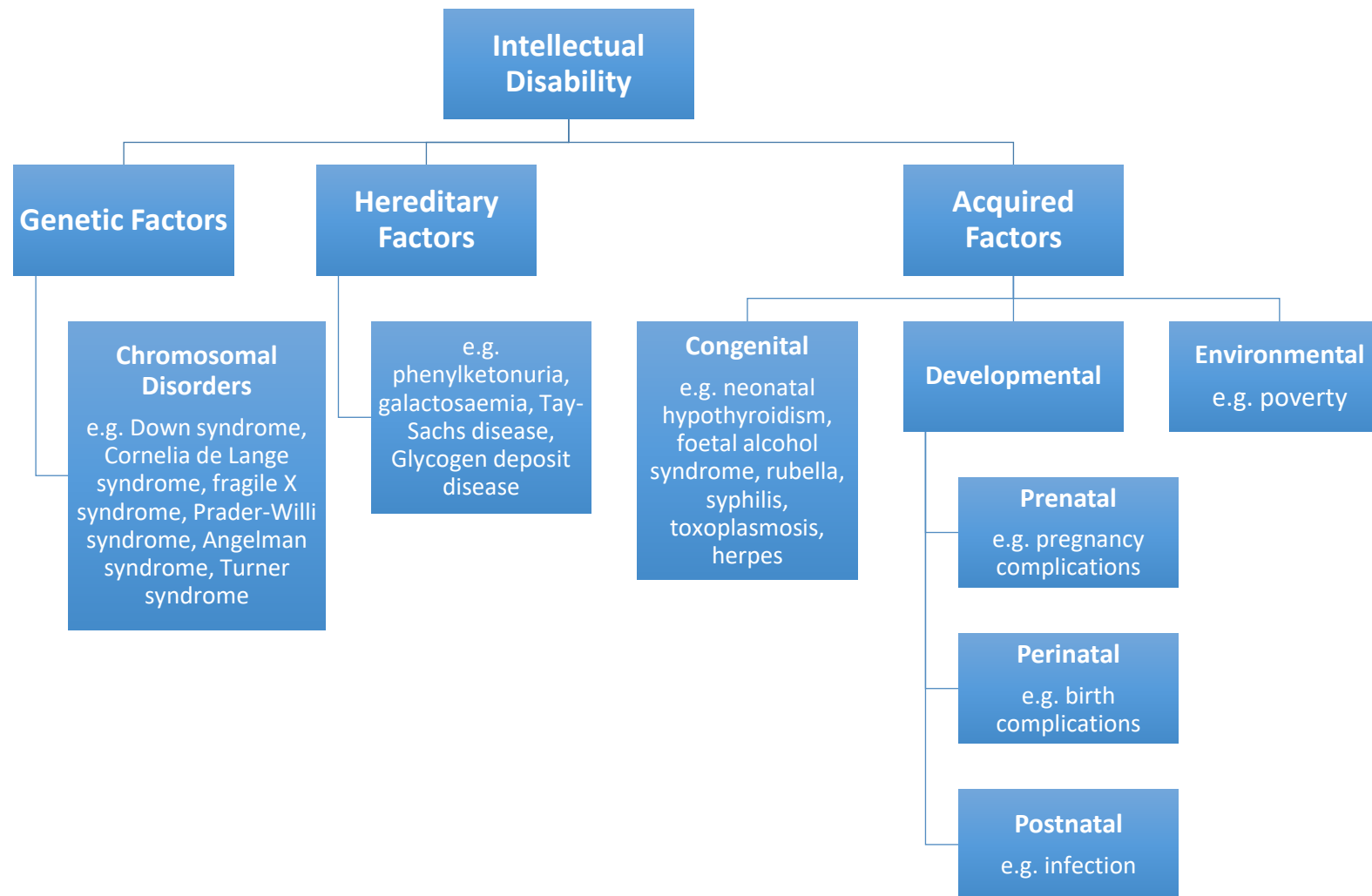


Figure 1.1 Aetiology of Intellectual Disability

Acquired factors may be congenital or developmental. Congenital factors are metabolic (such as neonatal hypothyroidism – often caused by failure of thyroid gland to develop properly (17)), toxic (foetal alcohol syndrome, prenatal exposure to substance, lead poisoning) or infectious (rubella, cytomegalovirus, syphilis, toxoplasmosis and herpes) (8). Developmental factors may be prenatal, perinatal or postnatal (8). Cerebral palsy, a disorder of development, may occur during foetal development or in the infant brain. It causes both motor disturbances and disorders of sensation, cognition, communication, perception and/or behaviour. Seizures are also common in this condition (18). Pregnancy complications, such as toxæmia, uncontrolled diabetes, intrauterine malnutrition, vaginal haemorrhage, placenta previa and umbilical cord prolapse may all contribute to developmental ID (8). Perinatally, birth complications, neonatal anoxia, asphyxia, incorrect use of forceps and poorly applied fundal pressure can cause ID (8). Postnatally, brain damage from jaundice (kernicterus), head injury and infections can cause ID (8). Environmental and socioeconomic factors such as poverty affect quality of natal health and could contribute to development of ID (8).

However, identifiable causes of ID usually only account for a minority of cases. 60% of people with ID do not have a known cause recorded (19, 20). This is particularly important for older people, because the techniques and programmes to elucidate the genetic causes are recent developments and as invasive, expensive procedures are only applied retrospectively to specific sub-groups for research purposes.

### **1.1.2 Ageing and Intellectual Disability**

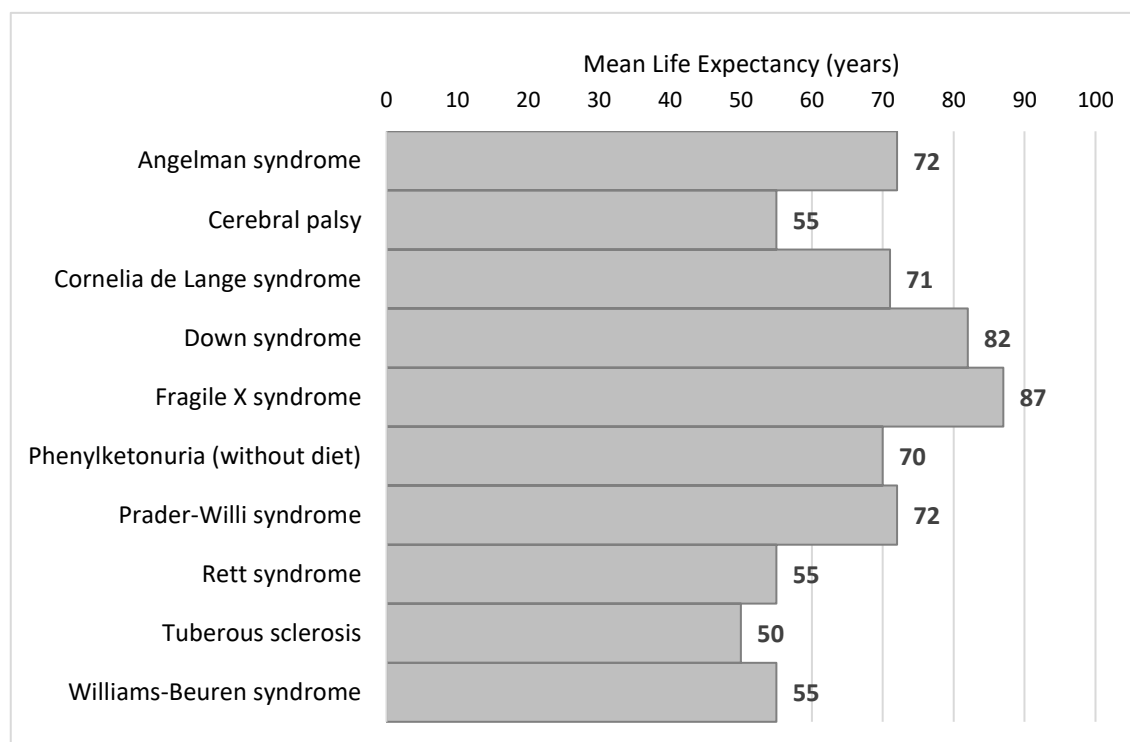
Historically, people with ID had greatly reduced life expectancy compared to those without ID (10); however, in recent years the life expectancy among this group has increased and people with ID are living into middle and old age (10, 21). The increased life expectancy is most pronounced in individuals with mild to moderate level of ID. Much of the improvement in life expectancy can be attributed to better medical interventions, especially treatment of congenital heart disease and respiratory infections (10). The introduction of antibiotics in the 1950s appears to have been a key factor in the extended life expectancy for people with Down syndrome, where life expectancy has risen from 9 years in 1929 to over 70 years in 2013 (10, 22). In addition, the move from institutionalised settings to community-based models of care has positive effects on morbidity and life expectancy (10). This is evidenced by an observational European multinational study which compared countries in the earlier stages of deinstitutionalisation with those in advanced stages. Countries in the earlier stages of

deinstitutionalisation reported higher levels of myocardial infarctions, chronic bronchitis, osteoporosis and gastric or duodenal ulcers among its individuals with ID (23).

There still remains disparity in life expectancy for people with ID when compared to those in the general population, as their life expectancies are still typically lower – in Ireland life expectancy at birth was found to be 19 years lower than for people without ID, and death occurs earlier the more severe the level of ID (24, 25). The Confidential Inquiry into premature deaths of people with ID in the United Kingdom (UK) found that mortality which could be prevented by good quality healthcare was more common among people with ID (26). Factors identified as contributing to deaths were lifestyle choices, dependence on others for mobility and feeding, inadequate accommodation for the person's needs, families/carers not feeling listened to, problems with advanced health and care planning, problems with recognising needs and adjusting care as needs change, problems with coordination of care and information sharing, problems with record keeping and accessing records, problems with the Mental Capacity Act being followed and delays in diagnosis and treatment of healthcare problems (26).

Age-related changes tend to occur earlier in the lives of people with ID, including those with Down syndrome, cerebral palsy, Cornelia de Lange syndrome, Prader-Willi syndrome and fragile X syndrome (10). These age-related changes can include early menopause (Down syndrome; fragile X syndrome), Alzheimer's disease (Down syndrome), degenerative arthritis and faster musculoskeletal system ageing (cerebral palsy) and early development of osteoporosis and premature greying of hair (Cornelia de Lange syndrome) (10, 27). Some of the mean life expectancies for a number of aetiologies of ID are presented in *Figure 1.2*.

Figure 1.2 Mean Life Expectancies (adapted from Coppus et al, 2013 (10))



The concept of an ageing population with ID is therefore relatively novel, both in the field of pharmacoepidemiology and elsewhere.

### 1.1.3 Law and Policy around Intellectual Disability in Ireland

Traditionally in Ireland, people with ID were institutionalised into special residential centres which were primarily operated by philanthropic organisations and religious orders (28, 29). However, since the 1950s, community-based services were beginning to be introduced to integrate people with ID into the general population rather than the life of segregation previously experienced. Public policy in Ireland since the 1980s has been focused on equality, rights and citizenship of people with ID (28).

In 1995, the NIDD, a service planning tool for people with ID, was established (30). The database collates information on the specialised health services used or required by people with ID and it informs planning for ID services (31). It produces annual reports outlining figures and geographical distribution of those registered with the database. In addition to ensuring people with ID can access the services available to them, the NIDD provides a database which enables research into this population. Initial research using data from the NIDD identified the variations around numbers of adults with ID known to services across and within regions in Ireland in order to ensure equitable funding and service delivery (32), investigated inequalities around respite

service provision in Ireland (33) and identified the average age at death of people with ID (34). The NIDD provided the sampling frame for the study on which this thesis is based – the Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing (IDS-TILDA), a nationally representative study on ageing in ID. Much of the knowledge of medication exposure in older adults with ID in Ireland comes from IDS-TILDA. IDS-TILDA has now completed three waves of data collection – Wave 1 (2009/2010), Wave 2 (2013/2014) and Wave 3 (2016/2017). This thesis is based on the data obtained from Wave 2. IDS-TILDA will be described in detail in *Chapter 2*. Published data from Wave 1 of the study provides a baseline of information which the findings of this thesis build upon.

In 2004, the Irish Government launched the National Disability Strategy in order to consolidate the law and policy surrounding disability (35). The Disability Act 2005 followed, allowing for assessment of needs for people with disability, improving access to buildings, services and information, Government department plans for improvement and fair employment of people with disabilities (35). In 2007, Ireland signed the United Nations Convention on the Rights of Persons with Disabilities, and this was ratified by the State in 2018 (36). This Convention underpins rights including equality, social protection, living independently, access to information, access to justice, education, health, work and respect for privacy (37).

A number of subsequent reports, strategies and implementation plans have been launched in the last ten years. In 2011, the congregated settings report “Time to Move on from Congregated Settings - A Strategy for Community Inclusion” was adopted as national policy. This report defined congregated settings as those “where ten or more people reside in a single living unit or are campus based” (28). The move from congregated settings to community group homes or personalised arrangements has been found to produce better outcomes for people with ID, and they experience improvements in social connectedness, well-being, choice and participation in leisure activities (38, 39). However, there is still variability around the results from studies of the outcomes of deinstitutionalisation, reinforcing that it is by no means a “cure-all” for the challenges experienced by people with ID (40). The “New Directions” report (2012) provided a review of Health Service Executive (HSE) day services for adults with ID and the implementation plans for future service provision (29). The National Disability Strategy Implementation Plan 2013 – 2015 provided recognition of the goals of the National Disability Strategy and the actions and timeframes for their delivery (41). This initial implementation plan, however, was hindered by the economic and fiscal constraints of the time (42). The National Disability Inclusion Strategy 2017 – 2021 followed on from the National Disability Strategy in order to provide improvement in a number of areas, including service provision, accommodation, health, employment,



transport and education (42). *Figure 1.3* provides a timeline of the law and policy discussed above.

The Health Information and Quality Authority (HIQA) is the independent authority responsible for setting standards for health and social services, regulation, monitoring children's services, monitoring healthcare quality and safety, health technology assessment and health information in Ireland. It reports to the Minister for Health and the Minister for Children and Youth Affairs. Its remit extends to public, private and voluntary sector services. HIQA issues standards for service providers, such as its "National Standards for Residential Care Settings for Older People in Ireland" (43), "National Standards for Residential Services for Children and Adults with Disabilities" (44) and guidance, which includes its "Medicines Management Guidance" (45). However, little guidance is provided around use of medications in people with ID.

There still remains wide variation among ID service provision in Ireland. Services may be provided directly by the HSE or by voluntary bodies receiving grant aid from the HSE. This leads to heterogeneity in service provision across the country, which has been particularly identified in day services (29). Traditionally, larger residential services employed one or more pharmacist(s) for full time medication management (Mulryan, N, consultant psychiatrist, personal communication, 4<sup>th</sup> February 2019). As deinstitutionalisation has become more engrained into policy and practice, much of the pharmaceutical care for people with ID has been shifted to community pharmacies providing medications to the service or directly to the individual with ID, often with support from their keyworker. Many of the community-based home settings for people with ID do not receive services from a registered nurse in intellectual disability (RNID) full-time, and care staff have recently begun to be trained in medications administration (Safe Administration of Medicines (SAM) courses) for these situations. Education programmes for self-management of medications and health have also been introduced for people with ID in order to empower them to manage their own healthcare (Burke, E, RNID, personal communication, 31<sup>st</sup> January 2019). Hospital passports have been introduced as a new initiative to aid people with ID when accessing secondary healthcare in the HSE (46).

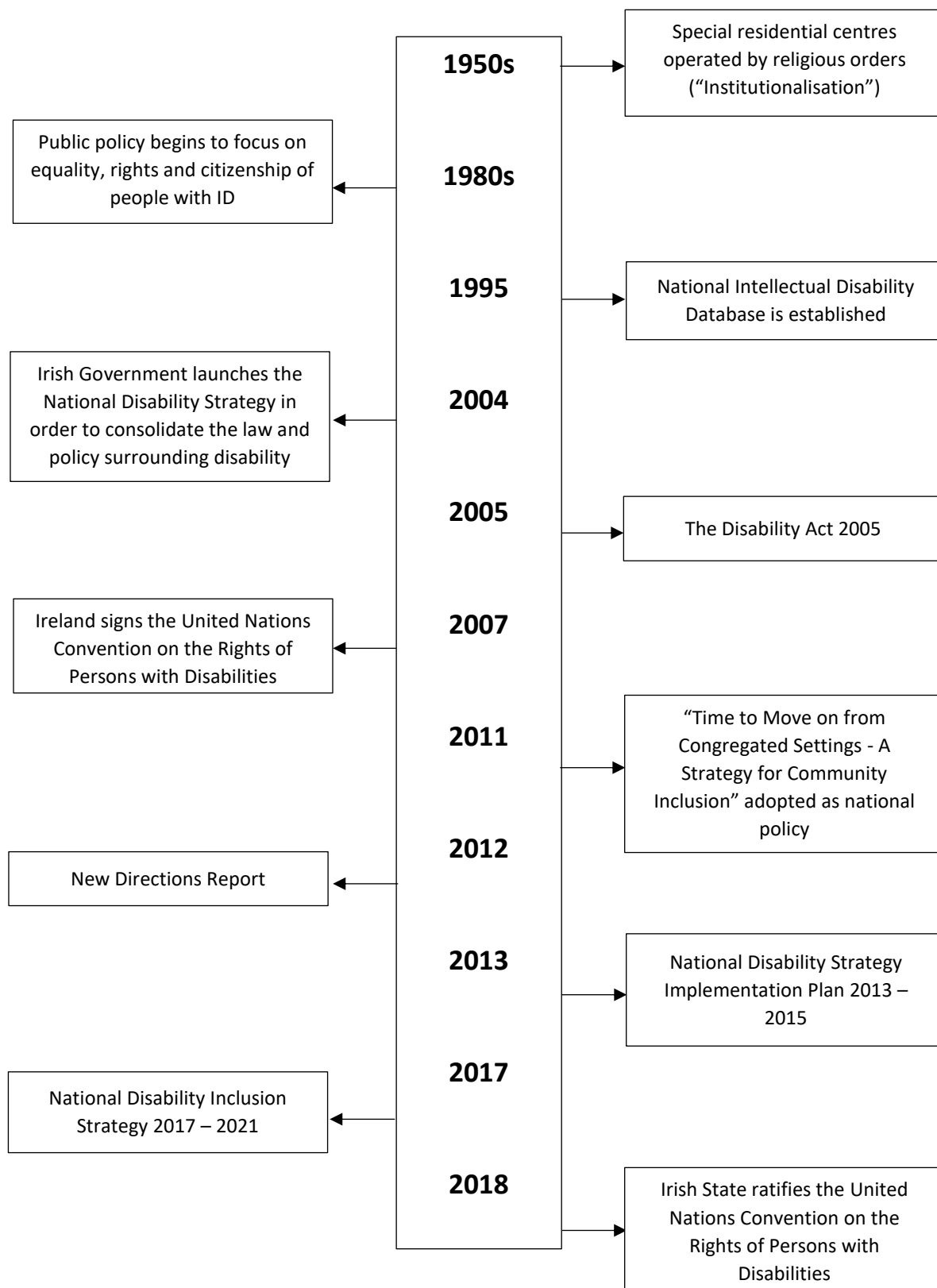


Figure 1.3 Law and Policy around Intellectual Disability in Ireland

Larger ID services typically have a Drugs and Therapeutics Committee to provide input from allied health professionals, including nursing staff, RNIDs, psychiatrists, general practitioners (GPs) and pharmacists as well as non-clinical stakeholders. These committees are responsible for writing local policy around medication use in the service, such as format of drug kardexes, medication administration records (MARs), nurse prescribing, and SAM training for non-clinical staff (Mulryan, N, consultant psychiatrist, personal communication, 4<sup>th</sup> February 2019).

The National Clinical Programme on Epilepsy has been developed in Ireland to improve epilepsy service provision in Ireland. One of its projects is to decentralise epilepsy care by forming Group Based Epilepsy Centres. It involves bringing the clinic to the ID service in order to provide a familiar environment for patients and limit the waiting times which are often extended in outpatient clinics (47).

#### **1.1.4 Healthcare for People with Intellectual Disabilities**

Many issues impact on the provision of healthcare to people with ID. They face unique challenges when they seek healthcare, distinct from the general population. Difficulties in communication are experienced by both verbal and non-verbal individuals in addition to disparities in receptive and expressive communication abilities (48). While patients with ID may find it helpful to have a carer present during consultations, they may also feel “talked over” and ignored by the practitioner in this situation (49). Attending healthcare services may also be a frightening or intimidating experience for a person with ID, especially if the procedure has not been clearly explained to them (49). Diagnostic overshadowing, when symptoms of a physical or mental illness are incorrectly attributed to the person’s ID, can lead to delays in accessing appropriate healthcare (49). There is a lack of appropriate health promotion to people with ID which can have an impact on preventable medical conditions such as obesity and diabetes (50).

Healthcare professionals may also face challenges in providing adequate healthcare to people with ID. A lack of knowledge and little focus on this group during training may make it more difficult for practitioners to address the health needs of people with ID (51). The movement of people with ID from congregated settings where they received very specialised health services, to primary care practitioners, while on the whole beneficial, can result in reduced expertise in managing the chronic conditions unique to people with ID.

Family members and carers play an integral role in the provision and coordination of healthcare for people with ID. They also experience barriers in healthcare access for the patient with ID due to service complexity and lack of support (49).

### **1.1.5 Provision of Healthcare in Ireland**

In Ireland, people may avail of medications under the Primary Care Reimbursement Service (PCRS). A General Medical Services (GMS) card is a means-tested scheme which allows an individual to avail of free General Practitioner (GP) visits and medications subject to a levy of €2 per item up to €20 per month. Medical card holders over the age of 70 pay a reduced levy of €1.50 per item (since April 2019). Adults with ID are entitled to hold a GMS card, and the vast majority have reported holding a GMS card (over 90%) (52).

A Long-Term Illness (LTI) book is issued to individuals with one or more of 16 approved conditions. This enables a person to receive medications directly associated with that condition free of charge. Prior to December 2013, persons holding a GMS card could not also benefit from holding an LTI book. In December 2013, a policy change enacted by the HSE allowed patients holding a GMS card to also avail of LTI eligibility where applicable (53). One of the conditions allowed under the LTI scheme is Intellectual Disability, and this scheme covers a broad range of medications, including corticosteroids, antibiotics, antiepileptics, inhaled preparations, anti-allergic agents, cardiac medicines, anxiolytics, hypnotics, proton-pump inhibitors, histamine H<sub>2</sub> antagonists, needles, syringes, giving sets, laxatives and special medical foods (54). Other conditions covered by the LTI scheme may also be relevant for a person with ID – cerebral palsy, epilepsy and phenylketonuria are also conditions which are eligible for LTI cover (55).

The introduction of both schemes under the Health Act 1970 (56) also shifted the medical costs from the individual charities providing care to people with ID to the State.

### **1.1.6 Morbidity and Intellectual Disability**

People with ID experience different patterns of medical conditions to people in the general population. Two categories of the morbidity experienced by people with ID have been suggested: associated (primary) health conditions and secondary conditions (48, 50).

Associated health conditions refer to conditions which are directly related to the ID, such as epilepsy, mobility problems (including cerebral palsy), visual and hearing problems, mental health problems and dementia. Syndrome-related conditions refer to conditions which are co-occurring in an individual with ID and may be genetically related to the presence of the ID; for example, hypothyroidism in Down Syndrome (48).

Secondary conditions are those which occur at higher rates in people with ID than in the general population, but are considered to be preventable; for example, obesity, gastro-oesophageal reflux, constipation, dental caries, pneumonia, or bowel obstruction (48, 50).

Recent research from Wave 1 of IDS-TILDA on older adults with ID in Ireland identified that the most prevalent morbidities, in order of prevalence, were as follows: eye disease, mental health disease, neurological disease, gastrointestinal disease, endocrine disease, joint disease, hypertension, heart disease, lung disease, cancer, stroke and liver disease (57). Age standardised percentage prevalence for the five most common morbidities were: 51% (eye disease), 48% (mental health disease), 36% (neurological disease), 27% (gastrointestinal disease) and 21% (endocrine disease) (57). Older adults with ID have also been found to be 20% more likely than the general population to have a diagnosis of diabetes mellitus (58). Wave 1 of the IDS-TILDA study found that seven out of ten adults with ID over 40 experience multimorbidity (57). Co-occurrence of mental illness with neurological disease is most prevalent when considering multimorbidity patterns in older adults with ID. In contrast, multimorbidity patterns in older adults without ID tend to be cardiovascular/metabolic and liver/lung/joint/eye patterns (57, 59).

The morbidity occurring in people with ID is generally caused by a number of factors. The underlying cause of ID may also increase morbidity in other areas, such as Mowat-Wilson syndrome and Rubenstein Taybi syndrome, which often cause chronic, lifelong constipation (60, 61). Cerebral palsy, Rett syndrome, tuberous sclerosis, adrenoleukodystrophy and Down syndrome are often associated with co-occurring seizure disorders (18, 62-65). The occurrence of epilepsy is suggested to be as a result of the underlying neurological damage which caused the ID initially (66). Down syndrome has a strong association with the early development of Alzheimer's dementia (16).

### **1.1.7 Mental Health Conditions**

Historically it was thought that a person with ID could not also experience mental health conditions, as they were unable to support the psychological processes which could lead to mental illness (67, 68). It is now widely acknowledged, however, that a person with ID can experience mental illness, and in fact they report higher prevalence of mental health conditions than the general population (67). The current underlying theories of mental illness, including the monoamine hypotheses, support the concept of increased prevalence of mental health conditions among people with ID, as the brain's neurochemical pathways can be disrupted by the damage which underpins the presence of ID (67). Psychosocial factors may also have an

influence on the development of mental health conditions, due to prejudicial views of people with ID promoting the development of a “disabled personality” which itself perpetuates overdependence, low self-esteem and helplessness (67, 69). Deinstitutionalisation and independent living, while on the whole beneficial, may lead to isolation and loneliness for people with ID (67). Underdiagnosis of physical illness among people with ID could also lead to secondary mental health conditions (67). People with ID may have atypical presentations of certain mental illness symptoms, including psychosis, and less pronounced symptoms may be overlooked by physicians. The cognitive distortion typical of mental illness may be difficult for a person with ID to express due to the complex and abstract concepts involved (67).

Diagnosed mental health conditions have been reported in 48% of older adults with ID in Ireland (57). High point prevalence of mental health conditions among people with ID has been reported in Scotland, including psychotic disorder (4.4%), affective disorder (6.6%) and anxiety (3.8%) (70, 71). In spite of mood stabiliser use in 22% of adults with ID, 2-year incident mania was found to be 1.1% in a recent prospective cohort study, which is higher than that observed in the general population (71). This study also found incidence of depression among adults with ID was similar to that observed in the general population which, considering higher prevalence of depression in ID, suggests it is a more enduring and potentially undertreated mental health condition (71). Sleep initiation and latency can also be an issue for older people with ID (72). Circadian disorders, including insomnia, difficulty initiating and/or maintaining sleep, hypersomnia, narcolepsy, sleep apnoea, nightmares, sleepwalking/talking, limb movements, enuresis, bruxism and movement problems are all issues which can affect sleep in people with ID (67). These sleep disorders may be associated with mental health conditions, neurological conditions, medications, sensory impairment, as well as specific disorders including autism and cerebral palsy (67). Chronic disturbances in restful sleep can affect adaptive functioning, leading to emotional consequences and increased frustration and may exacerbate pre-existing behaviours that challenge (67).

The concept of behaviours that challenge is controversial. Behaviours that challenge in people with ID are defined as any behaviour which:

*“(1) is a barrier to a person participating in and contributing to their community (including both active and passive behaviours);*

*(2) undermines directly or indirectly a person’s rights, dignity or quality of life; and*

*(3) poses a risk to the health and safety of a person and those with whom they live and work”* (73, 74).

Many behaviours that challenge are thought to emerge as a result of the individual's difficulty in communicating, functional dependence on others and deficits in social skills (75, 76). For example, a person with severe ID experiencing pain may scream as this is their only means of communicating the symptom they are experiencing (75). Some behaviours are a characteristic manifestation of certain aetiologies. For example, Smith Magenis syndrome typically produces a behavioural phenotype of self-injurious behaviour (including insertion of objects into body orifices) (16); self-injurious behaviour and hand stereotypy are characteristic of fragile X syndrome (16); and temper outbursts with a high level of uncontrollability and apparent physiological arousal are observed in those with Prader-Willi syndrome (16). Aggression and self-injurious behaviour, two common manifestations of behaviours that challenge, have been found at point prevalence of 9.8% and 4.9% respectively (77, 78). It is reported that between 14 and 30% of individuals with ID who receive psychotropic medications are doing so in order to manage behaviours that challenge (75). The prevalence of aggression increases with the severity of ID, and this is thought to be as a result of neurological damage (76). Fluctuations of behaviours that challenge may be as a result of natural variation of serotonin and noradrenaline (76). Epilepsy, pain, allergies and hormonal disorders are all thought to influence behaviours that challenge in people with ID (76). There is much debate around the efficacy of psychotropics for the management of behaviours that challenge. A Lancet study in 2008 found that in a randomised controlled trial of risperidone, haloperidol and placebo for aggressive challenging behaviour, the placebo group displayed the greatest reduction in aggressive behaviours (79). However, a Cochrane review found inconclusive results from studies of antipsychotic use in behaviour problems without mental illness (80, 81).

#### **1.1.8 Neurological Conditions**

Neurological conditions, in particular epilepsy, also occur more frequently among people with ID. Epilepsy has a reported prevalence of 31% in older adults with ID in Ireland (82). A recent meta-analysis found pooled data from 38 studies provided an estimate of 22.2% prevalence of epilepsy, compared to an estimated prevalence of 1.1% in the general population (83-85). Increasing severity of ID has been found to be associated with seizure prevalence, with up to 50% of people with severe ID experiencing seizures (67). In addition, people with ID may present with different manifestations of epilepsy in terms of seizure types and frequencies and atypical presentation may occur due to presence of autism, motor abnormalities, sensory disturbances, behaviours that challenge and concomitant use of psychotropic medications (86-88). Seizure

types include partial and generalised seizures; atonic, atypical absence, myoclonic and tonic seizures as well as status epilepticus (67). Hyperpyrexia may lead to seizures, coma and permanent brain damage (67). The onset of seizure activity may also be associated with disorders such as Alzheimer's disease and dementia, especially among people with Down syndrome (67). Refractory or medication-resistant epilepsy is also observed in this population, and this is thought to be as a result of structural abnormalities in the nervous system and atypical response to antiepileptic medication (87, 88). Other conditions may occasionally be misdiagnosed as epilepsy among people with ID, including vacant staring and motor stereotypies (86).

## **1.2 Medication Use in Older Adults**

Many older adults experience multiple medical conditions, including hypertension, arthritis, heart disease, cancer and diabetes. As a result, they may be exposed to multiple medications (89). Older adults experience changes in the pharmacokinetic and pharmacodynamic effects of medications. Reduced hepatic blood flow, decreased availability of albumin for protein binding and reduced phase I metabolism influence the hepatic clearance of drugs substantially and reduced renal mass, decreased glomerular filtration and reduced tubular secretion impact on renal clearance, changes which lead to prolonged drug half-lives (90-92). Increased body fat leads to an increased volume of distribution of lipophilic medications and as a result the elimination half-life is increased (91, 92). Ageing reduces the ability to metabolise medications, thought to be due to physiological changes such as an approximately 40% reduction in liver volume and a decrease in the expression of cytochrome P450 enzymes (91). This can pose problems even long after a drug is discontinued – for example, fluoxetine's long half-life and influence on cytochrome P450 microsomal enzymes must be considered to avoid interactions and drug accumulation and toxicity in older adults [58].

Older adults are particularly susceptible to age-related changes associated with Central Nervous System (CNS) medications. Medications such as phenytoin, amitriptyline, venlafaxine, diazepam, zolpidem and haloperidol could produce increased adverse effects and/or increased sensitivity to therapeutic effects in this population (90).

Polypharmacy (use of multiple medicines; defined in more detail in *Section 1.3*) in older people is associated with a reduction in both physical and social function, increased risk of falls, delirium and hospitalisation (89, 93-95). The age-related physiological changes which occur in older



adults in combination with polypharmacy often increases the risk of adverse drug events (ADEs) (96). The risk of ADEs has been found to be strongly associated with multimorbidity, use of high-risk medications such as warfarin and increasing number of medicines (89). Polypharmacy may cause harm through increased drug interactions, increased risk of ADEs, inappropriate prescribing and medication errors and lack of monitoring (97). Barriers to deprescribing include an underappreciation of the potential for polypharmacy-related harm, narrow focus on lists of potentially inappropriate medications, prescriber reluctance and patient ambivalence (93).

Individual medication classes also present specific adverse effects. First generation antipsychotic medications are typically associated with extrapyramidal symptoms such as akathisia, tardive dyskinesia and dystonia (98). Second generation antipsychotics, while producing less extrapyramidal adverse effects than first-generation antipsychotics, have particular adverse effects including weight gain, metabolic changes and cardiovascular adverse effects (99). Anticholinergic medications, described in more detail in *Section 1.4*, also carry risks when used in older people both with and without ID.

### **1.3 Medication Use in Older Adults with Intellectual Disabilities**

Patterns of medication and supplement use among older adults with ID are considerably different to older adults in the general population. Use of medication in older adults with ID in independent and community settings is substantially higher than in the general population of older adults – almost three-quarters of the ID population in Ireland reported medication and/or supplement use versus just under half of older adults without ID (100). Polypharmacy is six times more prevalent among older adults with ID and the diversity of medication use is also much greater (100, 101). In particular, alimentary tract medications, dermatological treatments and nervous system agents were the most frequently reported medications. Use of immunomodulatory agents and cardiovascular medications is lower in the ID population compared to those without ID (100). Older adults with ID are more likely to receive medications with anticholinergic properties, intermediate and long-acting benzodiazepines and antipsychotics than older adults in the general population (102).

As a result of the multimorbidity experienced by older adults with ID, they may be exposed to high levels of medication use. In a recent IDS-TILDA study, polypharmacy (use of 5 – 9 medications) and excessive polypharmacy (use of 10 or more medications) have been reported at 31.5% and 20.1% respectively in this population and the most commonly reported therapeutic

classes of medications were antipsychotics (43.2%), antiepileptics (39.0%), laxatives (37.8%), analgesics (37.6%) and antidepressants (26.2%) (87, 101). In addition, IDS-TILDA data demonstrated exposure to anticholinergic medications is high in this population, and has been associated with adverse effects such as constipation and daytime drowsiness (103). Intraclass polypharmacy has been identified in the three most frequent therapeutic classes in this population – antipsychotics, antiepileptics and laxatives (101). Antiepileptic medications are frequently prescribed as part of polytherapy, with half of older adults with a diagnosis of epilepsy reporting exposure to multiple antiepileptic medications (87).

An observational study comparing community-dwelling older adults with ID to those without ID found distinctly different patterns of medication use between the two groups (*Table 1.1*). There was also marked heterogeneity in the prevalence of medication use between older adults with ID living in community-based versus community-based and residential settings combined. Peklar et al, 2017 (100) conducted the comparison analysis based on older adults with ID living either independently or in small groups in community group homes, in order to provide a more accurate comparison with medication use from the Irish Longitudinal Study on Ageing (TILDA), as TILDA samples only community-dwelling older adults and not those in nursing home settings. Use of psycholeptic medications was higher in IDS-TILDA than TILDA (11.0% versus 3.1%), while use of agents acting on the renin-angiotensin system were lower in IDS-TILDA than TILDA (5.3% versus 10.2%) (100). In comparison with the findings from community-dwelling older adults with ID, when the IDS-TILDA population was looked at as a whole, medication use in each class was substantially higher (101). Antipsychotic use among the total population was reported at four times the prevalence as reported among community-dwelling participants alone, and antiepileptic use was eight times higher (101).

Table 1.1 Comparison of medication use among older adults with and without ID

| <b>IDS-TILDA Wave 1<br/>(n = 238; excluded those<br/>living in residential care<br/>settings) (100)</b> | <b>TILDA Wave 1<br/>(n = 8,061; included<br/>community-dwelling older<br/>adults without ID aged ≥<br/>50 years) (100)</b> | <b>IDS-TILDA Wave 1<br/>(n = 736; included<br/>community-dwelling and<br/>those living in residential<br/>care settings) (101)</b> |
|---------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|
| Psycholeptics<br>(antipsychotics, anxiolytics,<br>hypnotics)<br>11.0%                                   | Psycholeptics<br>(antipsychotics, anxiolytics,<br>hypnotics)<br>3.1%                                                       | Antipsychotics<br>43.2%                                                                                                            |
| Psychoanaleptics<br>(antidepressants,<br>stimulants)<br>6.1%                                            | Psychoanaleptics<br>(antidepressants,<br>stimulants)<br>3.0%                                                               | Antidepressants<br>26.2%                                                                                                           |
| Drugs for obstructive<br>airway diseases<br>6.1%                                                        | Drugs for obstructive<br>airway diseases<br>4.8%                                                                           | Inhaled adrenergics<br>7.0%                                                                                                        |
| Agents acting on the renin-<br>angiotensin system<br>5.3%                                               | Agents acting on the renin-<br>angiotensin system<br>10.2%                                                                 | Agents acting on the renin-<br>angiotensin system<br>6.5%                                                                          |
| Antiepileptics<br>4.8%                                                                                  | Antiepileptics<br>1.3%                                                                                                     | Antiepileptics<br>39.0%                                                                                                            |

Another area of medication use which is of note in people with ID is the receipt of psychotropic medications. While it has been reported that between 20 and 45% of individuals with ID received psychotropics, up to 30% receive psychotropics to manage behaviours that challenge, typically aggression and self-injurious behaviour (75). An IDS-TILDA study of psychotropic use in older adults with ID found 59.1% of the sample were exposed to any psychotropic, and of these two thirds reported psychotropic polypharmacy (104). Furthermore, behaviours that challenge have been found to be independently associated with antipsychotic use and high prevalence of complex psychotropic polypharmacy has been reported among those with behaviours that challenge in IDS-TILDA (105). Psychotropic use has been highlighted as an area for concern in older adults with ID who also have a diagnosis of epilepsy, due to the epileptogenic potential of certain antipsychotics, including chlorpromazine, aripiprazole, quetiapine, olanzapine and risperidone. Depot antipsychotic preparations have also been identified as requiring caution due to the difficulty in withdrawing this medication should seizures occur (87). Care is required with other psychotropic medications in patients with concomitant epilepsy, particularly tricyclic antidepressants, which can lower the seizure threshold, and citalopram, venlafaxine and lithium, which are pro-convulsive in overdose (87).

Despite the high levels of medication use among older adults with ID, there are still certain areas of treatment which appear to be neglected – a Swedish study found that medications for pain

management were less likely to be reported by older adults with ID compared to the general population, potentially as a result of poor recognition and under-prescribing for pain among these people (102).

As a result of the types of morbidity experienced by people with ID, they are often prescribed medications with anticholinergic and sedative effects (101). Antiepileptics are used for both management of epilepsy and for mood stabilisation; antidepressants are used for mental health disorders such as anxiety and depression; anxiolytics and hypnotics are used for anxiety and sleep problems; antipsychotics are used for mental health conditions and for behaviours that challenge; and anticholinergics are used to manage side effects associated with antipsychotics, for urinary incontinence and for gastrointestinal symptoms (101, 105).

The evidence base for medication use among older adults typically comes from younger patients with few morbidities (90), and an even smaller amount of evidence-based medicine information exists for older adults with ID (106). For example, much of the data on use of antipsychotics comes from studies of patients with schizophrenia rather than ID (106). This is thought to be due to a number of factors, including a primary research focus on specific therapeutic classes in this population, in addition to smaller study sample sizes for people with ID and convenience sampling (107). There is a significant gap in the literature surrounding methods of measuring potentially inappropriate prescribing among older adults with ID (107, 108). This is an important stimulus to promote research into the area of measuring drug burden in this population. In addition, there is evidence to suggest that people with ID in an older age profile may have different susceptibility to medication adverse effects, in particular anticholinergic and sedative medications. People with ID have been found to be more likely to suffer from the movement related side effects of antipsychotic medications in recent UK evidence (109).

The neurological damage underlying ID may lead to different sensitivity to medication and challenges when selecting appropriate doses (110, 111). The brain of a person with ID can differ from those without in four main areas:

- a. Quantity: For people with ID, there may be quantitatively less brain substrate and as a result fewer receptors with which medications interact.
- b. Quality: Differences in brain anatomy, histology, neurochemistry and function have all been observed in people with some types of ID, epilepsy and developmental disorders. These can include enzyme deficits, structural displacements, irregular cell growth and imbalance in sizes of competing neurological pathways.

- c. Developmental stage: Some patients with higher mental ages benefit more significantly from treatments for hyperactivity, such as methylphenidate.
- d. Degeneration: The premature ageing and prevalence of Alzheimer's disease in people with ID leads to degeneration of the brain, both due to neuronal loss and reduced qualitative functioning (111).

With regard to pharmacokinetics, differences for people with ID may potentially be mediated by increased body fat and obesity compared to the general population (112), genetic abnormalities and expression of metabolic enzymes responsible for degradation of medications (111). There is more variety of physical stature and physiological function among people with ID, and this may lead to different electrolyte and blood values, different volumes of distribution for medications and differences in kidney and liver capacity (110). Loss of response to melatonin treatment has been attributed to decreased activity of CYP1A2 microsomal enzyme in a small sample people with ID. Whether this was due to a polymorphism in the CYP1A2 gene specific to ID has not been established, but it provides some evidence of genetic differences in metabolism (113).

## 1.4 Anticholinergic Medications

Anticholinergic medications are antagonists of acetylcholine receptors. Of the two acetylcholine receptor types – nicotinic and muscarinic – the majority of therapeutic agents target muscarinic receptors, with nicotinic receptor antagonists primarily used as muscle relaxants in anaesthesia (114, 115).

There are five subtypes of muscarinic receptors: M<sub>1</sub>, M<sub>2</sub>, M<sub>3</sub>, M<sub>4</sub> and M<sub>5</sub>. A summary of the functional responses of each receptor subtype and the disease relevance is shown in *Table 1.2*. The five muscarinic receptor subtypes are widely distributed in both the CNS and peripheral tissue (114, 115).

Table 1.2 Muscarinic Receptor Subtypes (114, 115)

| Receptor Subtype     | Functional Response                                                                                                                        | Disease Relevance                                                                         |
|----------------------|--------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|
| <b>M<sub>1</sub></b> | ↑ Cognitive function<br>↑ Seizure activity<br>↓ Dopamine release<br>↑ Secretions                                                           | Alzheimer's disease<br>Cognitive dysfunction<br>Schizophrenia                             |
| <b>M<sub>2</sub></b> | ↓ Heart rate<br>↑ Smooth muscle contraction                                                                                                | Alzheimer's disease<br>Cognitive dysfunction<br>Pain                                      |
| <b>M<sub>3</sub></b> | ↑ Smooth muscle contraction (predominantly bladder)<br>↑ Secretions (predominantly salivary glands)<br>↑ Food intake<br>↓ Dopamine release | Chronic obstructive pulmonary disease<br>Urinary incontinence<br>Irritable bowel syndrome |
| <b>M<sub>4</sub></b> | Analgesia<br>Cataleptic activity<br>Facilitates dopamine release                                                                           | Parkinson's disease<br>Schizophrenia<br>Neuropathic pain                                  |
| <b>M<sub>5</sub></b> | Facilitates dopamine release<br>↑ Drug-seeking behaviour and reward                                                                        | Drug dependence<br>Parkinson's disease<br>Schizophrenia                                   |

Muscarinic receptor antagonists block the binding of acetylcholine to muscarinic receptors. They can be categorised as:

- 1) naturally occurring alkaloids (e.g. atropine and scopolamine);
- 2) semisynthetic derivatives of these alkaloids (e.g. homatropine, tropicamide, ipratropium and tiotropium); and
- 3) synthetic derivatives, some of which show selectivity for subtypes of muscarinic receptors (e.g. darifenacin and solifenacin, which have selectivity for M<sub>3</sub> receptors).

However, selective antagonism is difficult in drug development because the orthosteric sites remain conserved across the receptor subtypes (115).

The autonomic nervous system (ANS) is largely outside of voluntary control, and it mainly regulates contraction and relaxation of vascular and visceral smooth muscle, heartbeat and energy metabolism (114). As a result, the ANS is the target of the peripheral actions of anticholinergics. Therapeutically, muscarinic receptor antagonists (also referred to as antimuscarinics, anticholinergics or parasympatholytic drugs) are used for pupil dilatation (mydriasis – for ophthalmological examination), prevention of motion sickness, treatment of Parkinson's disease, inhibition of bronchoconstriction in chronic obstructive pulmonary disease, as antispasmodic agents in the gastrointestinal tract and to lower intravesicular pressure and

frequency of contractions in bladder smooth muscle, therefore treating overactive bladder (114, 115).

The role of CNS cholinergic transmission in cognitive impairment is well characterised. Abnormalities such as changes to choline transport, acetylcholine release, expression of receptors, neurotrophin support and axonal transport are implicated in both cognitive and peripheral effects of problems in the cholinergic system. Cholinergic neuron dysfunction in the forebrain leads to a low level of acetylcholine, contributing to the cognitive and behavioural presentations of Alzheimer's disease, dementia and delirium (116). In addition to the cognitive effects of cholinergic activity in the CNS, nausea and motion sickness occur as a result of cholinergic transmission. Motion sickness occurs due to exposure to unfamiliar motion. While the inner ear is responsible in part for motion sickness, it is the central nervous system which controls feelings of nausea and eventual emesis – mediated through muscarinic acetylcholine receptors. Anticholinergic medications such as scopolamine act on the CNS to block neural muscarinic receptors, allowing faster adjustment to new sensory inputs by reducing the sensory mismatch signals (117).

People with ID may be exposed to anticholinergic effects from a range of medications, only some of which have antimuscarinic activity as their principal mechanism of therapeutic effect and many which do not. It is the cumulative effect of these medications that will give rise to effects on the peripheral nervous system and variable effects on the CNS as the blood-brain barrier individually influences their CNS penetration.

Of the adverse effects precipitated by medications, Type A are dose-dependent effects related to the pharmacological actions of the drug. Physical and cognitive impairment caused by psychotropic and anticholinergic medications are classified as Type A adverse effects (90). Anticholinergic medications produce an extensive spectrum of adverse effects to which older adults are particularly susceptible (118). These are broadly categorised as mild, moderate and severe and may affect multiple systems both centrally and peripherally, including cardiovascular, gastrointestinal, ocular, oral, neurological and urinary systems (118-120). Depending on the anticholinergic activity of the drug and the load of anticholinergic medications an individual is exposed to, older patients may experience adverse effects ranging from mild discomfort (e.g. modest dry mouth) to more serious conditions, such as faecal impaction or seizures (118-120). *Figure 1.4* is adapted from Mintzer & Burns, 2000 (118), Collamati et al, 2016 (119) and De Vreese et al, 2018 (120).

## 1.5 Sedative Medications

Sedative medications and medications with sedative effects mediate these effects through multiple receptors in the CNS. These include the benzodiazepine binding site in the gamma ( $\gamma$ )-aminobutyric acid A (GABA<sub>A</sub>) receptor complex, histamine H<sub>1</sub>-receptors,  $\alpha_1$ - and  $\alpha_2$ -adrenergic receptors and  $\mu$ -opioid receptors (121).

GABA, the primary inhibitory neurotransmitter in the brain, acts on the GABA<sub>A</sub> receptor, a pentameric complex coupled to chloride channels and composed of five subunits – two  $\alpha$ , two  $\beta$  and one  $\gamma$  (*Figure 1.5*). GABA binds at the interfaces between the  $\alpha$  and  $\beta$  subunits while benzodiazepines bind at the  $\alpha/\gamma$  interface. GABA binding causes opening of the chloride channel, reducing membrane excitability. Benzodiazepines facilitate the action of GABA, explaining the anxiolytic, hypnotic, sedative and inhibitory effect of these medications. Similarly, antiepileptic medications inhibit abnormal neuronal discharge by enhancing GABA action, with sedation as an adverse effect. Antiepileptic medications also inhibit sodium and calcium channels, thereby reducing membrane excitability. Valproate and vigabatrin act slightly differently, by also inhibiting GABA transaminase, the enzyme responsible for inactivation of GABA, thereby increasing the availability of this neurotransmitter (114).



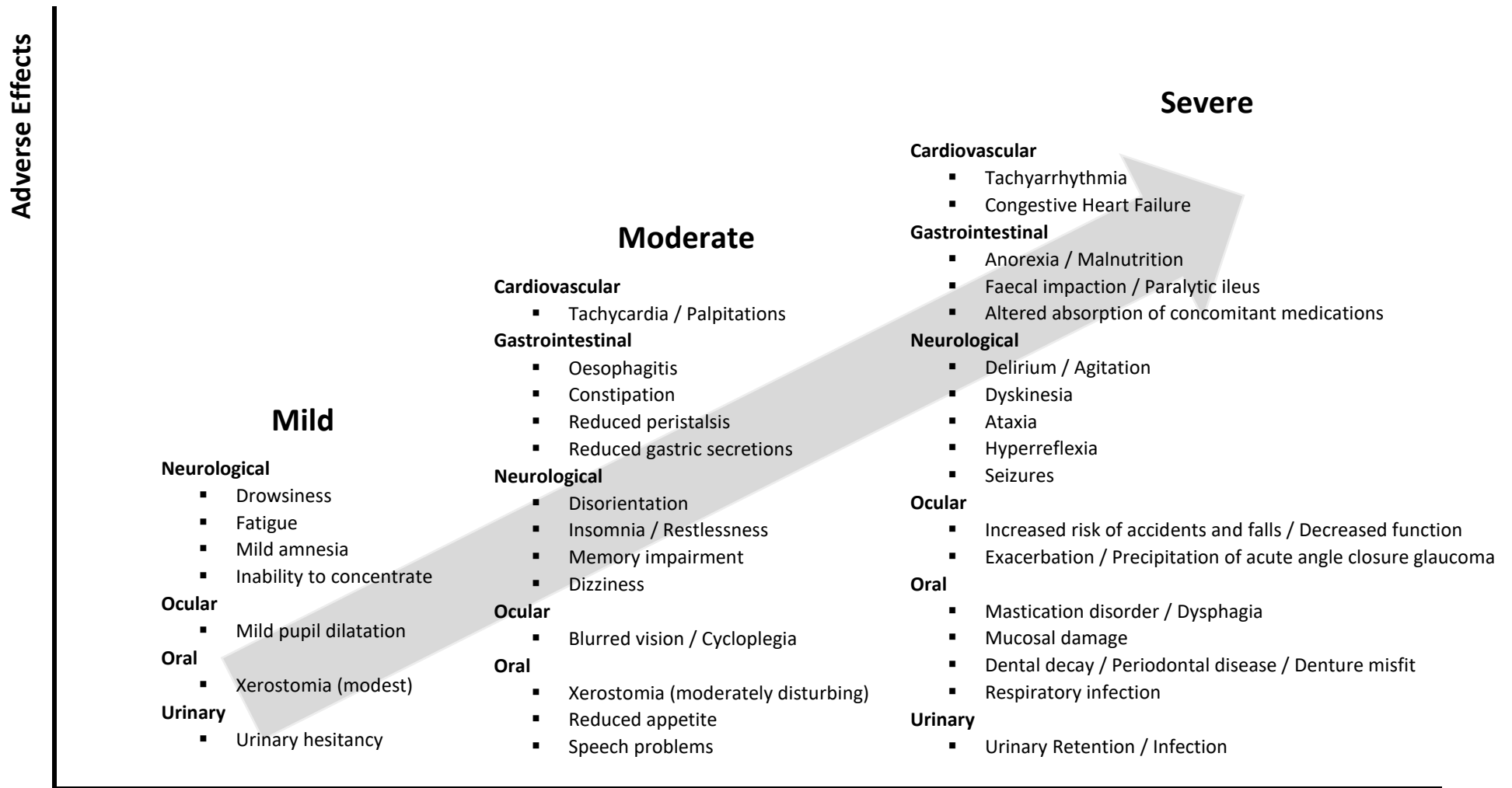


Figure 1.4 Anticholinergic Adverse Effects  
(adapted from (118-120))

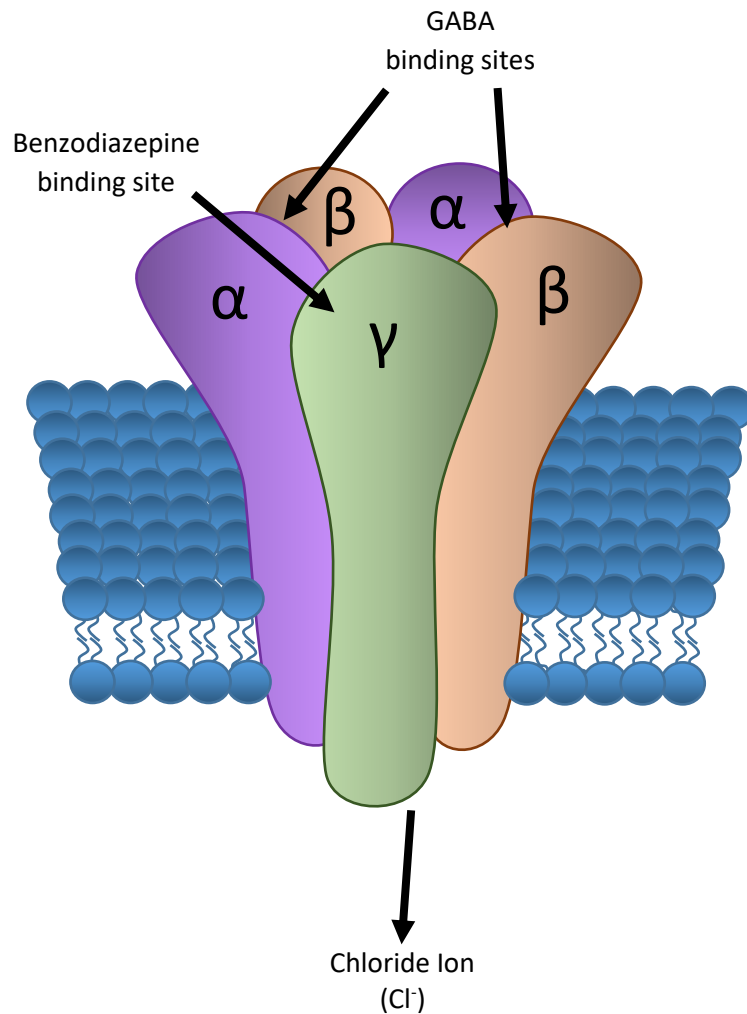


Figure 1.5 Gamma-Aminobutyric Acid A Receptor Complex (adapted from Rang et al, 2016 (114))

Histamine, a monoamine transmitter, is involved in numerous CNS functions. Histamine release occurs in a circadian pattern, and neurons are activated during the day and silent at night.  $H_1$  receptors are responsible for arousal and wakefulness, and as a result, histamine  $H_1$  receptor antagonists (such as antihistamines) can have sedative effects (114).

Sedation is an adverse effect from adrenergic agonists, particularly  $\alpha_2$  adrenergic agonists which are centrally acting, such as methyldopa and clonidine. Activation of these receptors decrease discharges in sympathetic fibres and suppress the release of noradrenaline. Similarly, antagonists of the  $\alpha_1$  adrenergic receptor can cause sedation (115).

Binding of opioid analgesics to endogenous  $\mu$ -opioid receptors is responsible not only for most of the pain-relieving effects, but also the adverse effects, including sedation, respiratory depression and constipation (114).

Sedation as an adverse effect of medications is rarely caused by one type of receptor interaction alone, however, and it is important to consider the multiple mechanisms that may cause sedation. A typical example is that of the antipsychotics, which act not only on their therapeutic target, the dopamine receptor and glutamate pathway, but also on  $\alpha_1$  receptors, histamine  $H_1$  receptors and muscarinic acetylcholine receptors (114). Medications indicated for somatic conditions can also act on these receptors without being direct psychotropics, thereby causing sedation as a potential adverse effect, e.g. clonidine and methyldopa (115).

Sedative medications and medications with sedative potential also affect the ageing brain differently. Older patients are more susceptible to the adverse effects of psychotropics, including sedation, delirium, extrapyramidal symptoms, arrhythmias and postural hypotension (92, 122). Decreased metabolism and clearance of these types of medications may lead to drug accumulation (122). Medications which are known to affect cognition in older adults are opiates, benzodiazepines, antiepileptics, antipsychotics and antidepressants. Medications which cross the blood-brain barrier may also affect cognitive ability. Depression, anxiety and neurodegenerative diseases affecting often poly-medicated older adults must be treated with careful consideration of adverse drug reactions and interactions, bearing also in mind that the clinical evidence base for psychotropic medications often comes from younger patients with few or no co-morbidities (90, 123). Sedative medications are also a cause of morbidity from ataxia, falls and fractures (122). Evidence exists which suggest a link between benzodiazepine use and Alzheimer's disease which may increase with use of long-acting benzodiazepines, higher cumulative dose and longer duration of use (122, 124, 125). However, sudden withdrawal of these medications is also not advisable due to adverse withdrawal effects associated with sedatives, including confusion and convulsions (122).

## **1.6 Methods of Measuring Drug Burden**

A number of indicators for the measurement of medication burden in older adults have been developed.

### **1.6.1 Polypharmacy**

Polypharmacy is one measure used for assessing the burden of medications in older adults. While it is a term used very commonly in the literature, a universally accepted characterisation does not exist, and is generally defined as use of five or more medications (101, 126-129). Excessive polypharmacy or hyper-polypharmacy are also identified in the literature, typically

referring to the use of ten or more medications, though again, this definition is variable (129). Polypharmacy has been identified as a risk factor for potentially inappropriate prescribing (107, 130). High rates of polypharmacy have been reported among older adults with ID ((101); *Section 1.3*). However, polypharmacy as a measure of drug burden is relatively crude, as it refers only to the number of medications without assessing appropriateness or dose, and lacks a standard definition (97). While polypharmacy may be useful for triggering medication review, it is not an independent predictor of the functions necessary in order for older people to maintain independence (131). Attention has begun to turn from this simplistic measure of drug burden to others based pharmacokinetic and pharmacodynamic principles, including therapeutic class and dose response. Finding a measure of medication burden which is associated with functional outcomes has important implications for improving prescribing practices, guiding effective medication review and producing positive clinical and functional outcomes.

### **1.6.2 Medicines Regimen Complexity Index**

The Medicines Regimen Complexity Index is another method of assessing burden, this time with focus on the dosage forms, frequencies and additional directions for each medication a patient takes. It rates the complexity of an individual's medicine regimen by giving a rating for the ease of administration of certain dosage forms (e.g. capsules/tablets have a scoring of 1, while nebuliser administration has a score of 5). More frequent administration has higher weighting for complexity, and directions such as breaking or crushing tablet or alternating doses also contribute to the complexity. Scores on each of the three aspects (dosage forms, frequencies and additional directions) are summed together for each drug a patient takes to give an overall complexity score. This tool was developed by consensus of an expert panel (132).

Assessment of medication burden can also focus more directly on pharmacological principles that target specific types of medications. This is particularly useful for studies of medication use in older adults with ID, because they are exposed to high levels of psychotropics and medications with anticholinergic and sedative effects (101), therefore much of their drug burden can be assessed using specific methods of detecting these kinds of medication exposure.

### **1.6.3 Measuring Exposure to Anticholinergic Medications**

The anticholinergic activities of medications have been measured using three methods:

1. Serum radioreceptor anticholinergic activity assay (SAA)
2. *In vitro* measurement of drug affinity to muscarinic receptors
3. Expert-bases consensus lists of medications with anticholinergic activity (116).

Methods 1 and 2 (SAA and *in vitro* receptor binding studies) are well standardised but tend to identify medications with clear peripheral effects rather than those with central effects. Method 3 is useful to identify clinically significant anticholinergic medications but can be prone to bias and lacks uniformity across studies (116).

There are a number of scoring systems which have been developed in order to assess the extent of anticholinergic burden in older adults. These include the Anticholinergic Cognitive Burden Scale, the Anticholinergic Drug Scale, Anticholinergic Burden Classification, Chew et al (2008), Clinical-rated Anticholinergic Score, Anticholinergic Risk Scale, Anticholinergic Activity Scale and Anticholinergic Loading Scale (133-140). These scales typically categorise anticholinergic medications into high potency, low potency or no/improbable anticholinergic activity (141). The cumulative exposure to anticholinergic medications of a patient is calculated by summation of individual drug scores.

The Anticholinergic Drug Scale takes into account both regular and as required (*pro re nata*; *prn*) medications with anticholinergic activity. It classifies medications as: level 0 (no known anticholinergic properties); level 1 (potentially anticholinergic as evidenced by receptor binding studies); level 2 (anticholinergic adverse events sometimes noted, usually at excessive doses); and level 3 (markedly anticholinergic). The Anticholinergic Drug Scale was found to be associated with SAA; however, it is not certain if there are clinically significant outcomes associated with SAA levels – some drugs with normal SAA levels have been described as causing cognitive impairment, and some studies have reported that SAA has no association with the number of anticholinergic medications an individual is exposed to (116, 133).

The Anticholinergic Burden Classification focuses on cognitive impairment as an outcome. This tool combines both knowledge of serum radioreceptor assay of drug induced muscarinic blockade and average estimated clinical effects of specific drugs in its selection of the medication inventory. It classifies anticholinergic burden as 0 (no anticholinergic drugs used), 1 (drugs used with no likely effect), 2 (drugs used with low effect) and 3 (drugs used with high effect). Long term anticholinergic exposure measured by this method was found to be significantly associated with cognitive deficits in a cohort of older adults which was similar to deficits observed when younger adults were administered scopolamine (134).

Chew et al (2008) also performed a study on *in vitro* measurement of drug binding affinity to muscarinic receptors for 104 of the medications most commonly dispensed to older adults living in term care facilities plus three extra medications with reports of anticholinergic activity. The medications with anticholinergic activity identified were similar to those identified in other studies of anticholinergic medications. However, the clinical significance of this method of evaluation is uncertain as it used rat forebrain and striatum homogenate as its source of muscarinic receptors, thereby limiting its applicability to human older adults. However, it presents another useful source of medication inventory for agents with anticholinergic activity (135).

The Clinical-rated Anticholinergic Score was developed to assess the effect of anticholinergic medications on severity of delirium in older adults. Scores ranged from 0 (no anticholinergic activity) to 3 (high anticholinergic activity) and values were selected by consensus of three clinicians (geriatric psychiatrists) (142). The scale has been found to have good concurrent criterion validity against other anticholinergic inventories and SAA. Long term anticholinergic exposure as measured by this tool was associated with poor verbal memory and executive function in older men (137).

The Anticholinergic Risk Scale is another tool developed to evaluate the risk of adverse effects from anticholinergic medications. The inventory was identified by consensus and excludes topical, ophthalmic, otologic and inhaled medicines. Medications are ranked according to anticholinergic activity as 0 (limited or none), 1 (moderate), 2 (strong) and 3 (very strong). Higher scores were found to be associated with statistically significantly increased risk of anticholinergic adverse effects in older patients (136).

The Anticholinergic Activity Scale was modelled on the findings of Chew et al (2008) (135) and transformed this gradation to scores from 0 to 4. Cognitive decline, as measured by Mini-Mental State Examination, was higher in those with exposure to anticholinergic medications in older adults with Parkinson's disease. However, as with Chew et al (2008) (135), SAA may not adequately reflect anticholinergic effects on the brain (central effects) (138).

The Anticholinergic Loading Scale, similar to the Anticholinergic Burden Classification, used data from both SAA and clinician-rated scores to form the inventory, and scored medications on a scale from 0 (no effect) to 3 (strong effect). Outcome measures were once again based on cognitive tests, and high Anticholinergic Load was associated with slower response speed in measures of cognition (139).

The Anticholinergic Cognitive Burden (ACB) Scale is a scale which used data on anticholinergic activity from all three methods of measurement: SAA, receptor-binding studies and expert consensus. It rates drugs as follows: 1 (possible anticholinergic effects based on SAA or *in vitro* affinity to muscarinic receptors lab tests but no evidence of clinically relevant cognitive effects) and 2 or 3 (drugs with established clinical anticholinergic effects based on permeability to the blood-brain barrier and delirium). Drugs not listed have a score of 0 (116, 140).

#### 1.6.4 Measuring Exposure to Sedative Medications

Several measurement scales exist for measuring sedative burden (121). The Sedative Load Model (143, 144) and Sloane Model (145) both use similar methods of quantifying sedative burden – by classifying the sedative potential of medications into groups. The Sedative Load Model classifies medications as primary sedatives (Group 1), drugs with a sedating component (Group 2), drugs with sedation as a potential adverse effect (Group 3) and drugs with no known sedation (Group 4). Drugs within these classes are assigned scores of 2, 1, 0 and 0 respectively. The difference between this Sedative Load Model and the Sloane Model lies in that the Sloane Model includes fewer medications in Group 1 (primary sedatives), transfers a number of medications from Group 1 to Group 2, and modifies Group 3 to include only drugs with sedation as a potential adverse effect that can persist beyond initiation of the drug. Group 4 remains the same, and scores are assigned 6, 3, 1 and 0 respectively. In addition, the Sloane Model takes into account the dose each participant is exposed to each day of the study period using the following formula:

$$SL_{ij} = \sum_{k=1}^m \frac{Dose_{ijk} \times SR_k}{ADMD_k}$$

Where  $m$  is the number of sedative medications for resident  $i$  on day  $j$ ;  $Dose_{ijk}$  is the quantity of medication  $k$  received by participant  $i$  on day  $j$ ;  $SR_k$  is the sedation rating (1, 3, 6) for sedating medication  $k$  and  $ADMD_k$  is the average daily maintenance dose for medication  $k$ . Of note, the Sloane Model was developed as a control variable for sedative and analgesic medication use in clinical trials (121).

The other two models are the Drug Burden Index (146) and Central Nervous System (CNS) Drug Model (147, 148), which both include an element of dose-dependency. Drug Burden Index will be discussed in more detail in *Section 1.6.5*. The CNS Drug Model examines the relationship between CNS active medications and adverse effects, primarily cognitive function and falls. It

measures the effects of opioids, benzodiazepines, antidepressants and antipsychotics only (147, 148). As a result, it includes a more limited inventory than other models of sedative exposure (121, 147, 148).

#### **1.6.5 Drug Burden Index**

The Drug Burden Index (DBI) is an internationally validated, dose-related measure of exposure to anticholinergic and sedative medications by taking into account the relationship between prescribed dose and the dose response curve (146). Scores from the relevant medications are added together to give a total DBI score for the individual (146, 149). Associations between DBI scores and objective function measures have been analysed in order to identify the effect of these types of medications on cognitive and physical performance in older adults. A higher DBI score has been associated with a number of negative outcomes: poor cognitive and physical performance; reduced gait speed and grip strength; poorer performance in instrumental activities of daily living (IADLs); frailty; and falls (146, 149-155). There is currently no core list of medications for inclusion in DBI analysis. At the beginning of this project, DBI had not previously been studied in older adults with ID. To date, no studies of DBI in older adults with ID exist other than that outlined in this thesis.

*Table 1.3* contains a summary of the strengths and limitations of each anticholinergic and sedative measurement tool.



Table 1.3 Strengths and Limitations of Anticholinergic and Sedative Measurement Tools

| Measurement Tool                                         | Strengths                                                                                                                                                                                                                                                                                                                                                                                                                                         | Limitations                                                                                                                                                                                                                                                                                                           | Application in Population with ID                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|----------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Anticholinergic Burden Measures</b>                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Anticholinergic Cognitive Burden Scale <b>(116, 140)</b> | <ul style="list-style-type: none"> <li>• Simple to calculate</li> <li>• Used two methods to determine anticholinergic properties – literature review and expert interdisciplinary team review</li> <li>• Scoring system is based on SAA or <i>in vitro</i> affinity to muscarinic receptors, clinically relevant cognitive effects and blood-brain barrier permeability</li> <li>• Most frequently validated on adverse outcomes (156)</li> </ul> | <ul style="list-style-type: none"> <li>• Dose is not considered</li> <li>• Required modification for use in a population of older adults with ID (103) as it was not fully comprehensive</li> <li>• Effect of drug-drug interactions were not determined</li> <li>• Does not evaluate duration of exposure</li> </ul> | <ul style="list-style-type: none"> <li>• Studied in people with ID (103, 120)</li> <li>• Prevalence of ACB exposure among older adults without ID has been found at 34 - 61% (157-159)</li> <li>• Irish cross-sectional study (IDS-TILDA, Wave 1): 71% reported exposure to anticholinergic medications. Anticholinergic burden was associated with age, reporting a mental health condition, daytime drowsiness and constipation (103)</li> <li>• Italian multicentre cross-sectional study: 35% reported exposure to anticholinergic medications. Anticholinergic burden was associated with living in a residential setting, reporting a mental health condition and reporting a neurological condition (120)</li> </ul> |
| Anticholinergic Drug Scale <b>(133)</b>                  | <ul style="list-style-type: none"> <li>• Found to be associated with SAA</li> <li>• Dose-related measure</li> <li>• Provided list of drugs explicitly considered to have no anticholinergic properties (141)</li> </ul>                                                                                                                                                                                                                           | <ul style="list-style-type: none"> <li>• Clinical significance of SAA is not known</li> <li>• More complex calculation</li> <li>• Effect of drug-drug interactions were not determined</li> <li>• Does not evaluate duration of exposure</li> </ul>                                                                   | <ul style="list-style-type: none"> <li>• Not studied in people with ID</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

| Measurement Tool                            | Strengths                                                                                                                                                                                                                                                                                                                                                                                             | Limitations                                                                                                                                                                                                                                                                                                                                                                                                                                               | Application in Population with ID                                                 |
|---------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| Anticholinergic Burden Classification (134) | <ul style="list-style-type: none"> <li>• Simple to calculate</li> <li>• Used two methods to determine anticholinergic properties – literature review and expert interdisciplinary team review</li> <li>• Found to be associated with cognitive decline</li> <li>• Takes into account route of drug administration, potential drug interaction effects and blood-brain barrier permeability</li> </ul> | <ul style="list-style-type: none"> <li>• Assessed only cognitive performance</li> <li>• Dose is not considered</li> <li>• Does not evaluate duration of exposure</li> </ul>                                                                                                                                                                                                                                                                               | <ul style="list-style-type: none"> <li>• Not studied in people with ID</li> </ul> |
| Chew et al (2008) (135)                     | <ul style="list-style-type: none"> <li>• Simple to calculate</li> <li>• Useful reference inventory</li> <li>• Provided list of drugs explicitly considered to have no anticholinergic properties (141)</li> </ul>                                                                                                                                                                                     | <ul style="list-style-type: none"> <li>• Based only on most frequently dispensed medications from one pharmacy provider, with three additional medications (may not be fully comprehensive)</li> <li>• Clinical significance of methods for measuring anticholinergic effects is not known</li> <li>• Dose is not considered</li> <li>• Effect of drug-drug interactions were not determined</li> <li>• Does not evaluate duration of exposure</li> </ul> | <ul style="list-style-type: none"> <li>• Not studied in people with ID</li> </ul> |
| Clinical-rated Anticholinergic Score (137)  | <ul style="list-style-type: none"> <li>• Simple to calculate</li> <li>• Developed by expert consensus</li> </ul>                                                                                                                                                                                                                                                                                      | <ul style="list-style-type: none"> <li>• Dose is not considered</li> <li>• Effect of drug-drug interactions were not determined</li> <li>• Based on physicians' clinical judgment only</li> <li>• Does not evaluate duration of exposure</li> </ul>                                                                                                                                                                                                       | <ul style="list-style-type: none"> <li>• Not studied in people with ID</li> </ul> |

| Measurement Tool                     | Strengths                                                                                                                                                                                                                                                                                        | Limitations                                                                                                                                                                                                                                                                                                                                                                                                                                           | Application in Population with ID                                               |
|--------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|
| Anticholinergic Risk Scale (136)     | <ul style="list-style-type: none"> <li>Simple to calculate</li> <li>Measures both peripheral and central anticholinergic effects (160)</li> </ul>                                                                                                                                                | <ul style="list-style-type: none"> <li>Not based on systematic review of evidence (116)</li> <li>Did not use standardised cognitive assessment (116)</li> <li>Dose is not considered</li> <li>Does not evaluate duration of exposure</li> </ul>                                                                                                                                                                                                       | <ul style="list-style-type: none"> <li>Not studied in people with ID</li> </ul> |
| Anticholinergic Activity Scale (138) | <ul style="list-style-type: none"> <li>Simple to calculate</li> <li>Provided list of drugs explicitly considered to have no anticholinergic properties (141)</li> </ul>                                                                                                                          | <ul style="list-style-type: none"> <li>Clinical significance of anticholinergic effects is not known</li> <li>Developed in a cohort of patients with Parkinson's disease</li> <li>Dose is not considered</li> <li>Does not evaluate duration of exposure</li> </ul>                                                                                                                                                                                   | <ul style="list-style-type: none"> <li>Not studied in people with ID</li> </ul> |
| Anticholinergic Loading Scale (139)  | <ul style="list-style-type: none"> <li>Simple to calculate</li> <li>Used two methods to determine anticholinergic properties – data on SAA and expert interdisciplinary team review</li> <li>Provided list of drugs explicitly considered to have no anticholinergic properties (141)</li> </ul> | <ul style="list-style-type: none"> <li>Dose is not considered</li> <li>Effect of drug-drug interactions were not determined</li> <li>Only considered highest anticholinergic load of medications a participant was exposed to, which does not represent true load for those taking more than 1 anticholinergic medication</li> <li>Inconclusive findings in relation to cognitive function</li> <li>Does not evaluate duration of exposure</li> </ul> | <ul style="list-style-type: none"> <li>Not studied in people with ID</li> </ul> |
| <b>Sedative Burden Measures</b>      |                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                 |
| Sedative Load Model (143, 144)       | <ul style="list-style-type: none"> <li>Simple to calculate</li> <li>Found to be associated with frailty</li> <li>Includes weighting depending of the sedative potential of the medication</li> </ul>                                                                                             | <ul style="list-style-type: none"> <li>Original inventories based broadly on therapeutic classes of medications rather than individual drugs</li> </ul>                                                                                                                                                                                                                                                                                               | <ul style="list-style-type: none"> <li>Not studied in people with ID</li> </ul> |

| Measurement Tool                     | Strengths                                                                                                                                                                                                                                                                                                                  | Limitations                                                                                                                                                                                                                                       | Application in Population with ID                                               |
|--------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|
| Sloane Model (145)                   | <ul style="list-style-type: none"> <li>Includes element of dose-dependency</li> <li>Includes weighting depending of the sedative potential of the medication</li> </ul>                                                                                                                                                    | <ul style="list-style-type: none"> <li>Complex calculation</li> <li>More limited medication inventory compared to Sedative Load Model</li> <li>Developed as a control measure for epidemiological studies rather than a burden measure</li> </ul> | <ul style="list-style-type: none"> <li>Not studied in people with ID</li> </ul> |
| Central Nervous System Model (147)   | <ul style="list-style-type: none"> <li>Includes element of dose-dependency</li> </ul>                                                                                                                                                                                                                                      | <ul style="list-style-type: none"> <li>Complex calculation</li> <li>Includes a limited inventory – opioids, benzodiazepines and antidepressants, antipsychotics only</li> </ul>                                                                   | <ul style="list-style-type: none"> <li>Not studied in people with ID</li> </ul> |
| <b>Composite Drug Burden Measure</b> |                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                   |                                                                                 |
| Drug Burden Index (146)              | <ul style="list-style-type: none"> <li>Measures burden from medications with anticholinergic and sedative effects</li> <li>Includes element of dose-dependency</li> <li>Internationally validated</li> <li>Found to be associated with both cognitive and physical function deficits in older adults without ID</li> </ul> | <ul style="list-style-type: none"> <li>Complex calculation</li> <li>Requires development of specific inventory and minimum effective daily doses for study populations</li> </ul>                                                                 | <ul style="list-style-type: none"> <li>Not studied in people with ID</li> </ul> |

## 1.7 Selection of Drug Burden Measures

Three tools were selected for the measurement of drug burden among older adults with ID for this thesis. These are the Drug Burden Index, Anticholinergic Cognitive Burden Scale and Sedative Load Model. They were selected for the following reasons:

1. Both dose-dependent (Drug Burden Index) and non-dose dependent tools (Anticholinergic Cognitive Burden Scale and Sedative Load Model) are represented and considered.
2. Quantification of anticholinergic and sedative potency is considered (Anticholinergic Cognitive Burden Scale and Sedative Load Model).
3. The Drug Burden Index provides a cumulative measure of both anticholinergic and sedative medication burden which may also be analysed separately using the anticholinergic and sedative sub-scores.
4. The Anticholinergic Cognitive Burden Scale has previously been investigated in a population of older adults with ID in Ireland at Wave 1 of IDS-TILDA with respect to association with adverse effects (103), but not with regard to measures of dependency, physical function (such as grip strength or timed up and go) and frailty.
5. The Sedative Load Model has previously been investigated in a population of older adults without ID in Ireland (161), so a basic inventory specific to an Irish population already exists and can be adapted to an older population with ID.
6. These three measures cover a comprehensive range of medications.
7. Previous evidence has highlighted that older adults with ID are exposed to high levels of medications with anticholinergic and sedative activity (101, 103, 104).
8. Other tools of medication exposure, for example Screening Tool of Older People's Prescriptions (STOPP), were developed for use in the general population over 65 years of age to be applied to healthy and robust older adults. These criteria are not as suitable for studying medication use in vulnerable populations, including a cohort of older adults with ID (162)
9. Systematic review has identified that the Anticholinergic Cognitive Burden scale was the most frequently validated expert-based anticholinergic scale for adverse outcomes (156).
10. All three measures were designed for clinical practice and/or pharmacoepidemiologic evaluation.

## 1.8 Medication and Physical Function

### 1.8.1 Definition and Importance of Physical Function

Physical function can be defined as:

*“one’s ability to carry out activities that require physical actions, ranging from self-care (activities of daily living) to more complex activities that require a combination of skills, often with a social component or within a social context” (163).*

Physical function is an important marker of functional independence in older adults (164). Functional independence has begun to be recognised as a key therapeutic goal among older people (131). As a result, measures of physical function may be important outcomes of medication exposure (131). Functional impairment has been identified as a strong independent predictor of admission to care homes (131). Functional independence is particularly important among older adults with ID, who typically experience lifelong dependency on others due to deficits in adaptive functioning. Maintaining the level of independence that they do possess is important in order to maintain quality of life and dignity.

### 1.8.2 Measuring Physical Function

Physical function can be assessed in a number of ways. Objective measures of physical function which have been examined in relation to DBI and anticholinergic and sedative medication exposure include the Short Physical Performance Battery (SPPB), which includes three measures – standing balance, gait speed and chair stands (165). Higher DBI score was found to be associated with poorer performance in SPPB both cross-sectionally and longitudinally (146, 150, 166). Anticholinergic drug exposure alone has also been found to be associated with poorer performance in SPPB (167). Grip strength and timed up and go (TUG) are two additional measures of physical function which have been examined in older adults with respect to medication burden (146, 150, 151, 164, 166). Anticholinergic and sedative drug burden has been found to be associated with weaker grip (167, 168). Exposure to DBI drugs was found to be associated with poorer performance in TUG (164).

Activities of daily living (ADLs) and IADLs are two of the most frequently reported outcome measures for studies of drug burden, in particular DBI (151, 164, 168, 169). An observational cross-sectional study of adults aged 75 years and older (n = 700) found exposure to DBI medications was significantly associated with difficulties in Barthel Index ADLs and IADLs (164).

A larger observational study of older men ( $n = 1,705$ ;  $\geq 70$  years) found DBI was associated with poorer performance in IADLs (151). In patients admitted to two acute geriatric wards in the UK, every unit increase in DBI was associated with being in a higher Barthel Index quartile, indicating poorer performance (169). Barthel Index ADLs (170) and Lawton's IADLs (171) are two of the most commonly used international measures of dependency. Barthel Index ADLs include measures of basic functional dependence, including mobility, climbing stairs, dressing, bathing, grooming, feeding, transfer (getting into and out of bed), toileting, and bladder and bowel continence. Lawton's IADLs include telephone use, grocery shopping, food preparation, housekeeping, laundry, transportation, medication management and finances. Among people with ID, Barthel Index ADLs and Lawton IADLs have both been found to be significantly affected by level of ID and mobility. However, Barthel Index tends to be more influenced by mobility than level of ID, while Lawton IADLs are more frequently affected by level of ID than mobility (172). For this reason, Barthel Index ADLs are a more appropriate outcome measure for physical function and dependency. In addition, the capacity to perform IADLs is usually lost prior to the more basic ADLs (173).

*Table 1.4* presents a summary of the methods of measuring physical function in older adults which have been investigated with respect to anticholinergic and sedative medication exposure.

Table 1.4 Methods of Measuring Physical Function in Older Adults

| Type of Measure                                  | Method                                                                                                                                                                                          |
|--------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Objective Measures</b>                        | Short Physical Performance Battery (165) <ol style="list-style-type: none"> <li>1. Standing balance</li> <li>2. Gait speed</li> <li>3. Chair stands</li> </ol> Grip strength<br>Timed up and go |
| <b>(Instrumental) Activities of Daily Living</b> | Barthel Index Activities of Daily Living<br>Lawton Instrumental Activities of Daily Living                                                                                                      |

### 1.8.3 Comorbidities

The presence of comorbidities can have an important influence on physical function. When studying the impact of medication exposure on physical performance, it is particularly important to adjust for confounding factors, especially other health conditions. The Functional Comorbidity

Index (FCI) (174) is a measure which was specifically developed and validated with respect to physical function. The FCI offers a comprehensive range of morbidities, and is particularly suitable for use in a population of older adults with ID because it encompasses not only the most frequently reported medical conditions among older adults in the general population (cardiovascular disease and cancer) but also includes arthritis, neurological conditions, depression, anxiety, and visual and hearing impairment, which are known to be more common among people with ID (67) and could be more influential on results. This makes it a valuable adjuster in a study of drug effects on physical function by eliminating the bias associated with poor physical function as a result of morbidity.

The main alternative measure of comorbidity in observational studies is the Charlson Comorbidity Index (CCI) (175). While the CCI is a valuable tool in longitudinal analysis, its inventory of comorbidities is much more limited than that of the FCI and it focuses primarily on cardiovascular disease and cancer. While this is very relevant for use in a population without ID, considering these are the medical conditions most likely to affect this group and cause mortality, the pattern of morbidity among people with ID is different. It has the advantage of providing a weighting for each disease type. Also, it was designed to classify comorbid conditions which might alter the risk of mortality, rather than those which might affect function. This would make it more useful in a study assessing mortality.

In addition, the FCI was shown to have a stronger association with physical function than the CCI (174).

#### **1.8.4 Medication Use and Physical Performance**

Medication use, particularly of agents with anticholinergic and sedative effects, may impact significantly on physical function in older adults, both directly and indirectly. Studies have repeatedly found an association between anticholinergic exposure and cognitive decline (176). Anticholinergic medications have been found by some studies to be associated with delirium in older adults; however, this evidence is still inconclusive, and more research is required to identify a definitive link (176, 177). The physical function outcomes which have been studied include grip strength, chair stands, reaction time, walking speed, balance, ADLs, IADLs and SPPB (151, 178). The association between anticholinergic exposure and physical function has been found to be stronger, with a number of studies identifying anticholinergic exposure was associated with reduced physical function, in particular grip strength, ADLs and IADLs (137, 150, 151, 176, 179). These associations have been found when using the ACB (116, 140), DBI (146),



Anticholinergic Drug Scale (133), Anticholinergic Risk Scale (136) and Chew et al, 2008 (135) as exposure measures. In addition, anticholinergic medications can cause visual disturbance through pupil dilatation, inability to accommodate and exacerbation of glaucoma, increasing risk of falls and accidents and decreasing functional ability; reduced appetite, malnutrition and weight loss as a result of dental decay, difficulty chewing and swallowing and impaired perception of food taste and texture, potentially leading to sarcopenia and frailty (118-120).

Sedative medications have been associated with slow walking speed, balance difficulties, poor grip strength, frailty and poorer function in older adults (144, 151, 161, 180). One study found that the association with poorer performance in grip strength and IADLs was stronger for the sedative than for the anticholinergic component of the DBI (151). The DBI sedative component has also been found to be associated with poorer performance in Barthel Index ADLs (169). An Irish study of community-dwelling older adults recently found that Sedative Load was significantly associated with frailty as measured by both Fried's frailty phenotype and an accumulation of deficits frailty model (161).

However, despite the high levels of medications of these therapeutic classes used by older adults with ID, research into the effects of these medicines on physical function in this group is very limited. Measures such as Barthel Index ADLs, grip strength, timed up and go and frailty have not previously been examined in this population in relation to medication burden. Indeed, it is only in recent years that physical fitness measurements have begun to be assessed in older adults with ID (181, 182).

This represents a significant gap in the literature, as while we have a good understanding of the effect of medication exposure on physical function in older adults in the general population, it would not be correct to simply extrapolate this data to older adults with ID, since they belong to a population with distinct health requirements and medication use patterns.

## **1.9 Frailty**

The conceptual definition of frailty is widely accepted as that put forward by Campbell and Buchner in 1997:

*"a condition or syndrome which results from a multi-system reduction in reserve capacity to the extent that a number of physiological systems are close to, or past, the threshold of symptomatic clinical failure; and as a consequence the frail person is at increased risk of disability and death from minor external stresses" (183).*

Evaluation of frailty is of great importance. Recognising frailty can allow early identification of those at risk of unstable disability, it draws attention to underappreciated aspects of health such as nutritional state, lower limb strength and balance and it emphasises the importance of non-pharmacological interventions for health such as exercise, dietary supplementation and social activity (183). Frailty is associated with a number of adverse outcomes among older adults without ID, including falls, hospitalisation, worsening disability, care home admission, mortality, functional decline, acute and chronic disease, reduced quality of life and care dependency (184, 185). Evaluation and prevention of frailty in older adults with ID is an emerging concept which is of importance as a result of the increasing life expectancy of people with ID, deinstitutionalisation, and planning for future service provision requirements. Similar to physical function, the absence of frailty can have important implications for the quality of life and independence of older people with ID.

Much of the research into frailty among older adults both with and without ID to this point has been cross-sectional, and as a result risk factors or determinants of frailty in this population have not yet been clearly identified. However, the evidence to date has suggested a number of possible risk factors, outlined in *Table 1.5*.

Table 1.5 Possible Risk Factors for Frailty

(adapted from Espinoza & Fried, 2007 and McKenzie et al, 2016 (186, 187))

| Category                               | Possible Risk Factors for Frailty in Older Adults (186)                                                                                     | Possible Risk Factors for Frailty in Older Adults with ID (187) |
|----------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------|
| <b>Physiologic</b>                     | Activated inflammation<br>Immune system dysfunction<br>Anaemia<br>Endocrine system changes<br>Underweight or overweight<br>Age              | Age<br>Sarcopenia                                               |
| <b>Medical<br/>Illness/Comorbidity</b> | Cardiovascular disease<br>Diabetes<br>Stroke<br>Arthritis<br>Chronic Obstructive Pulmonary Disease<br>Cognitive impairment/cerebral changes | Cognitive impairment<br>Mental illness or addiction<br>Dementia |

Table 1.5 Possible Risk Factors for Frailty (continued)

| Category                                  | Possible Risk Factors for Frailty in Older Adults (186)                   | Possible Risk Factors for Frailty in Older Adults with ID (187) |
|-------------------------------------------|---------------------------------------------------------------------------|-----------------------------------------------------------------|
| <b>Sociodemographic and Psychological</b> | Female gender<br>Low socioeconomic status<br>Race/ethnicity<br>Depression | Female gender (inconclusive)                                    |
| <b>Disability</b>                         | Activity of daily living disability                                       | Level of ID (inconclusive)<br>Down syndrome                     |

However, operationalisation of a definition of frailty has encountered much disagreement. Two main approaches for measuring of frailty have been proposed: the frailty phenotype approach and the accumulation of deficits frailty measure. The frailty phenotype approach utilises five criteria for the measurement of frailty: (1) shrinking; (2) exhaustion; (3) weakness; (4) slowness; and (5) low physical activity. The accumulation of deficits frailty approach counts a set of specific health- and age-related deficits such as symptoms, signs, disabilities, diseases, and laboratory measurements (185, 188)

In line with the increased life expectancy among older adults with ID, several attempts have been made to assess frailty. These measures include a modified version of the Cardiovascular Health Study (Fried's) Frailty Phenotype (189, 190), the Vienna Frailty Questionnaire (191), the Tilburg Frailty Indicator (185); and the accumulation of deficits, or Frailty Index, approach (185, 188). The Vienna Frailty Questionnaire includes measures in social, physiological, cognitive and psychological domains (191), while the Tilburg Frailty Indicator is a multidimensional operational definition of frailty (185). The Dutch "Healthy Ageing and Intellectual Disability" (HA-ID) study developed a 51-item frailty index (192) and found frailty to be significantly associated with mortality (193) and disabilities in daily functioning (194).

Among older adults without ID, polypharmacy, anticholinergic medication exposure and sedative medication exposure have been found to be significantly associated with frailty using both phenotype models and frailty index models. Number of medications has also been found to be significantly associated with transitions in frailty states, particularly transitions from robust to pre-frail, frail and death (152, 161, 195-200).

Several studies of frailty have been performed in people with ID using a number of different measures. The Vienna Frailty Questionnaire identified frailty at a prevalence of 17.7% and pre-

frailty also as 17.7% (191). HA-ID first developed a modified form of the Fried's frailty phenotype which identified 13% of the population as frail and 60% as pre-frail. Frailty according to this phenotype was found to be significantly associated with motor disability (190). HA-ID followed the frailty phenotype with an accumulation of deficits frailty index, where it was reported that the mean frailty index score for the population was 0.27, where 0 indicates no deficits and 1 indicates the presence of all deficits measured. This is higher than the mean score in the general population. Frailty in this population also appeared to begin at a younger age than in adults without ID. More severe level of ID and presence of Down syndrome were significantly associated with higher frailty index scores (192). Frailty Index has been found to be related to increased risk of higher medication use, alimentary tract and metabolic comorbidities among older adults with ID, but not with falls, fractures or hospitalisation (201). Frailty Index was found to predict institutionalisation, and individuals admitted to long-term care were more likely to be frail or pre-frail (68%) (202) Sarcopenia, a risk factor for frailty among the general population, was found in 14.3% of older people with ID, thought to be due to low physical activity levels and long-term mobility impairments, though sarcopenia was negatively associated with Body Mass Index, which is typically higher among people with ID than the general population (203, 204).

Very little research has been performed on the association between medication use and frailty among older adults with ID, despite the known high levels of exposure to polypharmacy and medications with anticholinergic and sedative effects. This presents an important opportunity for research in older adults with ID.

As a result, the focus of this thesis is examination of medication burden using a number of tools and identifying the association of medication exposure with performance in measures of physical function. The specific aims and objectives of this thesis are outlined in detail in *Section 1.11*.

## **1.10 Research Question**

How can we assess the complexity of medication burden among older adults with ID, and how is this associated with potential adverse effects, functional limitations, physical function, and frailty?

## 1.11 Aims of Project

1. To investigate anticholinergic and sedative exposure using the Drug Burden Index tool in a cohort of older adults with intellectual disabilities, and to evaluate its association with demographic characteristics, dependency and potential adverse effects.

The primary objectives were:

- a) To create a version of the Drug Burden Index suitable for use in an Irish population of older adults with ID;
  - b) To determine the characteristics in an older population with ID that are associated with the drug burden measured by the DBI;
  - c) To describe the drug burden in older adults with ID and the most frequently reported therapeutic classes contributing to total burden;
  - d) To examine the association between drug burden and potential adverse effects (daytime dozing, chronic constipation and falls) and Barthel Index ADLs.
2. To examine the association between Drug Burden Index and performance in two physical function measures, grip strength and timed up and go, and a measure of dependency, Barthel Index ADLs, in a cohort of older adults with ID at a cross-sectional level to establish if exposure in people with ID leads to the same functional effects as has been reported in the general population.

More specifically, the objectives were to identify associations and adjusted means for:

- a) Grip strength
- b) Timed up and go
- c) Barthel Index

with respect to exposure to DBI medications, DBI medications with anticholinergic activity (DBA) and DBI medications with sedative activity (DBS) and three-level, dose-related categorical DBI, DBA and DBS scores.

3. To describe frailty and examine the cross-sectional association between anticholinergic and sedative medication exposure using four tools (polypharmacy, Drug Burden Index, Anticholinergic Cognitive Burden and Sedative Load) with frailty in a cohort of older adults with intellectual disabilities.

More specifically, the objectives were:

- a) To describe frailty and by creating a modified version of the Fried's Frailty Phenotype and examine its association with performance in Barthel Index ADLs and comorbidities as measured by the Functional Comorbidity Index;
- b) To update an existing inventory and scoring system for measuring anticholinergic burden (Anticholinergic Cognitive Burden) and sedative burden (Sedative Load);
- c) To identify associations between polypharmacy, Drug Burden Index, Anticholinergic Cognitive Burden and Sedative Load model with frailty as measured by frailty phenotype.

*Table 1.6* displays the project aims and objectives mapped to the relevant thesis chapters.

Table 1.6 Mapping Aims and Objectives to Thesis Chapters

| Aims                                                                                                                                                                                                                                                                                      | Objectives                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Thesis Chapter                                                                                                                                                                                                                      |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Aim 1:</b> To investigate anticholinergic and sedative exposure using the Drug Burden Index tool in a cohort of older adults with intellectual disabilities, and to evaluate its association with demographic characteristics, dependency and potential adverse effects.               | a) To create a version of the Drug Burden Index suitable for use in an Irish population of older adults with ID;<br>b) To determine the characteristics that are associated with Drug Burden Index;<br>c) To describe the drug burden in older adults with ID and the most frequently reported therapeutic classes contributing to total burden;<br>d) To examine the association between drug burden and potential adverse effects (daytime dosing, chronic constipation and falls) and Barthel Index ADLs.                                              | <b>Chapter 2</b> Methods<br><b>Chapter 3</b> Drug Burden Index to Define the Burden of Medicines in Older Adults with Intellectual Disabilities: An Observational Cross-Sectional Study<br><b>Chapter 6</b> Discussion              |
| <b>Aim 2:</b> To examine the association between Drug Burden Index and physical function measures and dependency, in a cohort of older adults with intellectual disabilities.                                                                                                             | To identify associations and adjusted means for<br>a) Grip strength,<br>b) Timed up and go and<br>c) Barthel Index ADLs<br>with respect to exposure to Drug Burden Index medications, Drug Burden Index medications with primarily anticholinergic activity and Drug Burden Index medications with sedative only activity.                                                                                                                                                                                                                                | <b>Chapter 2</b> Methods<br><b>Chapter 4</b> Association of Drug Burden Index with Physical Function Measures in Older Adults with Intellectual Disabilities: An Observational Cross-Sectional Study<br><b>Chapter 6</b> Discussion |
| <b>Aim 3:</b> To describe frailty and examine the cross-sectional association between medication exposure using four tools (polypharmacy, Drug Burden Index, Anticholinergic Cognitive Burden and Sedative Load) with frailty in a cohort of older adults with intellectual disabilities. | a) To describe frailty by creating a modified version of the Fried's Frailty Phenotype and examine its association with Barthel Index ADLs and comorbidities as measured by the Functional Comorbidity Index;<br>b) To update existing inventory and scoring system for measuring anticholinergic (Anticholinergic Cognitive Burden) and sedative burden (Sedative Load);<br>c) To identify associations between polypharmacy, Drug Burden Index, Anticholinergic Cognitive Burden and Sedative Load model with frailty as measured by frailty phenotype. | <b>Chapter 2</b> Methods<br><b>Chapter 5</b> Association of Medication Burden with Frailty in Older Adults with Intellectual Disability: An Observational Cross-Sectional Study<br><b>Chapter 6</b> Discussion                      |

*Chapter 2* of this thesis outlines the Methods and Tools used across the studies, providing more detail in order to complement and expand on the methods described in each individual chapter.

Three studies are presented in this thesis. *Chapter 3* describes the development of the DBI inventory for use in an Irish population of older adults with ID and the characteristics of the study population. Multinomial logistic regression analysis was performed to analyse the association of DBI score with three potential adverse effects – daytime dozing, constipation and falls in the previous year. An Analysis of Covariance (ANCOVA) was performed in order to assess the association between DBI score and performance in Barthel Index ADLs, an important measure of dependency among older adults. This chapter is based on a publication in the British Journal of Clinical Pharmacology.

*Chapter 4* follows on from *Chapter 3* by using the DBI to assess associations with performance in two specific measures of physical function in older adults – grip strength and timed up and go. The DBI is separated into its two component scores, anticholinergic only drug burden and sedative only drug burden, in order to provide further insight into burden in the population and examine if one specific type of burden has more or less association than the other. An ANCOVA is performed for Barthel Index ADLs according to anticholinergic only DBI and sedative only DBI, to assess if one type of burden has greater association with performance in Barthel Index ADLs. This chapter is based on a publication in BMC Geriatrics.

*Chapter 5* expands on the DBI by adding two data additional measures of anticholinergic and sedative burden – the Anticholinergic Cognitive Burden and Sedative Load Model, two non-dose dependent measures of medication exposure. A measure of frailty for the cohort of older adults with ID is constructed based on a modification of Fried’s frailty phenotype. This frailty measure incorporates data from the physical performance measures (grip strength (weakness) and timed up and go (slowness)) described in *Chapter 4* in addition to data on weight loss, physical activity and exhaustion. The findings of this chapter are discussed in the context of the pharmacokinetic changes which occur in normal ageing, frailty and in ID itself.

*Chapter 6* provides a more in-depth discussion of the findings of the thesis under each aim and the implications on practice.



## Chapter 2

### Methods and Tools

## 2.1 Study Design

The data for this research was drawn from the Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing (IDS-TILDA). This is a large scale, nationally representative longitudinal study which examines the ageing of people with ID (52, 205). At the initial recruitment, participants were aged 40 years or older to account for the reduced life expectancy and presentation of older age conditions at a younger age in people with ID (10). This study was the first of its kind in Europe and was designed to directly compare the ageing of people with ID with the general population (206). The IDS-TILDA study is underpinned by seven key values and a comprehensive conceptual framework. The key values are inclusion, choice, empowerment, person-centredness, promotion of people with ID, promotion of best practice and to contribute to the lives of people with ID (206). The conceptual framework (*Figure 2.1*) outlines the areas of research interest and sub-sections contributing to each.

Two groups provided critical input to the study design – people with ID and the International Scientific Advisory Committee. People with ID were involved at each stage of the study design, especially with regard to development of accessible materials and dissemination of findings through easy-read materials and short films depicting the study findings (206).

The International Scientific Advisory Committee advised on development of protocols, inclusion of ID-specific material and comparability with international studies (206).

IDS-TILDA has now completed three waves of data collection: Wave 1 (2009/2010), Wave 2 (2013/2014) and Wave 3 (2016/2017).

This thesis is based on the data obtained from Wave 2 of IDS-TILDA.

### 2.1.1 Connection with the Irish Longitudinal Study on Ageing

IDS-TILDA is a study which runs in parallel to the Irish Longitudinal Study on Ageing (TILDA). TILDA is an observational study of community-dwelling older adults (aged 50 years and older) in Ireland (207). TILDA began in 2009, and over 8,500 individuals participated (207). The study design of TILDA involved geographical sampling facilitated by RANSAM, a computer-based system which was developed by the Economic and Social Research Institute (ESRI) based on the Irish Geodirectory (207). This produced a list of addresses which provided a nationally representative sample of adults over 50 in Ireland (207). The ageing of people with ID is not represented in TILDA data, which led to the inception of IDS-TILDA. Due to the greater

distribution of individuals with ID in residential centres, the Geodirectory approach was not suitable for IDS-TILDA sampling (208). IDS-TILDA questionnaires are modelled on those of TILDA in order to allow some comparability between the two studies (208). This is the justification behind the questions and measures selected for use in IDS-TILDA, in particular the measures selected for the health assessment (*Section 2.1.4*). Some questions were modified in order to make them accessible for people with ID, and the consent process (described in more detail in *Section 2.1.3*) was also modified to make it easy-read and accessible.

### **2.1.2 Ethical Approval and Compliance with Data Protection**

Approval for the study was granted by Faculty of Health Sciences Research Ethics Committee in Trinity College Dublin (*Appendix 1*). In addition, local and/or regional ethical committee approval was granted from each service provider (n = 138) (206). IDS-TILDA complies with the requirements of the General Data Protection Regulation (GDPR). The author completed the online GDPR learning module provided by Trinity College Dublin Blackboard Learning prior to the implementation of GDPR on 25<sup>th</sup> May 2018.

The author was not involved in the ethical approval or recruitment processes for the study. Data was pseudonymised by assigning each study participant a Personal Identification Number (PIN). The author was not involved in this pseudonymisation process and did not have access to the identification keys for the study.

The General Data Protection Regulations (GDPR) 2018 and Health Research Regulations (HRR), 2018 came into effect after this present research commenced in March 2016. Much of GDPR reiterated good data protection principles which were already being followed by IDS-TILDA. For example, data from the IDS-TILDA study has always been kept secure; it cannot be removed from the study's main office and any identifiable personal data is only accessible to the Principal Investigator, the Project Manager and the Senior Executive Officer.

Following the implementation of GDPR, the Department of Health produced the HRR. These regulations insisted that consent by the data subject to process data must be a prerequisite to health research taking place, unless a Consent Declaration was sought in cases where that was not possible.

Consent in the field of ID research had already been a live issue, particularly due to the Assisted Decision Making (Capacity) Act, 2015 and its presumption of capacity to consent. The capacity to participate, and to consent to that participation, had been part of the study design of IDS-

TILDA from its inception. For example, the consent form and information booklets used in the study were developed to be easy-read and accessible to people with ID in order to maximise the potential for people to make an informed decision about participation. In addition, each field researcher has been trained on how best to seek consent, in line with the values of the study. The consent form is also accompanied by a method of “process consent” throughout the interview, whereby consent has been reaffirmed regularly throughout the interview, at least at the beginning of each section.

From the beginning, however, in some cases, for a person with ID, they may not have the capacity to provide informed consent. In this case, proxy respondents have been invited to participate on the person’s behalf. Under the HRR, however, this is no longer permissible. The implications of this were that any data collected in the past using a proxy respondent could no longer be processed or held without a Consent Declaration.

IDS-TILDA made an application to the Health Research Consent Declaration Committee (HRCDC) on July 3rd, 2019 for a Consent Declaration in order to continue to process data from the previous waves of IDS-TILDA which had been gathered through proxy respondents and to proceed with data gathering for Wave 4 of the study. This application was made in advance of a July 7<sup>th</sup>, 2019 deadline for any studies that wished to retain previously gathered data where consent was not obtained and re-consenting of data subjects was not possible. On August 15th, the HRCDC Secretariat clarified that ‘because IDS-TILDA is an ongoing study and commenced prior to the Regulations, your team can continue with the study. Whilst the application is ‘pending’ HRCDC review, you will not be considered in breach of the Regulations because you met the deadline to submit an application prior to July 7<sup>th</sup>’.

The Consent Declaration application was considered on October 17<sup>th</sup> by the HRCDC. As of 11<sup>th</sup> November 2019, the HRCDC decision involved a “Conditional Declaration”. *Appendix 2* includes correspondence from the HRCDC with regard to this conditional declaration for IDS-TILDA.

The HRCDC has, however, acknowledged the risk that the HRR may be inadvertently excluding research participants like those involved in IDS-TILDA. The HRCDC has advised the Department of Health to consider an amendment to that effect. The following is an excerpt relating to a proposed amendment from a note issued by the HRCDC to the Department of Health in April 2019:

*“An amendment aimed at finding a workable basis for the processing of personal data for health research where an adult lacks capacity to consent. The Department is of the view that the requirement for explicit consent in the case of someone who lacks capacity to consent*

*means that the very people who might benefit from particular research studies will not be able to allow their personal data to be used for such research and that is not consistent with public policy and the values underpinning a patient centred health system. An amendment has therefore been prepared reflecting the core principles set out in the Assisted Decision-Making (Capacity) Act 2015 and the HSE National Consent Policy (209)."*

### **2.1.3 Study Population and Recruitment Process**

The study population is drawn from the National Intellectual Disability Database (NIDD), a service planning tool which was established in 1995 to capture data on the usage of and the need for specialist disability services among people with ID (30). The database collates information on the specialised health services used or required by people with ID and it informs planning for ID services (31). At the time of the initial wave of IDS-TILDA, there were 26,066 individuals registered with NIDD (30, 206). This includes people with all levels of ID and in the full range of residential circumstances. There were 10,725 people (41.1%) aged 35 years and over, and almost one-third (29%, n = 3,154) of these were aged 55 years and over (30). Each person with an ID is assigned a PIN when registered with the NIDD. Permission to use the NIDD as a sampling frame was granted after review by the NIDD Committee (206). A total of 1,800 PINs of people with ID aged 40 years and over were randomly selected by staff at NIDD. NIDD released the PIN numbers of potential participants to the regional disability database administrator (RDDA), and in order to preserve confidentiality prior to gathering consent, the RDDA addressed and posted the invitation pack to the person associated with each PIN (206). The invitation pack also contained a consent form. Whereby an individual was unable to provide consent independently, a family member/guardian could sign a letter of agreement for their family member to participate. A total of 753 individuals participated in Wave 1 of the study (2009/2010). Of these, 708 completed Wave 2 (2013/2014). This thesis examined data from Wave 2.

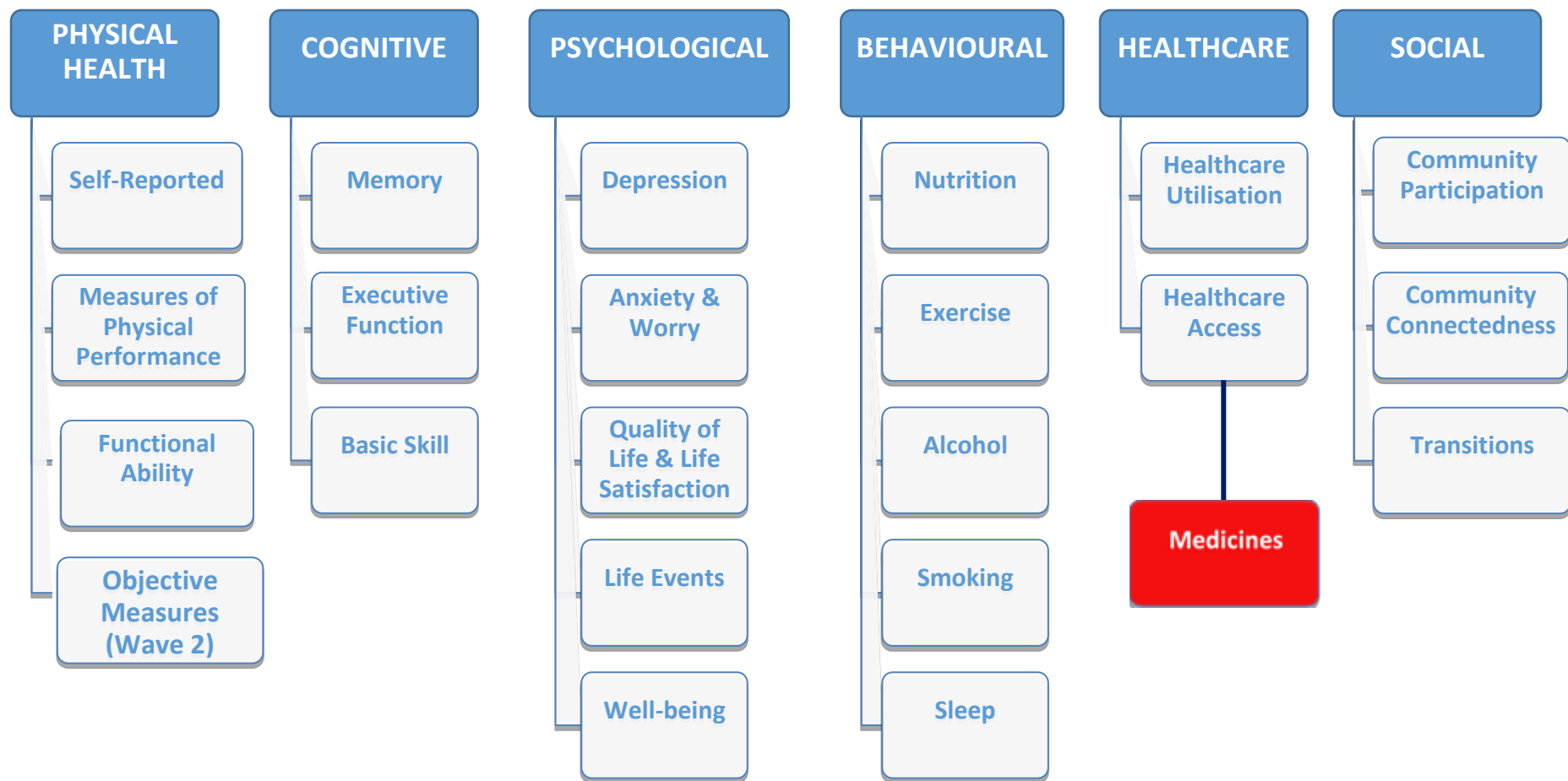


Figure 2.1 Conceptual Framework of IDS-TILDA

#### 2.1.4 Field Researchers and Data Collection

Field researchers for each wave of data collection were all individuals with experience working with people with ID. They were provided with comprehensive training in managing their caseload, scheduling interviews, data collection, data protection and adaptive communication skills. Training on collection of medication data was provided by a pharmacist.

Data collection involved three parts:

1. One week prior to scheduled interview, each participant was provided with a Pre-Interview Questionnaire (PIQ), which was to be filled out prior to face-to-face interview with a field researcher. This was carried out as some data required accessing medical records. The PIQ contained the section for medication data collection. *Appendix 3* shows the medication data collection template from Wave 2.  
The PIQ also contained sections on eye health, heart health, other health conditions, chronic lung disease, arthritis, cancer, Parkinson's disease, mental health, epilepsy, constipation, medical tests and screening, female health conditions, male health conditions, healthcare utilisation and medication.
2. The face-to-face interview with a field researcher involved a Computer Assisted Personal Interview (CAPI). The CAPI contained sections on demographics, including living circumstances and religion; cognitive health, including memory and cognitive domains; social participation, including general activities, social activities and transport; social connectedness; personal choices; ageing perceptions; occupation, including employment, sheltered work, day services, unemployment and retirement; sources of income; voluntary work; life-long learning, including reading, writing, numeracy, money and technology; physical health, including overall health, eyesight, hearing, general communication, oral health, nutritional health, foot health, falls, fear of falling, steadiness and fractures, falls efficacy, pain, bladder incontinence, bowel incontinence; mental health; behavioural health, including smoking, alcohol, diet, physical activity and sleep; (Instrumental) Activities of Daily Living ((I)ADLs) and helpers, including functional limitations, dressing, walking, getting about the home, bathing and showering, oral hygiene, eating, getting in and out of bed, using the toilet, support with activities of daily living, preparing a hot meal, shopping for groceries, making telephone calls, managing money, doing household chores and support with IADLs.

3. A Health Assessment was carried out at Wave 2 by a registered nurse in intellectual disability (RNID), who captured data on body mass index (BMI), waist circumference, mid upper arm circumference, blood pressure, grip strength, timed up and go and bone density using Quantitative Heel Ultrasound (QUS).

Copies of the complete PIQ and CAPI are available online at: <https://idstilda.tcd.ie/about/resultsw2.php>.

Interview styles could be self-report, proxy-only or a combination of both. A proxy was a person (family member, carer or keyworker) known to the person with ID for a period of at least six months.

The author was not involved in data collection for Wave 2 of the study as data collection for this wave had been completed prior to the commencement of the thesis. The author played an active role in data cleaning for Wave 2 medication data. This involved checking Anatomical Therapeutic Classification (ATC) codes, checking doses for relevant medications, re-examining hardcopies of PIQs to resolve queries regarding medication name, ATC codes and dose and identifying errors (duplicates) in medication data recorded.

The author was actively involved in data collection at Wave 3 (2016/2017) of the study. The author was a field researcher for this wave of data collection and was assigned a caseload of participants to interview. The author was also responsible for the input of medication data and assigning ATC codes to each entry along with a second pharmacist for Wave 3 data. These entries and codes were double-checked by a third pharmacist.

### **2.1.5 Access to Data**

Due to the unique and vulnerable nature of the participants of the study, there is a high risk that combining variables may allow identification of individuals. For this reason, no researcher has access to the complete dataset of variables. As a result, no public dataset of IDS-TILDA data is available. Access to data was granted by the Data Controller. In order to access variables, a request was made to the Data Controller with an explanation of the purposes of data use intended. This request was assessed. Access to the individual variables which were required for each study was provided. *Table 2.1* outlines the variables accessed for use in the three studies of this thesis. Access to data was only possible by accessing specific IDS-TILDA “hot desks”, and datasets could not be removed from these access points or transferred to personal computers.



Table 2.1 Variables accessed for the three studies performed in this thesis

|                | Carried from Wave 1 Data               | Pre-Interview Questionnaire                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Computer Assisted Personal Interview                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Health Assessment                                                                                                                                                                                                                                                                                                                                             |
|----------------|----------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Study 1</b> | <b>Demographic Data</b><br>Level of ID | <p><b>Demographic Data</b><br/>Gender<br/>Age range<br/>Age (continuous)</p> <p><b>Medication Data</b><br/>Medication Name<br/>ATC Code<br/>Strength<br/>Frequency<br/>Route of Administration<br/>Date Prescribed</p> <p><b>Adverse effects</b><br/>Have you ever had a doctor's diagnosis of chronic constipation?</p> <p><b>Modified Functional Comorbidity Index</b><br/>Have you ever had a doctor's diagnosis of...?</p> <ul style="list-style-type: none"> <li>• arthritis (including osteoarthritis or rheumatism)</li> <li>• osteoporosis/thin or brittle bones</li> <li>• scoliosis (all participants with scoliosis had evidence of osteoporosis/osteopenia)</li> <li>• asthma</li> <li>• chronic lung disease</li> <li>• angina</li> <li>• congestive heart failure</li> </ul> | <p><b>Demographic Data</b><br/>Type of residence</p> <p><b>Adverse effects</b><br/>How likely are you to doze off and fall asleep during the day?<br/>In the past year have you had any fall including a slip or trip in which you lost your balance and landed on the floor or ground or lower level?</p> <p><b>Modified Barthel Index</b><br/>Please indicate the level of difficulty, if any, you have with walking 100 yards<br/>Please indicate the level of difficulty, if any, you have with climbing one flight of stairs without resting.<br/>Please indicate the level of difficulty, if any, you have with dressing, including putting on shoes and socks.<br/>Please indicate the level of difficulty, if any, you have with bathing or showering.<br/>Please indicate the level of difficulty, if any, you have with cleaning your teeth/taking care of your dentures.<br/>Please indicate the level of difficulty, if any, you have with eating such as cutting up your food, use of utensils, drinking from a cup/glass etc?<br/>Please indicate the level of difficulty, if any, you have with getting in or out of bed.</p> | <p><b>Objective Measures</b><br/>Quantitative Heel Ultrasound (QUS) evidence for Osteoporosis and Osteopenia<br/>Body Mass Index (calculated from height and weight; ulnar length was used to estimate height where height could not be measured; Mid Upper Arm Circumference was used where weight or height could not be measured e.g. wheelchair user)</p> |

|  | Carried from Wave 1 Data | Pre-Interview Questionnaire                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Computer Assisted Personal Interview                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Health Assessment |
|--|--------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|
|  |                          | <ul style="list-style-type: none"> <li>• a heart murmur</li> <li>• an abnormal heart rhythm</li> <li>• other heart trouble</li> <li>• heart attack</li> <li>• Parkinson's disease</li> <li>• multiple sclerosis</li> <li>• Alzheimer's disease</li> <li>• spina bifida</li> <li>• dementia, organic brain syndrome or senility</li> <li>• epilepsy</li> <li>• cerebral palsy</li> <li>• muscular dystrophy</li> <li>• stroke</li> <li>• ministroke/transient ischaemic attack</li> <li>• diabetes</li> <li>• gastroesophageal reflux disease</li> <li>• stomach ulcers</li> <li>• depression</li> <li>• manic depression</li> <li>• anxiety condition</li> <li>• age related macular degeneration</li> <li>• glaucoma</li> <li>• cataracts</li> <li>• other eye disease</li> </ul> <p>Have you had cataract surgery?</p> <p>Have you ever had an angioplasty or stent?</p> <p>Have you ever had open heart surgery?</p> | <p>Please indicate the level of difficulty, if any, you have with using the toilet, including getting up or down.</p> <p>During the last 12 months, have you lost any amount of urine beyond your control?</p> <p>Did this happen more than once during a 1-month period?</p> <p>During the last 12 months, have you lost any amount of faeces beyond your control?</p> <p>Did this happen more than once during a 1-month period?</p> <p><b>Modified Functional Comorbidity Index</b></p> <p>What type of diet are you following?</p> <p>Diabetic diet</p> <p>Weight reducing diet</p> <p>Have you been prescribed glasses or contact lenses?</p> <p>Is your hearing (with or without a hearing aid) ... fair/poor?</p> <p>Do you use any of the following aids or appliances to help you with your hearing?</p> <p>Hearing aid (all of the time)</p> <p>Hearing aid (some of the time)</p> <p>Phone messaging service</p> <p>Amplifier</p> |                   |

|                | Carried from Wave 1 Data               | Pre-Interview Questionnaire                                                                                                                                                                    | Computer Assisted Personal Interview                                                                                                                                                                                                                                                                                                                                     | Health Assessment                                                                                                                    |
|----------------|----------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|
| <b>Study 2</b> | <b>Demographic Data</b> as for Study 1 | <b>Demographic Data</b> as for Study 1<br><b>Medication Data</b> as for Study 1<br><b>Modified Barthel Index</b> as for Study 1<br><b>Modified Functional Comorbidity Index</b> as for Study 1 | <b>Modified Barthel Index</b> as for Study 1<br><b>Modified Functional Comorbidity Index</b> as for Study 1<br><br>International Physical Activity Questionnaire (IPAQ) Category                                                                                                                                                                                         | <b>Objective Measures</b><br>Grip Strength (continuous)<br>Grip strength (categorical)<br>Timed up and go (continuous)               |
| <b>Study 3</b> | <b>Demographic Data</b> as for Study 1 | <b>Demographic Data</b> as for Study 1<br><b>Medication Data</b> as for Study 1<br><b>Modified Barthel Index</b> as for Study 1<br><b>Modified Functional Comorbidity Index</b> as for Study 1 | <b>Modified Fried's Frailty Phenotype</b><br>Within the last year, have you lost or gained ten pounds (4.5 kg) or more in weight when you weren't trying to?<br>International Physical Activity Questionnaire (IPAQ) Category<br>How much of the time during the past 4 weeks did you feel worn out?<br>How much of the time during the past 4 weeks did you feel tired? | <b>Objective Measures</b><br>Grip Strength (continuous)<br>Timed up and go (continuous)<br>Body Mass Index and height as for Study 1 |

## 2.2 Drug Burden Index

### 2.2.1 Medication Inventory for Drug Burden Index

Development of a Drug Burden Index inventory was required initially before study of this measure in the IDS-TILDA cohort could be carried out. The only published inventory was developed in the United States, and the inventory was drawn from reported medications in the Health, Ageing and Body Composition study (146, 150). As a result of formulary differences and the differing morbidity profiles of older adults with ID, this inventory alone was insufficient for use in this population. Another study, carried out in Finland, listed the most frequently used DBI medications among a population of older adults in the general population (i.e. medications used by >0.5% of the population) (164). However, similarly this inventory was neither exhaustive nor completely applicable to use in an Irish population. While a number of other DBI studies have been published, none have included the inventory used. *Table 2.2* provides a summary of 25 DBI studies carried out internationally and the availability of the medication inventory used. Fourteen studies did not provide any list of medications or therapeutic classes analysed; 6 studies provided a list of certain medications included from analysis, typically the most frequently reported; 4 studies reported therapeutic classes included in the inventory; and only one study provided the complete inventory of medications included.

Table 2.2 Review of Availability of Medication Inventories

| Study                               | Inventory Specified                                         |
|-------------------------------------|-------------------------------------------------------------|
| Best et al, 2013 <b>(210)</b>       | Partial (therapeutic classes listed)                        |
| Bosboom et al, 2012 <b>(211)</b>    | No                                                          |
| Castelino et al, 2010 <b>(212)</b>  | Partial (10 medications listed)                             |
| Dauphinot et al, 2014 <b>(213)</b>  | No                                                          |
| Dauphinot et al, 2016 <b>(214)</b>  | Partial (20 medications listed)                             |
| Floroff et al, 2014 <b>(215)</b>    | No                                                          |
| Gnjidic et al, 2009 <b>(151)</b>    | Partial (therapeutic classes listed)                        |
| Gnjidic et al, 2010 <b>(216)</b>    | Partial (therapeutic classes listed)                        |
| Gnjidic et al, 2012 <b>(164)</b>    | Partial (23 medications listed)                             |
| Gnjidic et al, 2012 <b>(166)</b>    | Partial (therapeutic classes listed)                        |
| Gnjidic et al, 2012 <b>(217)</b>    | No                                                          |
| Gnjidic et al, 2014 <b>(218)</b>    | Partial (21 medications listed)                             |
| Hilmer et al., 2007 <b>(146)</b>    | No                                                          |
| Hilmer et al., 2009 <b>(219)</b>    | Yes                                                         |
| Jamsen et al, 2016 <b>(196)</b>     | No                                                          |
| Lonnroos et al, 2012 <b>(220)</b>   | No                                                          |
| Lowry et al, 2012 <b>(169)</b>      | No                                                          |
| Narayan et al, 2013 <b>(221)</b>    | Partial (10 most common anticholinergic medications listed) |
| Nishtala et al, 2009 <b>(222)</b>   | Partial (18 medications listed)                             |
| Nishtala et al, 2014 <b>(223)</b>   | No                                                          |
| Pont et al, 2015 <b>(224)</b>       | No                                                          |
| Salahudeen et al, 2015 <b>(225)</b> | No                                                          |
| Wilson et al, 2012 <b>(226)</b>     | No                                                          |
| Wilson et al., 2011 <b>(154)</b>    | No                                                          |
| Wilson et al, 2010 <b>(178)</b>     | No                                                          |

As a result, attention was drawn to a number of sources of data for the development of the Irish inventory. The two published DBI drugs lists were included (146, 150, 164), in addition to the Anticholinergic Cognitive Burden inventory, previously examined in IDS-TILDA (103). As regards sedative medications, the Sedative Load Model was selected for identification of medications with sedative effects (143). One Irish published study in the Irish Longitudinal Study on Ageing

(TILDA) cohort included an inventory of sedative medications (161). The numbers of medications identified from each source are detailed in *Table 2.3*.

Table 2.3 Sources of DBI Inventory

| Source                                       | Number of Medications Identified |
|----------------------------------------------|----------------------------------|
| Hilmer et al, 2007/2009 <b>(146, 150)</b>    | n = 129                          |
| Gnjidic et al, 2012 <b>(164)</b>             | n = 23                           |
| O'Dwyer et al, 2015 <b>(103)</b>             | n = 114                          |
| Peklar et al, 2015 <b>(161)</b>              | n = 26                           |
| Linjakumpu et al, 2003 <b>(143)</b>          | n = 115                          |
| Literature Search of HPRA SmPCs <b>(227)</b> | n = 132                          |

After removing duplicates, n = 383 medications remained on the inventory for consideration.

A method of consensus between three pharmacists (JO'C, MO'D and MH) was used to select medications for inclusion in the final inventory. This consensus process involved literature review and development of a list of potential medications for inclusion by one pharmacist (JO'C), the list of medications was then reviewed individually by two pharmacists (MO'D and MH). All three pharmacists provided their assessment of whether each drug should be included or excluded. Disagreements were resolved by holding a consensus meeting where the rationale behind inclusion/exclusion of medications was discussed. All ACB medications were included, in addition to three others (Ziprasidone, Lofepramine and Dosulepin) identified to have anticholinergic properties but which were not included in the ACB inventory. As a result, n = 117 anticholinergic medications were selected.

Consensus in the same manner was also used for inclusion of medication with sedative properties. Sedative medications were considered on the basis of inclusion in the DBI inventories, inclusion in the Sedative Load Model (143), inclusion in the existing Irish study of Sedative Load (161) and reported adverse effects from the Summaries of Product Characteristics (SmPCs) of the Health Product Regulatory Authority (HPRA) (227). The Sedative Load Model (143) included therapeutic drug classes in addition to listing some individual medications. As a result, a comprehensive review of the licensed medications listed by the HPRA was carried out by using all identified 7 level Anatomical Therapeutic Classification (ATC) system codes (228) as search terms to identify additional medications licensed in Ireland which may possess sedative effects. The list of search terms used to identify sedative potential during review of the SmPC was modelled on those used in the sedative load model: sedating, sedative, drowsiness,

sleepiness, lassitude, exhaustion, tiresome, fatigability. This identified n = 132 medications for inclusion in the 383 list.

In order to further refine the list in order to ensure its appropriateness for use in an Irish setting, whereby a medication was unlicensed in both Ireland and the UK and no study participants reported the medication, it was excluded.

This provided a list of 117 anticholinergic medications and 141 sedative medications, n = 258 DBI medications in total (*Appendix 4 and Appendix 5*).

### **2.2.2 Choice of Minimum Effective Daily Doses**

The DBI measures degree of burden based on the dose of medication an individual is exposed to, with reference to a Minimum Effective Daily Dose, or MDD. This MDD represents the DR<sub>50</sub> or dose required to achieve 50% of maximal contributory effect at steady state (146).

Consideration was given to three sources for the derivation of the MDDs for use in the DBI in the IDS-TILDA cohort: (1) the HPRA SmPCs were inspected and MDDs were selected from product literature; (2) the British National Formulary (BNF) monographs were inspected and MDDs were selected from medication data; and (3) the WHO Defined Daily Doses (DDD) were examined for each medication. Data was also gathered for specific prescribing recommendations for older adults, or “elderly” as still used in current product literature. *Table 2.4* displays an example of five medications for which the data was gathered and considered. These three sources of dose data were examined for all 258 medications included in the DBI inventory.

HPRA-specified MDDs, with consideration for prescribing requirements for older adults, were selected for all medications licensed in Ireland, in order to meet the objective of creating a DBI tool for use in an Irish population. Whereby a medication was unlicensed in Ireland, the BNF MDD was selected.

The WHO DDD was carefully considered but was not selected as the source of MDDs. The DDD is defined as:

*“the assumed average maintenance dose per day for a drug used for its main indication in adults”* (229).

For a number of reasons, this is not the most appropriate approximation of the MDD for the DBI in a population of older adults with ID in Ireland:

1. The DDD will often differ on the basis of individual population characteristics, such as age.
2. Only one DDD is assigned per ATC code and route of administration. However, this represents a compromise based on evaluation of dose information in a variety of different countries. As a result, the specificity of the DDD for use in an Irish population is limited.
3. The DDD is typically larger than the MDDs identified from the HPRA and BNF. Utilising a larger dose in the DBI calculation may lead to an underestimation of the true effect of the medication dose reported by each individual.



Table 2.4 Sample of MDD Selection

| INN           | HPRA MDD                                                                                                                                                                                                                                                                | BNF MDD                                                                                                                                                                                                  | WHO DDD | Notes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|---------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Cimetidine    | 400mg                                                                                                                                                                                                                                                                   | 400mg                                                                                                                                                                                                    | 800mg   | Elderly: The normal adult dosage may be used unless renal function is markedly impaired.<br>(For adults: Dose range is 400mg – 2,600mg/day)                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Captopril     | <ul style="list-style-type: none"> <li>Hypertension: 100mg</li> <li>Hypertension in Active Renin-Angiotensin-Aldosterone System (RAAS): 50mg</li> <li>Heart Failure: 75mg</li> <li>Diabetic Nephropathy: 75mg</li> <li>Post-Myocardial Infarction (MI): 75mg</li> </ul> | <ul style="list-style-type: none"> <li>Hypertension: 100mg</li> <li>Hypertension in Active RAAS: 50mg</li> <li>Heart Failure: 75mg</li> <li>Diabetic Nephropathy: 75mg</li> <li>Post-MI: 75mg</li> </ul> | 50mg    | Elderly: As with other antihypertensive agents, consideration should be given to initiating therapy with a lower starting dose (6.25mg twice daily) in elderly patients who may have reduced renal function and other organ dysfunctions. Dosage should be titrated against the blood pressure response and kept as low as possible to achieve adequate control.<br>(For adults: Hypertension: 100 – 150mg/day; Active Renin Angiotensin Aldosterone System: 50 – 100mg/day; Heart Failure: 75 – 150mg/day; Type I Diabetic Nephropathy: 75 – 100mg/day; Post-Myocardial Infarction: 75 – 150mg/day) |
| Valproic Acid | <ul style="list-style-type: none"> <li>Manic episodes in bipolar disorder: 1000mg</li> <li>Epilepsy: 1000mg</li> </ul>                                                                                                                                                  | 750mg                                                                                                                                                                                                    | 1500mg  | Elderly: Dosage should be determined by seizure control. Decreased albumin binding so proportion of free drug is increased.<br>(For adults: Dosage range usually 1000 – 2000mg/ day. In epilepsy if control is not achieved dose may be increased to 2500mg/day)                                                                                                                                                                                                                                                                                                                                     |

| INN              | HPRA MDD                                                                                           | BNF MDD                                                                                            | WHO DDD                                   | Notes                                                           |
|------------------|----------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------|-------------------------------------------|-----------------------------------------------------------------|
| Prochlorperazine | Meniere's syndrome, nausea and vomiting: 10mg<br>Schizophrenia and other psychotic disorders: 75mg | Meniere's syndrome, nausea and vomiting: 10mg<br>Schizophrenia and other psychotic disorders: 75mg | 100mg (oral; rectal)<br>50mg (parenteral) | Elderly: Caution is advised, lower initial dose is recommended. |
| Alprazolam       | 0.5mg                                                                                              | 0.5mg                                                                                              | 1mg                                       | Elderly: 0.5-0.75 mg/day                                        |

## **2.3 Anticholinergic Cognitive Burden**

### **2.3.1 Medication Inventory for Anticholinergic Cognitive Burden**

The Anticholinergic Cognitive Burden (ACB) Scale was selected as an additional measure of anticholinergic burden in the IDS-TILDA population. This was due to its previous evaluation in the same cohort at Wave 1 of the study (103). This study provided the reference medication inventory and associated scores, which itself was derived from the updated 2012 Anticholinergic Cognitive Burden Scale (140), and modified to include drugs possessing anticholinergic properties used by participants of the IDS-TILDA study which were not previously included in the updated ACB Scale (103). For one medication reported in the IDS-TILDA cohort, benztropine, no Irish or UK SmPC was available, so the New Zealand Datasheet was utilised for information on anticholinergic activity (230).

In order to identify other anticholinergic medications which may not have been included in the IDS-TILDA version of the ACB scale, a recent systematic review of anticholinergic risk scales in older adults was examined (141). This review examined the medications included in seven anticholinergic risk scales but did not include the ACB scale. The scales included were the Anticholinergic Drug Scale, Anticholinergic Burden Classification, Chew et al, 2008, Clinical-rated Anticholinergic Score, Anticholinergic Risk Scale, Anticholinergic Activity Scale and Anticholinergic Loading Scale (133-139). Thirty-seven additional medications were included in this review. Of these medications, one (fexofenadine) was automatically excluded because the 2012 update of the ACB scale explicitly stated it was reviewed for inclusion but not added (140). Of the remaining 36 medicines, 12 were reported in the IDS-TILDA cohort. The Summaries of Product Characteristics for these medications were examined for statements with regard to anticholinergic activity (227). Three additional medications were found to possess anticholinergic properties from this review – dosulepin, morphine and oxycodone.

Following consultation with a specialist pharmacist in geriatric medicine, it was concluded that these three medications would be added to the current ACB inventory.

### **2.3.2 Choice of Anticholinergic Cognitive Burden Scores**

Medications were defined as having absent (ACB Score 0), possible (ACB score 1) or definite anticholinergic properties (ACB score 2 or 3) (140). The scores for the three additional medications identified for inclusion in the ACB inventory – dosulepin, morphine and oxycodone – were assigned as 2, 1 and 1 respectively.

These scores were derived from examining ACB scores for other drugs in the same class, examination of anticholinergic scores in other scales and, in the case of dosulepin, consultation of the Maudsley Prescribing Guidelines (231).

ACB score was calculated as the sum of the anticholinergic ratings at an individual level, for regularly used drugs. ACB scores of 0, 1 – 4, and 5+ indicated no, low, and high ACB respectively, as used previously (103).

## **2.4 Sedative Load Model**

### **2.4.1 Medication Inventory for Sedative Load Model**

The Sedative Load Model was selected as an additional measure of sedative burden in the IDS-TILDA population. This was due to its previous evaluation in TILDA with respect to frailty (161). The original Sedative Load Model drugs list was published in 2003 and was revised in 2011 (143, 144). Drugs are categorised as primary sedatives (group 1); drugs with sedation as a prominent side effect or preparations with a sedating component (group 2); drugs with sedation as a potential adverse effect (group 3); and drugs with no known sedation (group 4).

The medication inventory was adapted from the above mentioned study of Sedative Load of community-dwelling older adults in Ireland (161), which itself was derived from the original (2003) and updated (2011) Sedative Load Model (143, 144). The inventory was further modified to include other sedative medications in the IDS-TILDA population due to distinctly different patterns of medication and sedative use in older adults with ID. Detailed examination of the SmPCs of medications for the Republic of Ireland was carried out as for the DBI and ACB (227). Whereby a medication is not licensed in Ireland, the summary of product characteristics for the UK was examined (232). The same sedative search terms as used to identify sedative activity for the DBI were used for the Sedative Load Model inventory: “fatigue, asthenia, somnolence, sedation, lassitude, lethargy, tiredness and drowsiness”. In addition, the Maudsley Prescribing Guidelines were consulted for the relative adverse effects of antipsychotic and antidepressant medications (231).

### **2.4.2 Choice of Sedative Load Model Scores**

Drugs included in groups 1, 2, and 3 – 4 were assigned sedative ratings of 2, 1, and 0, respectively. Sedative Load was calculated as the sum of the sedative ratings at an individual

level, for regularly used drugs. Sedative Load scores of 0, 1 – 2, and 3 indicated no, low, and high Sedative Load respectively (161).

## **2.5 Measures of Adverse Effects, Physical Function and Frailty**

### **2.5.1 Potential Adverse Effects**

The potential adverse effects to be examined in relation to DBI score were selected on the basis of previous research (103) and the known adverse effects of anticholinergic medications (constipation, drowsiness) and sedative medications (sedation, ataxia, postural hypotension) (118, 119, 122). The association of ACB with chronic constipation, daytime dozing and falls has previously been examined in the same cohort older adults with ID at Wave 1 of the IDS-TILDA study (103). Sedative medications have been found to be associated with falls and daytime dozing in older adults without ID (122). DBI score has also been found to be associated with falls in older adults without ID (154). As a result, three potential adverse effects were selected to be examined with regard to DBI exposure – daytime dozing, chronic constipation and reporting a fall in the previous 12 months.

### **2.5.2 Barthel Index Activities of Daily Living**

Barthel Index ADLs are a measure of the level of dependence of an individual (170, 233). In IDS-TILDA, a modified version of the Barthel Index was developed. This is described in more detail in *Chapter 3*. Poorer performance in Barthel Index ADLs has been frequently reported to be associated with anticholinergic and sedative exposure in studies of anticholinergic burden and DBI (164, 169, 179). As a result, Barthel Index ADLs are an important outcome measure in the studies described in *Chapters 3, 4 and 5*.

### **2.5.3 Functional Comorbidity Index**

The Functional Comorbidity Index (FCI) (174) was selected as a measure of comorbidities in this population. *Table 2.5* details the conditions which were included in the original FCI. The FCI was developed in older adults without ID, and no modified version for use in a population of older adults with ID had previously been constructed.

The FCI was selected as the measure of comorbidities for three reasons – firstly, the FCI has been developed and validated as a means of calculating the number of comorbidities known to have an effect on physical function (174); secondly, the IDS-TILDA PIQ and CAPI provided detailed data on conditions experienced by the participants, which allowed for creation of a modified version of the FCI for use in the three studies performed in this thesis; thirdly, a number of previously published studies on DBI and functional outcomes also used modified versions of the FCI in their analyses (151, 154, 164, 166, 220). The modified version of the FCI is included in *Supporting Information Table S 3.2 in Chapter 3*. Two conditions included in the original version of the FCI were excluded from the modified version used for IDS-TILDA due to insufficient data - peripheral vascular disease and degenerative disc disease.

Modification of the FCI for use in the IDS-TILDA population was necessary for two reasons: firstly, available data from the self-report questionnaires was slightly different to that required for full construction of the FCI; and secondly, the population group of older adults with ID differs substantially in terms of morbidity patterns from the one in which the FCI was developed. Tailoring measures such as the FCI according to the population being studied is important

Much research around determinants of health among vulnerable older adults is drawn from self-report measures. Three options are typically available when considering use of measures which were developed and validated in a different population: (1) use the original measure, but take into account a caveat that scientific inferences from the results may be compromised; (2) create a new measure and consider the feasibility studies and validation required before scientific inferences may be made; or (3), modify or adapt an existing measure (234).

Comprehensive literature review was carried out investigating the other modified versions of FCI which had been used in studies of anticholinergic and sedative medication exposure among older adults without ID. The results of this review are displayed in *Table 2.5*. Of the five modifications identified, the two areas in which data from IDS-TILDA was missing (peripheral vascular disease and degenerative disc disease) were not included in three of the five modifications. This supported the decision to exclude these two items from the modified FCI in IDS-TILDA. In addition, IDS-TILDA provided data in two other areas which were frequently excluded from previous modified versions of the FCI – depression (excluded by three of the five modified versions) and anxiety or panic disorder (excluded by four of the five modified versions). It is important that these were included in the modified version of the FCI due to the high prevalence of mental health disorders among people with ID.

Table 2.5 Comparison of Modified Version of Functional Comorbidity Index

| <b>Original Functional Comorbidity Index Items (174)</b>                                                         | <b>Gnjidic et al, 2012 (164)</b>                                      | <b>Gnjidic et al, 2012 (166)</b>                                                | <b>Jansen et al, 2016 (196)</b>                    | <b>Lonnroos et al, 2012 (220)</b>                                      | <b>Wilson et al, 2011 (154)</b> |
|------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------|---------------------------------------------------------------------------------|----------------------------------------------------|------------------------------------------------------------------------|---------------------------------|
| <b>Arthritis (rheumatoid and osteoarthritis)</b>                                                                 | Arthritis (rheumatoid arthritis and other connective tissue diseases) | Arthritis (osteo and rheumatoid)                                                | Arthritis                                          | Rheumatoid arthritis and other inflammatory connective tissue diseases | Arthritis                       |
| <b>Osteoporosis</b>                                                                                              | Osteoporosis                                                          | Osteoporosis                                                                    | Osteoporosis                                       | Osteoporosis                                                           | Osteoporosis                    |
| <b>Asthma</b>                                                                                                    | Chronic asthma                                                        | Asthma                                                                          | Asthma                                             | Chronic asthma                                                         | -                               |
| <b>Chronic obstructive pulmonary disease (COPD), acquired respiratory distress syndrome (ARDS), or emphysema</b> | Chronic obstructive pulmonary disease                                 | Chronic obstructive pulmonary disease or acquired respiratory distress syndrome | Chronic obstructive pulmonary disease or emphysema | Chronic obstructive pulmonary disease                                  | -                               |
| <b>Angina</b>                                                                                                    | Angina (coronary artery disease)                                      | Angina                                                                          | Angina pectoris                                    | Coronary artery disease                                                | -                               |
| <b>Congestive heart failure (or heart disease)</b>                                                               | Congestive heart failure or heart disease                             | Congestive heart failure or heart disease                                       | Congestive heart failure or heart disease          | Heart failure                                                          | -                               |
| <b>Heart attack (myocardial infarct)</b>                                                                         | Myocardial infarction                                                 | Heart attack                                                                    | Myocardial infarction                              | Myocardial infarction                                                  | -                               |
| <b>Neurological disease (such as multiple sclerosis or Parkinson's)</b>                                          | Parkinson's disease or multiple sclerosis                             | Neurological disease; Parkinson's disease                                       | Parkinson's disease                                | Parkinson's disease or multiple sclerosis                              | Parkinson's disease             |
| <b>Stroke or transient ischemic attack (TIA)</b>                                                                 | Stroke                                                                | Stroke                                                                          | Stroke                                             | Stroke                                                                 | Stroke                          |
| <b>Peripheral vascular disease</b>                                                                               | -                                                                     | Peripheral vascular disease                                                     | Peripheral vascular disease                        | -                                                                      | -                               |
| <b>Diabetes types I and II</b>                                                                                   | Diabetes mellitus (type I and II)                                     | Diabetes mellitus (type I and II)                                               | Diabetes mellitus (type I and II)                  | Diabetes                                                               | Diabetes mellitus               |
| <b>Upper gastrointestinal disease (ulcer, hernia, reflux).</b>                                                   | -                                                                     | Upper gastrointestinal disease                                                  | Upper gastrointestinal disease                     | -                                                                      | -                               |
| <b>Depression</b>                                                                                                | Depressive symptoms                                                   | -                                                                               | -                                                  | Depression                                                             | -                               |
| <b>Anxiety or panic disorders</b>                                                                                | -                                                                     | Anxiety or panic disorders                                                      | -                                                  | -                                                                      | -                               |

| <b>Original Functional Comorbidity Index Items (174)</b>                                      | <b>Gnjidic et al, 2012 (164)</b>                  | <b>Gnjidic et al, 2012 (166)</b> | <b>Jansen et al, 2016 (196)</b> | <b>Lonnroos et al, 2012 (220)</b>                | <b>Wilson et al, 2011 (154)</b> |
|-----------------------------------------------------------------------------------------------|---------------------------------------------------|----------------------------------|---------------------------------|--------------------------------------------------|---------------------------------|
| <b>Visual impairment (such as cataracts, glaucoma, macular degeneration)</b>                  | Visual impairment                                 | Visual impairment                | -                               | Visual impairment                                | -                               |
| <b>Hearing impairment (very hard of hearing, even with hearing aids)</b>                      | Hearing impairment                                | Hearing impairment               | -                               | Hearing impairment                               | -                               |
| <b>Degenerative disc disease (back disease, spinal stenosis, or severe chronic back pain)</b> | -                                                 | Degenerative disc disease        | Back pain                       | -                                                | -                               |
| <b>Obesity and/or body mass index &gt;30 (weight in kg/height in meters<sup>2</sup>)</b>      | Obesity (body mass index > 30 kg/m <sup>2</sup> ) | -                                | -                               | Obesity (body mass index >30 kg/m <sup>2</sup> ) | -                               |
| <b>Conditions not included in Functional Comorbidity Index</b>                                | -                                                 | Cancer (excluding skin cancer)   | -                               | -                                                | -                               |



#### **2.5.4 Grip Strength**

Grip strength is a measure of maximum voluntary force of the hand (235) and has been found to be a valid and reliable instrument for measuring hand strength (236). Grip strength was assessed as part of the Health Assessment at Wave 2 of IDS-TILDA. It was measured using a Jamar Hydraulic Dynamometer, with two measurements on each hand. The instrument used has been found as a valid and reliable instrument for measuring hand grip strength (237). Grip strength was selected as a measure of physical function for two reasons. Firstly, DBI score has been found to be significantly associated with grip strength in studies of older adults without ID (150, 151, 164). Secondly, Hilgenkamp et al (181, 182) have examined the feasibility and reliability of physical function measures in this group and concluded that grip strength is an appropriate method of measuring function.

An important consideration when investigating grip strength among people with ID is the hypotonia which is associated with Down syndrome (238).

#### **2.5.5 Timed Up and Go**

TUG was used as a means of assessing the proximal muscle strength, balance and executive function of participants (239). Participants were directed to sit in a standard chair, get up from the sitting position, walk to the marked point three metres away, turn around, walk back to the chair and sit down. This procedure was timed (240). Poorer performance in TUG has been found to be associated with exposure to DBI medicines (164).

#### **2.5.6 Fried's Frailty Phenotype**

Fried's frailty phenotype had only been modified and examined once among older adults with ID (190). A modified version of Fried's frailty phenotype (189) was constructed specifically for use in the IDS-TILDA population. Two of the criteria (shrinking, weakness) were matched directly to the original Fried's frailty phenotype criteria. The other three criteria (poor endurance and exhaustion, slowness and low physical activity) were modified towards the measures included in the IDS-TILDA study. TUG has been found to identify frail members of the population well (241), and while it is not effective alone as a proxy for frailty (241), it is a suitable alternative measure for walking speed in a frailty phenotype. Modification of Fried's frailty phenotype has been used in several studies of medication exposure and frailty (152, 161, 242).

Table 2.6 Fried's Frailty Phenotype Comparison

| Criteria                      | Original Fried's Frailty Phenotype (189)                                                                                                                                                          | IDS-TILDA                                                                                                                                                                                            | Frailty Score |
|-------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------|
| Shrinking                     | In the last year, have you lost more than 10 pounds unintentionally (i.e., not due to dieting or exercise)? (Yes)                                                                                 | Within the last year, have you lost or gained ten pounds (4.5 kg) or more in weight when you weren't trying to? (Yes – lost weight)                                                                  | 1             |
| Weakness                      | Lowest sample quintile (20%) for grip strength, adjusted for gender and body mass index                                                                                                           | Lowest sample quintile (20%) for grip strength, adjusted for gender and body mass index                                                                                                              | 1             |
| Poor endurance and exhaustion | How often in the last week did you feel this way?<br>(a) I felt that everything I did was an effort;<br>(b) I could not get going.<br>(A moderate amount of the time (3–4 days)/most of the time) | How much of the time during the past 4 weeks did you feel worn out?<br>How much of the time during the past 4 weeks did you feel tired?<br>(All of the time/most of the time/a good bit of the time) | 1             |
| Slowness                      | Walking time/15 feet: slowest 20% (by gender, height)                                                                                                                                             | Lowest sample quintile (20%) for timed up and go, adjusted for gender and height.<br>Wheelchair users, walking aid users, participants requiring assistance to walk across a room                    | 1             |
| Low physical activity         | Short version of the Minnesota Leisure Time Activity questionnaire                                                                                                                                | International Physical Activity Questionnaire – Short Form (Low activity)                                                                                                                            | 1             |

*Chapter 5* describes in more detail the cut-offs applied for weakness, slowness and low physical activity.

Scores were calculated as the sum of scores from 0 to 5 and were classified as follows: 0: Robust; 1 – 2: Pre-Frail; 3 or more: Frail. This is the method used in the original Cardiovascular Health Study (189).

Not all participants were able to take part in all measures. Participants with two or more criteria missing were excluded from analysis (n = 107). This is similar to but more conservative than the method used by the Healthy Ageing in Intellectual Disability Study, where those with three or more criteria available were included in analysis. Details of missing data are also included in *Chapter 5*.

## 2.6 Contributions to Each Study

| Study                                                                                                                                                                                                                                                                                                                                                   | Contributors                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
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| <p><b>J O'Connell, É Burke, N Mulryan, C O'Dwyer, C Donegan, P McCallion, M McCarron, M C Henman, M O'Dwyer.</b></p> <p><b>Drug Burden Index to Define the Burden of Medicines in Older Adults with Intellectual Disabilities: An Observational Cross-Sectional Study. <i>British Journal of Clinical Pharmacology</i>. 2018. 84(3); pp 553-567</b></p> | <p><b>J O'Connell:</b> Overall conception and design of the study; search, retrieval and review of existing literature; data extraction; development of Drug Burden Index medication inventory; assignment of Minimum Effect Daily Doses to Drug Burden Index medications; calculation of Drug Burden Index scores; development of the modified Functional Comorbidity Index; collaboration on Barthel Index activities of daily living measure; proposed statistical methods; interpretation of results; writing first draft of the manuscript; collating co-author revisions of manuscript; submission of manuscript to <i>British Journal of Clinical Pharmacology</i>; management of revisions as suggested by peer review; publication guarantor.</p> <p><b>É Burke:</b> Contributed to overall conception and design of the study; revision of manuscript (from first draft to accepted publication).</p> <p><b>N Mulryan:</b> Contributed to overall conception and design of the study; revision of manuscript (from first draft to accepted publication).</p> <p><b>C O'Dwyer:</b> Contributed to overall conception and design of the study; created variable on behaviours which challenge; revision of manuscript (from first draft to accepted publication).</p> <p><b>C Donegan:</b> Contributed to overall conception and design of the study; development of the modified Functional Comorbidity Index; collaboration on Barthel Index activities of daily living measure; data extraction; revision of manuscript (from first draft to accepted publication).</p> <p><b>P McCallion:</b> Contributed to overall conception and design of the study; revision of manuscript (from first draft to accepted publication).</p> <p><b>M McCarron:</b> Contributed to overall conception and design of the study; revision of manuscript (from first draft to accepted publication); publication guarantor.</p> <p><b>M C Henman:</b> Contributed to overall conception and design of the study; development of Drug Burden Index medication inventory; assignment of Minimum Effect Daily Doses to Drug Burden Index medications; development of the modified Functional Comorbidity Index; collaboration on Barthel Index activities of daily living measure; interpretation of results; revision of manuscript (from first draft to accepted publication).</p> <p><b>M O'Dwyer:</b> Contributed to overall conception and design of the study; development of Drug Burden Index medication inventory; assignment of Minimum Effect Daily Doses to Drug Burden Index medications; development of the modified Functional Comorbidity Index; collaboration on Barthel Index activities of daily living measure; proposed statistical methods; interpretation of results; revision of manuscript (from first draft to accepted publication).</p> |

| Study                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Contributors                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
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| <p><b>J O'Connell, M C Henman, É Burke; C Donegan; P McCallion; M McCarron; M O'Dwyer</b></p> <p><b>Association of Drug Burden Index with Physical Function Measures in Older Adults with Intellectual Disabilities: An Observational Cross-sectional Study.</b></p> <p><b>(Published as: Association of drug burden index with grip strength, timed up and go and Barthel Index activities of daily living in older adults with intellectual disabilities: an observational cross-sectional study. <i>BMC Geriatrics</i>. 2019. 19(1); pp 173 -194)</b></p> | <p><b>J O'Connell:</b> Overall conception and design of the study; search, retrieval and review of existing literature; data extraction; development of Drug Burden Index, modified Functional Comorbidity Index and Barthel Index activities of daily living measure as described above; proposed statistical methods; interpretation of results; writing first draft of the manuscript; collating co-authors revisions of manuscript; submission of manuscript to BMC Geriatrics; publication guarantor.</p> <p><b>É Burke:</b> Contributed to overall conception and design of the study; undertook gathering of health assessment data (grip strength, timed up and go, Quantitative Heel Ultrasound); revision of manuscript.</p> <p><b>C Donegan:</b> Contributed to overall conception and design of the study; data extraction; development of the modified Functional Comorbidity Index; collaboration on Barthel Index activities of daily living measure; revision of manuscript.</p> <p><b>P McCallion:</b> Contributed to overall conception and design of the study; revision of manuscript.</p> <p><b>M McCarron:</b> Contributed to overall conception and design of the study; revision of manuscript; publication guarantor.</p> <p><b>M C Henman:</b> Contributed to overall conception and design of the study; development of Drug Burden Index, modified Functional Comorbidity Index and Barthel Index activities of daily living measure as described above; interpretation of results; revision of manuscript.</p> <p><b>M O'Dwyer:</b> Contributed to overall conception and design of the study; development of Drug Burden Index, modified Functional Comorbidity Index and Barthel Index activities of daily living measure as described above; proposed statistical methods; interpretation of results; revision of manuscript.</p> |

| Study                                                                                                                                                                                                                                                 | Contributors                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
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| <p><b><u>J O'Connell</u>, M C Henman, N McMahon, É Burke; P McCallion; M McCarron; M O'Dwyer</b></p> <p><b>Association of Frailty with Medication Burden in Older Adults with Intellectual Disability: An Observational Cross-sectional Study</b></p> | <p><b>J O'Connell:</b> Overall conception and design of the study; search, retrieval and review of existing literature; data extraction; development of Drug Burden Index, modified Functional Comorbidity Index and Barthel Index activities of daily living measure as described above; review and revision of Anticholinergic Cognitive Burden inventory and scores; development of Sedative Load Model appropriate to use in the study; calculation of medication exposure scores; development of modified Fried frailty phenotype; proposed statistical methods; interpretation of results; writing first draft of the manuscript; collating co-authors revisions of manuscript; publication guarantor.</p> <p><b>M C Henman:</b> Contributed to overall conception and design of the study; development of Drug Burden Index, modified Functional Comorbidity Index and Barthel Index activities of daily living measure as described above; review of Anticholinergic Cognitive Burden inventory and scores; review of Sedative Load Model inventory and scores; interpretation of results; revision of manuscript.</p> <p><b>N McMahon:</b> Review of Anticholinergic Cognitive Burden inventory and scores; review of Sedative Load Model inventory and scores.</p> <p><b>É Burke:</b> Contributed to overall conception and design of the study; undertook gathering of health assessment data (grip strength, timed up and go, Quantitative Heel Ultrasound).</p> <p><b>P McCallion:</b> Contributed to overall conception and design of the study; revision of manuscript.</p> <p><b>M McCarron:</b> Contributed to overall conception and design of the study; revision of manuscript.</p> <p><b>M O'Dwyer:</b> Contributed to overall conception and design of the study; development of Drug Burden Index, modified Functional Comorbidity Index and Barthel Index activities of daily living measure as described above; proposed statistical methods; interpretation of results; revision of manuscript.</p> |

## Chapter 3

# Drug Burden Index to Define the Burden of Medicines in Older Adults with Intellectual Disabilities: An Observational Cross-Sectional Study

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DRUG BURDEN INDEX TO DEFINE THE BURDEN OF MEDICINES IN OLDER ADULTS WITH INTELLECTUAL DISABILITIES: AN OBSERVATIONAL CROSS-SECTIONAL STUDY.

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**KEYWORDS:** PHARMACOEPIDEMIOLOGY; AGEING; DRUG UTILISATION

### 3.1 Abstract

**Aims:** The Drug Burden Index (DBI) is a dose-related measure of anticholinergic and sedative drug exposure. This cross-sectional study described DBI in older adults with intellectual disabilities (ID) and the most frequently reported therapeutic classes contributing to DBI and examined associations between higher DBI scores and potential adverse effects as well as physical function.

**Methods:** This study analysed data from Wave 2 (2013/2014) of the Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing (IDS-TILDA), a representative study on the ageing of people with ID in Ireland. Self- and objectively-reported data was collected on medication use and physical health, including health conditions. The Barthel Index was the physical function measure.

**Results:** The study examined 677 individuals with ID, of which 644 (95.1%) reported taking medication and 78.6% (n = 532) were exposed to medication with anticholinergic and/or sedative activity. 54.2% (n = 367) were exposed to high DBI score ( $\geq 1$ ). Adjusted multivariate regression analysis revealed no significant association between DBI score and daytime dozing, constipation or falls. After adjusting for confounders (gender, age, level of ID, comorbidities, behaviours that challenge, history of falls), DBI was associated with significantly higher dependence in the Barthel Index ( $p = 0.002$ ).

**Conclusions:** This is the first time DBI has been described in older adults with ID. Scores were much higher than those observed in the general population and higher scores were associated with higher dependence in Barthel Index activities of daily living (ADLs).

## 3.2 Introduction

People with intellectual disabilities (ID) may be exposed to high levels of polypharmacy, including medicines with sedative and anticholinergic effects (101, 103). People with ID become multimorbid with age and as a result they may be exposed to a high burden of medications (243). This multimorbidity includes a high prevalence of mental health conditions (such as depression, schizophrenia, bipolar affective disorder and anxiety disorders), neurological disease (such as epilepsy and dementia) and gastrointestinal disease (such as gastro-oesophageal reflux disease and peptic ulcer disease) (57).

Medications with sedative and/or anticholinergic activity may have a significant negative impact on the health of older people. Sedative medications commonly produce adverse cognitive and psychomotor events, increased falls and fractures liability and daytime fatigue – effects which become clinically significant in those with additional risk factors for falls and cognitive impairment (244-249). Use of medications with sedative effects has been associated with frailty and poorer performance in instrumental activities of daily living in older adults (161, 250).

Older adults in the general population can be particularly sensitive to medications with anticholinergic effects, and the classic adverse effects such as dry mouth, reduced gastric motility, blurred vision and sedation can be compounded in this population to produce difficulties in communication, constipation and falls (118, 251).

A high burden of medicines with anticholinergic properties has been reported in two-thirds of older adults with ID, with high levels of Anticholinergic Cognitive Burden (ACB) exposure in three in ten older adults with ID (101, 103). In contrast, community-dwelling older adults without ID have reported a total ACB exposure of 23% (118). Use of neuroleptic and antipsychotic medication in the ID population have been reported at between 21 – 50%, while sedative exposure has been reported at between 10 – 24% (101, 252-255) and total exposure to central nervous system (CNS) agents has been reported as high as 60%, compared to 10 – 25% in the population without ID (256). This burden in people with ID has been associated with a number of adverse effects, including chronic constipation and daytime drowsiness (103).

A number of alternative scales are available to quantify anticholinergic and sedative load separately. The ACB scale categorises medications as having absent (ACB Score 0), possible (ACB Score 1) or definite (ACB Score 2 or 3) anticholinergic properties (103). The Sedative Load model classifies medications as primary sedatives (Group 1), drugs with sedation as a prominent side



effect (Group 2), drugs with sedation as a potential adverse effect (Group 3) and drugs with no known sedative effect (Group 4) (143). The Drug Burden Index (DBI) is a tool which quantitatively evaluates the burden of both anticholinergic and sedative medications on an individual. The DBI offers a dose-related measure of burden, unlike these other indices available, by taking into account the relationship between prescribed dose and the dose response curve. Scores from the relevant medications are added together to give a total DBI score for the individual (146, 149). Associations between DBI scores and objective function measures have been analysed in order to identify the effect of these types of medications on cognitive and physical performance in older adults. A higher DBI score has been associated with a number of negative outcomes: poor cognitive and physical performance; reduced gait speed and grip strength; poorer performance in instrumental activities of daily living (IADLs); frailty; and falls (146, 149-155).

The DBI can be tailored to evaluate appropriate prescribing in a number of settings, and has been validated internationally (149, 225). The index includes a range of medications with sedative properties, offering a broader evaluation than previous research which only examined single classes of sedatives (250). A recent systematic review identified the DBI as the most suitable tool for use in the evaluation of anticholinergic burden in longitudinal studies of older adults (257).

Failure to identify the side effects of anticholinergics in older people in the general population occurs due to reduced health expectations and misinterpretation of side effects as age related illness (118), a difficulty which is further compounded in the population with ID due to their additional difficulties in communication and diagnostic overshadowing (50, 258). Even though people with ID have a high drug burden, there is a lack of research into specific measurement of drug burden of sedative and anticholinergic medicines and guidance for intervention in this population. Given evidence to date of high sedative and anticholinergic burden in older adults with ID, the aim of this study was to evaluate and describe the cumulative drug burden for older people with ID.

In Ireland, similar to the practice in other developed countries, current policy emphasises deinstitutionalisation of people with ID. This specifically aims to encourage movement from congregated settings (i.e. housing units of 10 or more people) into community housing alongside the general population. While community based models appear to achieve better outcomes for people with ID, loss of specialist medical services and greater utilisation of general primary care

practices may mean the medical needs of people with ID as they age are not fully addressed (52, 101).

The primary objectives of this study were:

- a) To create a version of the Drug Burden Index suitable for use in an Irish population of older adults with ID;
- b) To determine the characteristics in an older population with ID that are associated with the drug burden measured by the DBI;
- c) To describe the drug burden in older adults with ID and the most frequently reported therapeutic classes contributing to total burden;
- d) To examine the association between drug burden and potential adverse effects (daytime dozing, chronic constipation and falls) and Barthel Index activities of daily living (ADLs).

### 3.3 Methods

#### 3.3.1 Study Population

The data for this study was drawn from Wave 2 (2013/2014) of the Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing (IDS-TILDA); a large scale, nationally representative longitudinal study which examines the ageing of persons with ID. This study has been described in detail elsewhere (52, 205). The National Intellectual Disability Database (NIDD) collates information for all people in the Republic of Ireland with an ID eligible for or receiving services and it provided the sampling frame for Wave 1 of the study. A total of 1,800 personal identification numbers (PINs) were randomly selected by staff at NIDD. An invitation pack was sent to each potential participant with a consent form. Whereby an individual was unable to provide consent independently, a family member/guardian could sign a letter of agreement for their family member to participate. Participants lived independently/with family, in community group homes or in residential settings. A total of 753 individuals participated in Wave 1 of the study (2009/2010). Participants were aged 40 years or older to account for the reduced life expectancy and presentation of older age conditions at a younger age in people with ID (10). Approval for the study was granted by Faculty of Health Sciences Research Ethics Committee in Trinity College Dublin. In addition, local and/or regional ethical committee approval was granted from each service provider (n = 138).

All living Wave 1 participants (n = 719) were invited to participate in Wave 2 (2013/2014). The study population with available medication data was 677 (95.6%) (*Figure 3.1*).

Participants were invited to complete a Pre-Interview Questionnaire (PIQ) and these answers were confirmed in the face-to-face interview with a computer-assisted personal interview (CAPI). The PIQ contained a section on medication use. The design of this medication data section was improved from Wave 1 to Wave 2 of the study to collect more consistent, accurate information on dose and frequency data. To further facilitate data capture, the PIQ was sent to each participant/carer one week in advance of interview to allow time to access medical files if necessary. In the majority of cases (92.8%; n = 628), this data was recorded by proxy (key worker or family member known to participants for at least six months).

Field researchers came from a variety of backgrounds but all had experience in working with people with ID. They were provided with three full training days in data collection and a further refresher day prior to beginning interviews. A pharmacist (MO'D) provided medication data capture training to all field researchers. Several interview styles were utilised – direct interview

with the participant, assisted interview where a proxy assisted the participant and interview where questions were answered by a proxy only, with or without the participant present.

In addition, a health assessment was included to obtain objective physical health measures which included body mass index (BMI) and Lunar Achilles GE Quantitative Ultrasound (QUS) (52). The health assessments were conducted separate from the main interview by a registered nurse in intellectual disability who was a researcher in the IDS-TILDA study. Each of the Wave 2 participants were invited to take part and to facilitate and support the individual's participation, adaptable and accessible materials and methods were developed. This component has been described in detail elsewhere, for further details see Burke et al., 2014, 2016a & 2016b (52, 240, 259).

The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guidelines for cross-sectional studies were used (260, 261).

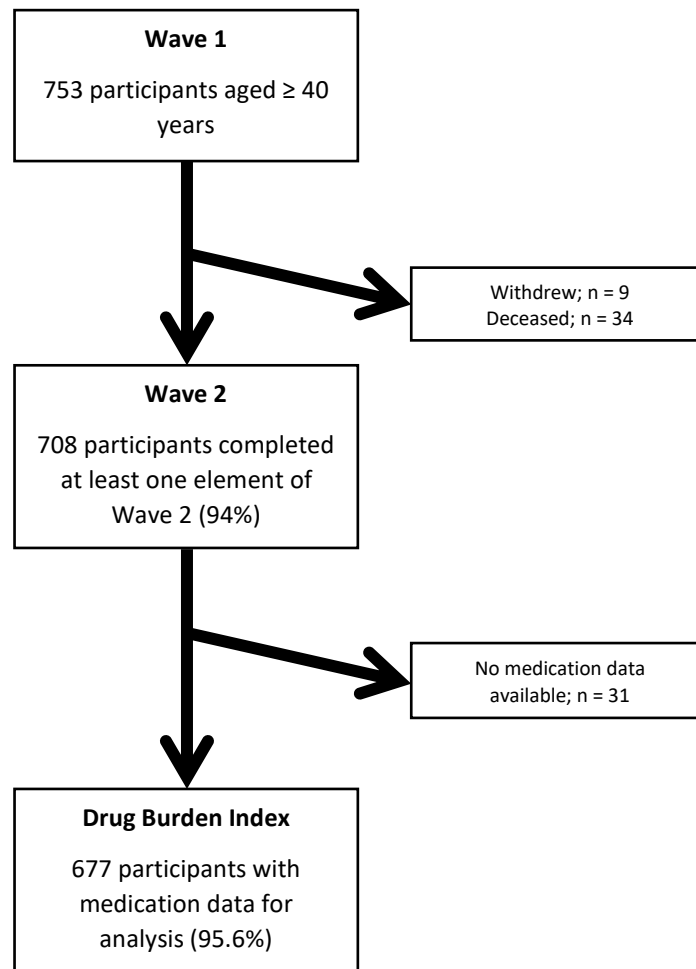


Figure 3.1 Flow Chart of IDS-TILDA Study

### 3.3.2 Medication Exposure

Participants/proxies were asked: “Can you tell me what medications (including prescribed or over the counter (OTC)) and supplements you take on a regular basis (like every day or every week)?”

The participant/proxy recorded their medication data by brand name/International Non-Proprietary Name (INN), dose, frequency, route of administration and date on which medicine was initiated in the PIQ.

Medications were categorised by Anatomical Therapeutic Chemical (ATC) code and verified by two pharmacists (228). Medicines recorded for indications which were not regular (for example: treatments for pre-dental/medical procedures, pre-phlebotomy treatments, alternate month usage of antihistamines) were excluded from the calculations. As per previous studies, “as required” or “prn” medications were also excluded from DBI calculations because the

contribution to the burden of anticholinergic and/or sedative activity from the intermittent use of these medications cannot be reliably estimated (146, 212, 222).

### 3.3.3 Medication Inventory of Sedative and Anticholinergic Medicines

Medications with clinically significant anticholinergic and/or sedative activity were identified by reference to relevant studies (103, 140, 143, 146, 150, 161, 164) in addition to detailed examination of the licenced product information (Summary of Product Characteristics, SmPC) for the Republic of Ireland as available from the Health Products Regulatory Authority (HPRA) (227). The final list of 258 medications (117 anticholinergic, 141 sedative) was decided upon by consensus by three pharmacists (MH, MO'D & JO'C) (*Figure 3.2*).

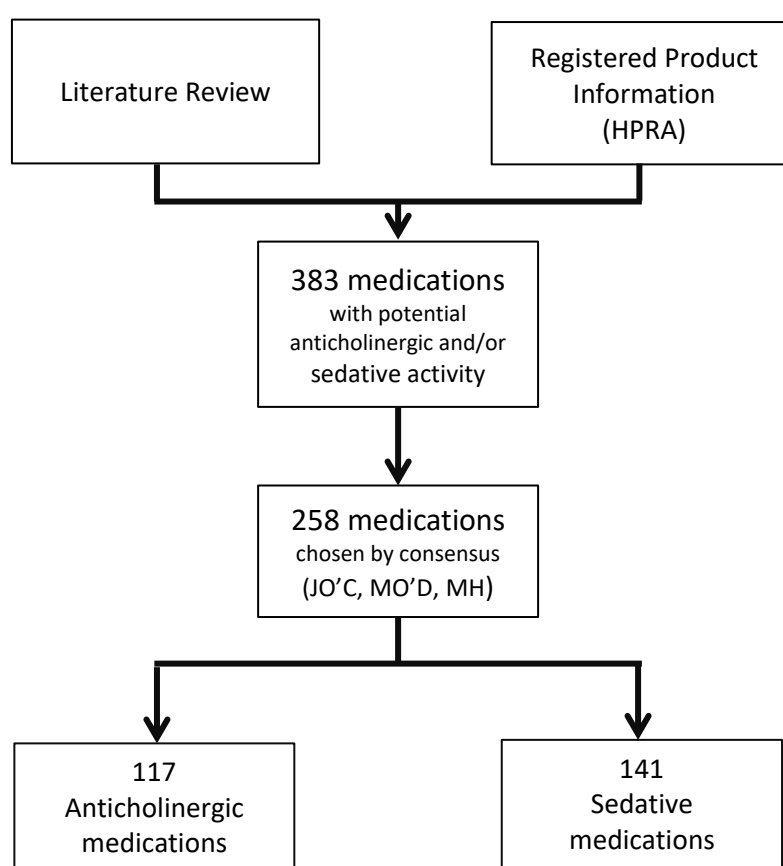


Figure 3.2 Development of Medication Inventory

*Table 3.1* represents a summary of the search terms used to identify sedative potential during review of the SmPC. The list of search terms which were used were modelled on those used in

the Sedative Load Model: “sedating, sedative, drowsiness, sleepiness, lassitude, exhaustion, tiresome, fatigability.”(143)

Table 3.1 Sedative Search Terms

| Sedative Search Terms                                                                                                                           | Clinically Significant Adverse Effect Frequency                                                                                                           |
|-------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>• Fatigue</li> <li>• Asthenia</li> <li>• Somnolence</li> <li>• Sedation</li> <li>• Drowsiness</li> </ul> | <ul style="list-style-type: none"> <li>• Very Common: Occurring in &gt;1/10 users</li> <li>• Common: Occurring in &gt;1/100 and &lt;1/10 users</li> </ul> |

This inventory of medications was categorised according to the nature of the burden. Medications with both anticholinergic and sedative effects were classified primarily as anticholinergic as per previous studies (146, 150, 164, 166).

- Prochlorperazine was recoded from the ATC code N05AB04 (Antipsychotics) to A04A (Antiemetics and Antinauseants) as the dosages reported by this population exclusively fell within the total daily dosage range used for treatment of Ménière’s syndrome, nausea and vomiting (10 – 40mg according to the Irish SmPC) as opposed to those indicated for psychotic episodes (75 – 100mg).
- Depot preparations administered less frequently than weekly (intramuscular flupentixol, fluphenazine, risperidone, zuclopenthixol) were also included due to their release profile.
- Topical products were excluded for the purposes of this analysis due to insignificant systemic effects. The only exception was ophthalmological atropine which was considered to have clinically significant systemic anticholinergic properties (262).
- Inhaled anticholinergic preparations (ipratropium and tiotropium) were excluded due to low prevalence of users (n = 11; 1.6%) and high proportion of missing dose information for these preparations (n = 7; 64%).
- Medicines for which the primary indication is acute seizure control (rectal diazepam, buccal midazolam) and migraine (sumatriptan), are used on an intermittent basis and were excluded as the DBI measures exposure to regularly used medications.

### 3.3.4 Calculation of Drug Burden Index

The accepted standard approach to calculation of the Drug Burden Index was utilized (146). Scores were calculated for each individual according to the formula:

$$Total\ Drug\ Burden = B_{AC} + B_S$$

where  $B_{AC}$  indicates the anticholinergic burden and  $B_s$  indicates the sedative burden (146). A model of pharmacological effect ( $E$ ) was developed which assumes that the anticholinergic and sedative burdens of individual drugs are additive linearly:

$$\frac{E}{\alpha} = \sum \frac{D}{D + DR_{50}}$$

$\alpha$  is a proportionality constant,  $D$  is the daily dose and  $DR_{50}$  is the daily dose to achieve 50% of maximal contributory effect at steady state (149). As the  $DR_{50}$  of anticholinergic and sedative activity is not easily identifiable, the Minimum Daily Dose (MDD) is used as a substitute. MDDs were selected based on the lowest effective daily dose listed in the Irish medicinal product authorisation from the HPRA.

The final version of the DBI calculation is as follows:

$$Drug\ Burden\ Index = \sum \frac{D}{\delta + D} \quad (146)$$

where  $\delta$  is the MDD.

DBI scores for participants were calculated as a continuous variable and then transformed into a categorical variable with three levels: DBI score 0 (no DBI exposure), DBI score  $0 < 1$  (low) and DBI score  $\geq 1$  (high). This reflects the categories used elsewhere in the literature (146, 150-155, 210, 212, 223).

### 3.3.5 Missing Dose Information

When dose information was missing for a medication ( $n = 43$ ), a median dosage figure was used. This is consistent with the strategy used in preceding DBI studies (146, 150, 151, 153). For one medication (diphenhydramine), no median dose was available, therefore the MDD was substituted.

### 3.3.6 Physical Function Measure

The Barthel Index is a measure of assessing disability in those receiving rehabilitation for neuromuscular and musculoskeletal conditions and has become a reliable method of measuring function in older populations. It consists of an ordinal scale of ten ADLs (range 0 – 20) (170, 263). It takes into account the level of dependence an individual has with regard to mobility, using stairs, dressing, bathing, grooming, feeding, transfer, toileting and bladder and bowel continence. A modified form of Barthel Index ADLs was created for this population (*Supporting Information Table S 3.1*). Each participant was given a composite score between 0 and 20 based on their self-/proxy-report of difficulty experienced with each activity. Lower scores indicated poorer physical function. Barthel Index scores were categorised as per Wade & Collin (1988)



classifications: total dependence (0 – 4), severe dependence (5 – 12), moderate dependence (13 – 18), mild dependence (19) and total independence (20) (233).

Participants with two or more missing values (i.e., those who answered “don’t know”, gave an unclear response or preferred not to answer) were excluded from the Barthel Index evaluation (n = 42). This method of handling missing data was as per a previous study (196).

### **3.3.7 Covariates**

*Demographic Characteristics:* Covariates were gender, age range (44 – 49 years; 50 – 64 years; 65+ years), level of ID (mild; moderate; severe/profound), type of residence (independent; community group home; residential care) and behaviours that challenge (yes/no).

Level of ID is correlated by intelligence quotient (IQ) scores as follows; mild (50 – 55 to approx. 70), moderate (35 – 40 to 50 – 55) and severe/profound (below 35 – 40) and correct classification was obtained from case notes for each participant (1). Those with unverified level of ID (n = 53) were excluded from regression analysis.

Community group homes are in a community setting with staff support for small groups of people with ID. Residential settings were defined as living arrangements where ten or more people share a single living unit or where the living arrangements are campus based.

Behaviours that challenge were defined as any behaviour which “(1) is a barrier to a person participating in and contributing to their community (including both active and passive behaviours); (2) undermines directly or indirectly a person’s rights, dignity or quality of life, and (3) poses a risk to the health and safety of a person and those with whom they live and work” (74). Behaviours that challenge were measured by response to a question on verbal aggression, physical aggression, destructive behaviour, self-injurious behaviour or other behaviours that challenge. A more detailed description of the definition of behaviours that challenge is available in *Supporting Information Description SD 3.1*. Behaviours that challenge were included as a covariate to adjust for potential confounding by indication due to evidence which already exists in the literature reporting the extensive use of psychotropic medication in the management of behaviours that challenge in the ID population (255, 264-266).

*Potential adverse effects:* Three potential adverse effects were selected for assessment due to previous associations identified in the general population in DBI studies and in Anticholinergic Cognitive Burden (ACB) studies of older adults with ID (103, 154).

- 1) *Daytime dozing*: This was identified by asking participants and/or proxies “How likely are you to doze off and fall asleep during the day?” Where a participant answered “most of the time” or “sometimes”, they were considered to have daytime dozing (yes), while “rarely” and “never” indicated no daytime sleep problem (no) (267).
- 2) *Chronic constipation*: Participants/proxies were asked “have you ever had a doctor’s diagnosis of chronic constipation?” to which they answered “yes”, “no” or “don’t know”.
- 3) *Fall in the previous 12 months*: Participants/proxies were asked “in the past year have you had any fall including a slip or trip in which you lost your balance and landed on the floor or ground or lower level?” to which they answered “yes”, “no” or “don’t know”.

*Functional Comorbidity Index*: A modified Functional Comorbidity Index (FCI) (*Supporting Information Table S 3.2*) was developed for the population and provided a continuous score between 0 and 16 by summing the presence of a reported doctor’s diagnosis (in response to the question “have you ever had a doctor’s diagnosis of...”) for the following conditions: arthritis; osteoporosis/osteopenia (self-/proxy-report of doctor’s diagnosis and/or objective evidence from QUS); asthma; lung disease; angina; congestive heart failure (or heart disease); myocardial infarction; neurological disease; stroke or transient ischaemic attack; diabetes mellitus type I or II; upper gastrointestinal disease (e.g. ulcer, hernia, reflux); depression (unipolar or bipolar); anxiety or panic disorder; visual impairment (e.g., cataracts, glaucoma, macular degeneration); hearing impairment; overweight/obese (data obtained from health assessment). Similar modified versions of the FCI have been used in a number of previous DBI studies adapted for the populations being studied (151, 154, 164, 166, 220). Participants with two or more missing conditions were excluded from the FCI score evaluation, reflecting the method used in a previous study (196). *Table 3.4* (multivariate regression analysis) and *Figure 3.3* (analysis of covariance for Barthel Index) were adjusted for comorbidities using the FCI.

*Polypharmacy*: This was measured as a categorical variable. Definitions were as follows:

- *Excessive polypharmacy*: Concurrent use of ten or more different drugs.
- *Polypharmacy*: Use of five to nine drugs.
- *No polypharmacy*: Use of four or less drugs (included those taking no medicines)(101).

### 3.3.8 Statistical Analysis

Analyses were performed using Microsoft Excel 2010 (Microsoft Corporation) and Statistical Package for Social Sciences (SPSS) version 21.0 (IBM Corporation). Statistical significance was set at  $p < 0.05$ .

Descriptive statistics (percentages and 95% confidence intervals) described the characteristics of the study populations. Medians and interquartile range (IQR) were reported as the data was not normally distributed. Univariate analysis was used to examine the associations between the three DBI levels (0,  $0 > 1$ ,  $\geq 1$ ) (the dependent variable) and the demographic and clinical variables. For the categorical variables, chi-squared ( $\chi^2$ ) tests for independence were used to test for significant associations between the three DBI levels.

Multinomial logistic regression was carried out to identify the relationship between DBI scores of  $0 > 1$  and  $\geq 1$  and potential adverse effects. The reference category was set as those with DBI score = 0. The model was adjusted for demographic variables – age, gender, level of ID, type of residence, behaviours that challenge, comorbidities (FCI) and number of non-DBI medicines; potential adverse effects included were daytime dozing, chronic constipation and fall in the previous 12 months. Those with unverified level of ID ( $n = 53$ ) were excluded from the regression analysis. Those living independently ( $n = 102$ ) or in community group homes ( $n = 298$ ) were combined as a single group ( $n = 400$ ) due to small numbers in the subgroups.

To test for multicollinearity between the independent factors, two strategies were employed. Variance Inflation Factors (VIF) and Spearman's correlation coefficients of the independent variables were examined. A VIF cut-off of  $>2$  was employed (268). If the VIF for one of the variables is greater than 2, there is collinearity associated with that variable. All VIFs were below the threshold of 2. Spearman's correlation coefficients were interpreted using Dancy and Reidy's categorisation (269). Here, correlations of  $\pm 1$  are interpreted as a perfect correlation, values between  $\pm 0.7$  to  $\pm 0.9$  are interpreted as strong correlations, values in the range  $\pm 0.4$  to  $\pm 0.6$  are categorized as moderate correlations, values between  $\pm 0.1$  to  $\pm 0.3$  are weak correlations and a value of 0 is zero correlation, implying there is no correlation. All of the correlations fell below 0.4, indicating only weak correlations and thus not of concern.

Analysis of covariance (ANCOVA) was used to compare the adjusted mean of the continuous variable for the Barthel Index between subjects exposed to three different levels of Drug Burden Index ranges (means were adjusted for gender, age, level of ID, behaviours that challenge,

comorbidities (FCI) and history of falls). This reflected the practice used in a similar study of DBI and physical function measures (151).

Sample size calculation for the logistic regression was based on the guideline of Peduzzi et al (270), (for a minimum number of cases (N) needed for the study;  $N = 10k/p$ , where p is the smallest of the proportions of negative or positive cases in the population and k is the number of covariates (independent variables) (270). For the multinomial logistic regression, there were 10 covariates and the proportion of negative cases (DBI 0) was 0.21, therefore a minimum sample size (N) of 476 was needed, which our sample size (n = 484) exceeded.

### **3.3.9 Missing Data**

Missing data for the Barthel Index and Functional Comorbidity Index analyses are described in *Supporting Information Table S 3.3*. Higher rates of missing data were observed in those with mild level of ID (26.8%; n = 40), those living in independent settings (32.4%; n = 33) and those in the younger age group (44 – 49 years; 24.6%; n = 46) for the Functional Comorbidity Index. Less data was missing overall for Barthel Index and the profile was slightly different, with more people with moderate ID (7.0%; n = 20), living in community group homes (7.7%; n = 23) and in the older age group (65+ years; 7.7%; n = 11) missing Barthel Index scores.

### 3.4 Results

Of the 708 participants who partook in Wave 2, 677 (95.6%) had available medication data. Of the study population (n = 677), 56.1% (n = 380) were female and 44.1% (n = 298) lived in a community group home (*Table 3.2*). The median number of medications per participant was 6.00 (IQR 6.00). Of the 677 participants, 95.1% (n = 644) reported taking medicines. Overall, 78.6% (n = 532) of the population were exposed to medications with anticholinergic and/or sedative effects (DBI Score > 0) and the median number of DBI medications was 2.00 (IQR 3.00) (*Table 3.2*). 51.3% (n = 347) of participants were exposed to anticholinergic medications only and 32.1% (n = 217) were exposed to sedative medications only. Median number of comorbidities (FCI) was 3.00 (IQR 2.00) and 41.2% (n = 264) of participants reported having neurological disease. With respect to potential adverse effects, 34.9% (n = 232) reported daytime dozing, 38.4% (n = 257) reported chronic constipation and 28.5% (n = 190) reported having a fall in the previous 12 months. 52.0% (n = 352) reported behaviours that challenge. Level of polypharmacy was high, with 62.2% (n = 421) reporting taking 5 or more medications. 21.4% (n = 145) of participants had no exposure to anticholinergic or sedative medications (DBI score = 0), while 24.4% (n = 165) had a DBI score 0 > 1 and 54.2% (n = 367) had a score of 1 or higher.

Table 3.2 Baseline characteristics of the study population

| Characteristics                                   | Number of Participants<br>% (95% CI) |
|---------------------------------------------------|--------------------------------------|
| <b>Gender (n = 677)</b>                           |                                      |
| Male (n = 297)                                    | 43.9 (40.16 – 47.64)                 |
| Female (n = 380)                                  | 56.1 (52.36 – 59.84)                 |
| <b>Age (n = 676)</b>                              |                                      |
| 44 – 49 years (n = 187)                           | 27.6 (24.23 – 30.97)                 |
| 50 – 64 years (n = 347)                           | 51.3 (47.53 – 55.07)                 |
| 65 years + (n = 142)                              | 21.0 (17.93 – 24.07)                 |
| <b>Level of ID (n = 624)</b>                      |                                      |
| Mild (n = 149)                                    | 23.9 (20.55 – 27.25)                 |
| Moderate (n = 287)                                | 44.0 (40.11 – 47.89)                 |
| Severe/Profound (n = 188)                         | 30.1 (26.5 – 33.7)                   |
| <b>Type of Residence (n = 676)</b>                |                                      |
| Independent (n = 102)                             | 15.0 (12.31 – 17.69)                 |
| Community Group Home (n = 298)                    | 44.1 (40.36 – 47.84)                 |
| Residential Care (n = 276)                        | 40.8 (37.1 – 44.5)                   |
| <b>Barthel Index (n = 635)</b>                    |                                      |
| Total Independence (n = 113)                      | 17.8 (14.9 – 21.0)                   |
| Mild Dependence (n = 50)                          | 7.9 (5.9 – 10.2)                     |
| Moderate Dependence (n = 274)                     | 43.1 (39.3 – 47.1)                   |
| Severe Dependence (n = 112)                       | 17.6 (14.8 – 20.8)                   |
| Total Dependence (n = 86)                         | 13.5 (11.0 – 16.5)                   |
| Median (IQR) FCI Score (n = 532)                  | 3.00 (2.00)                          |
| Neurological Disease (n = 641)                    | 41.2 (37.3 – 45.1) (n = 264)         |
| Depression (n = 673)                              | 28.4 (25.0 – 32.0) (n = 191)         |
| Anxiety (n = 673)                                 | 19.2 (16.3 – 22.3) (n = 129)         |
| Daytime Dozing (n = 665)                          | 34.9 (31.3 – 38.6) (n = 232)         |
| Chronic Constipation (n = 669)                    | 38.4 (34.7 – 42.2) (n = 257)         |
| Fall in previous 12 months (n = 667)              | 28.5 (25.07 – 31.93) (n = 190)       |
| Behaviours that Challenge (n = 677)               | 52.0 (48.2 – 55.8) (n = 352)         |
| <b>Polypharmacy (n = 677)</b>                     |                                      |
| No polypharmacy (n = 256)                         | 37.8 (34.1 – 41.6)                   |
| Polypharmacy (n = 258)                            | 38.1 (34.4 – 41.9)                   |
| Excessive polypharmacy (n = 163)                  | 24.1 (20.9 – 27.5)                   |
| Exposure to any Medications (n = 677)             | 95.1 (93.47 – 96.73) (n = 644)       |
| Median (IQR) no. of Medications                   | 6.00 (6.00)                          |
| Median (IQR) no. of DBI Medications               | 2.00 (3.00)                          |
| Median (IQR) no. of non-DBI Medications           | 4.00 (5.00)                          |
| <b>Exposure to DBI Medications</b>                |                                      |
| Anticholinergic only (n = 347)                    | 51.3 (47.5 – 55.1)                   |
| Sedative only (n = 217)                           | 32.1 (28.6 – 35.6)                   |
| Total (anticholinergic and/or sedative) (n = 532) | 78.6 (75.3 – 81.6)                   |
| <b>DBI Score</b>                                  |                                      |
| 0 (n = 145)                                       | 21.4 (18.31 – 24.49)                 |
| 0 > 1 (n = 165)                                   | 24.4 (21.16 – 27.64)                 |
| ≥ 1 (n = 367)                                     | 54.2 (50.45 – 57.95)                 |
| Median (IQR) DBI Score                            | 1.10 (±1.73)                         |
| Median (IQR) DBA Score                            | 1.00 (±1.13)                         |
| Median (IQR) DBS Score                            | 0.69 (±0.79)                         |
| Range (min-max)                                   | 0 – 5.47                             |

Table 3.3 displays the exposure of participants to at least one member of the individual therapeutic drug classes in descending order and classified by anticholinergic or sedative status. Overall, 44% (n = 298) of participants were exposed to one or more antipsychotic medications with risperidone being most common (15.7%, n = 106). The most commonly reported sedative class was the ATC class N05C (Hypnotics and Sedatives), and the most commonly reported drug within this class was zopiclone, which 2.8% (n = 19) of the participants reported taking on a regular basis. Valproic acid was the most commonly reported drug overall, with 19.4% (n = 131) of participants exposed to this medication. Other therapeutic classes reported by <5% in decreasing prevalence included in *Supporting Information Table S 3.4*.

Table 3.3 Prevalence of exposure to drug classes with anticholinergic and sedative activity

| Therapeutic DBI Drug Class and Most Frequently Reported Medicine within Each Class              | ATC Code                | % of Population Exposed, (95% CI) (n)                          |
|-------------------------------------------------------------------------------------------------|-------------------------|----------------------------------------------------------------|
| <b>Anticholinergic</b>                                                                          |                         |                                                                |
| <b>Antipsychotics</b><br>Risperidone                                                            | N05A<br>N05AX08         | 44.0 (40.26 – 47.74) (n = 298)<br>15.7 (12.9 – 18.4) (n = 106) |
| <b>Antiepileptics</b><br>Valproic Acid                                                          | N03A<br>N03AG01         | 42.4 (38.68 – 46.12) (n = 287)<br>19.4 (16.4 – 22.3) (n = 131) |
| <b>Antidepressants</b><br>Escitalopram                                                          | N06A<br>N06AB10         | 27.8 (24.43 – 31.17) (n = 188)<br>5.8 (4.0 – 7.5) (n = 39)     |
| <b>Anticholinergic Agents</b><br>Biperiden                                                      | N04A<br>N04AA02         | 13.0 (10.47 – 15.52) (n = 88)<br>8.7 (6.6 – 10.8) (n = 59)     |
| <b>Anxiolytics</b><br>Diazepam                                                                  | N05B<br>N05BA01         | 11.5 (9.1 – 13.9) (n = 78)<br>6.1 (4.3 – 7.9) (n = 41)         |
| <b>Diuretics</b><br>Furosemide                                                                  | C03(A, C, D)<br>C03CA01 | 7.4 (5.43 – 9.37) (n = 55)<br>5.0 (3.4 – 6.7) (n = 34)         |
| <b>Antihistamines</b><br>Cetirizine                                                             | R06A<br>R06AE07         | 5.5 (3.78 – 7.22) (n = 37)<br>1.6 (0.7 – 2.6) (n = 11)         |
| <b>Sedative</b>                                                                                 |                         |                                                                |
| <b>Hypnotics &amp; Sedatives</b><br>Zopiclone                                                   | N05C<br>N05CF01         | 7.1 (5.17 – 9.03) (n = 48)<br>2.8 (1.6 – 4.1) (n = 19)         |
| <b>Anti-Dementia Drugs</b><br>Donepezil                                                         | N06D<br>N06DA02         | 3.4 (2.03 – 4.77) (n = 23)<br>2.2 (1.1 – 3.3) (n = 15)         |
| <b>Drugs for Benign Prostate Hypertrophy</b><br>Tamsulosin                                      | G04C<br>G04CA02         | 1.8 (0.8 – 2.8) (n = 12)<br>1.8 (0.8 – 2.8) (n = 12)           |
| Other therapeutic classes reported by <5% listed in <i>Supporting Information Table S 3.4</i> . |                         |                                                                |

*Supporting Information Table S 3.5* displays the univariate analysis of DBI score and specific population parameters.

Table 3.4 Multivariate Analysis of DBI Scores and Potential Adverse Effects (n = 484)<sup>a</sup>

|                                                                                                                                                                                                                                                                                                                                   | DBI 0 > 1           |              | DBI ≥1              |              |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|--------------|---------------------|--------------|
|                                                                                                                                                                                                                                                                                                                                   | OR (95% CI)         | <i>p</i>     | OR (95% CI)         | <i>p</i>     |
| <b>Daytime Dozing</b>                                                                                                                                                                                                                                                                                                             |                     |              |                     |              |
| No                                                                                                                                                                                                                                                                                                                                | 1 (reference)       |              | 1 (reference)       |              |
| Yes                                                                                                                                                                                                                                                                                                                               | 1.108 (0.568;2.162) | <i>0.764</i> | 1.670 (0.916;3.044) | <i>0.094</i> |
| <b>Chronic Constipation</b>                                                                                                                                                                                                                                                                                                       |                     |              |                     |              |
| No                                                                                                                                                                                                                                                                                                                                | 1 (reference)       |              | 1 (reference)       |              |
| Yes                                                                                                                                                                                                                                                                                                                               | 1.276 (0.643;2.532) | <i>0.486</i> | 1.679 (0.902;3.123) | <i>0.102</i> |
| <b>Fall in the Previous 12 Months</b>                                                                                                                                                                                                                                                                                             |                     |              |                     |              |
| No                                                                                                                                                                                                                                                                                                                                | 1 (reference)       |              | 1 (reference)       |              |
| Yes                                                                                                                                                                                                                                                                                                                               | 0.611 (0.303;1.231) | <i>0.168</i> | 1.113 (0.605;2.046) | <i>0.731</i> |
| a. Reference category: DBI 0. P<0.05 is significant, all significant factors in bold. Cox and Snell $r^2 = 0.245$ , Nagelkerke $r^2 = 0.284$ . Data are adjusted odds ratio (OR). Model adjusted for gender, age, level of ID, type of residence, behaviours that challenge, comorbidities (FCI) and number of non-DBI medicines. |                     |              |                     |              |

Multivariate regression analysis of the relationship between DBI scores and potential adverse effects (*Table 3.4*), adjusted for gender, age, type of residence, level of ID, behaviours that challenge, comorbidities (FCI) and number of non-DBI medicines, revealed that daytime dozing, chronic constipation and history of falls were not significantly associated with DBI score > 0 ( $p = 0.764$  &  $0.094$ ;  $p = 0.486$  &  $0.102$ ;  $p = 0.168$  &  $0.731$ , respectively).



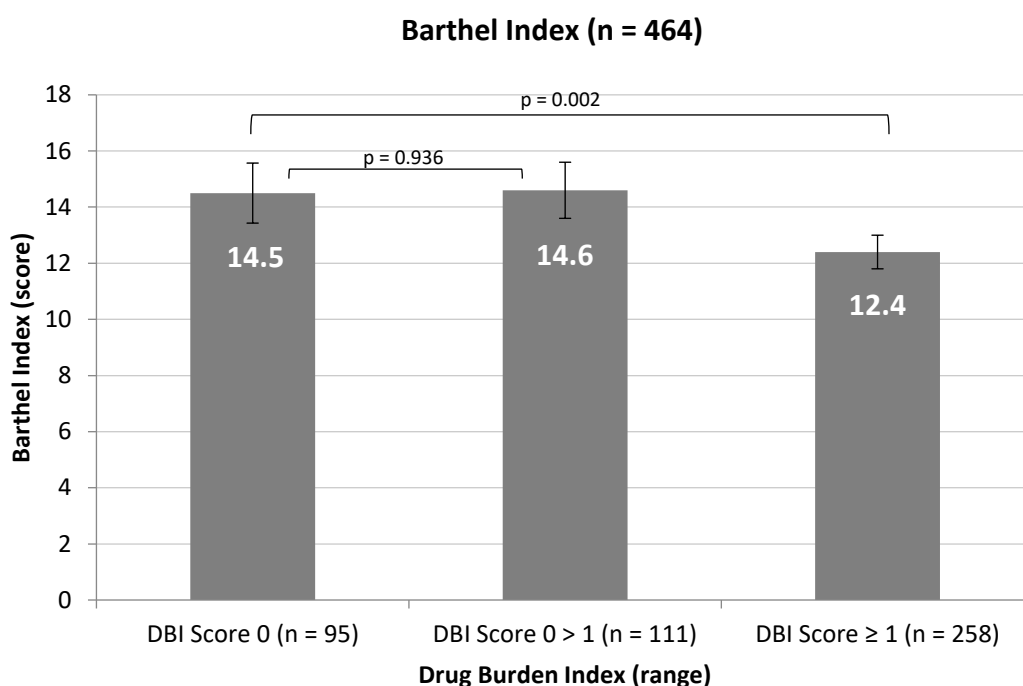


Figure 3.3 Analysis of Covariance for the association of adjusted means of Barthel Index with increasing Drug Burden Index. Means are adjusted for gender, age, level of ID, comorbidities (FCI), behaviours that challenge and history of falls. Drug Burden Index is grouped into three intervals (0, 0 > 1 and  $\geq 1$ ). Error bars show 95% confidence interval (CI). Barthel Index instrumental ADLs – lower score indicates worse function.

Figure 3.3 displays adjusted means for Barthel Index ADLs.

Significantly lower scores in Barthel Index ADLs were identified for those with a DBI score of  $\geq 1$  ( $p = 0.002$ ; mean score 12.4, 95% CI 11.7 – 13.0) compared to those with DBI 0 (mean score 14.5, 95% CI 13.4 – 15.6) after adjusting for cofounders (gender, age, level of ID, comorbidities (FCI), behaviours that challenge and history of falls).

## 3.5 Discussion

### 3.5.1 Principal findings

To our knowledge this is the first study to describe Drug Burden Index in a representative population of older adults with an intellectual disability. Our findings reveal that in contrast to existing studies on older adults without ID, older people with ID had higher cumulative exposure to both sedative and anticholinergic medicines; over three-quarters of the study population

were exposed to at least one anticholinergic or sedative medication (DBI Score > 0) (*Table 3.2*). This reflects the higher levels of multimorbidity in this population, in particular mental health and neurological morbidity (57). After adjusting for confounders, multivariate analysis identified that daytime dozing, chronic constipation and history of falls were not significantly associated with DBI score ( $p > 0.05$ , *Table 3.4*). Analysis of covariance identified higher levels of dependence in Barthel Index ADLs as DBI score increased ( $p < 0.05$ , *Figure 3.3*).

### **3.5.2 Comparison with other studies**

The magnitude of the DBI scores were much higher in our study than in published studies of older adults in the general population (*Supporting Information Table S 3.6*). Patterns of multimorbidity in people with ID differ substantially from those in people without ID (100, 243). In particular, depression rates varied between 9 – 22% in older adults without ID in preceding DBI studies, while lifetime prevalence was reported at 28% in IDS-TILDA participants. Patterns of neurological disease were also different. Epilepsy was the predominant neurological condition in IDS-TILDA (36%) (52), levels of epilepsy are higher in people with ID compared to those in the general population (82). Other DBI studies most commonly reported dementia or cognitive impairment (151, 153, 154, 164, 196, 210, 214, 220) both of which are difficult to assess in people with ID (*Supporting Information Table S 3.6*).

As a result, there is a noticeable contrast in exposure and contributing therapeutic classes observed in those with ID compared to older adults without ID. Antipsychotic and antiepileptic medicines are most prevalent in our cohort (44% and 42%, respectively, *Table 3.3*) and are frequently associated with anticholinergic effects (103), while only between 1 – 10% of participants in previous DBI studies of older adults have reported exposure to antipsychotics and 2% reported exposure to antiepileptics. (151, 154). In the population without ID, sedative exposure was higher in two of the five studies while anticholinergic exposure was substantially lower compared to the anticholinergic burden (51%) in this population (*Supporting Information Table S 3.6*).

### **3.5.3 Prevalence of therapeutic drug classes**

Antiepileptic medications (ATC N03A) accounted for over one-quarter of the overall burden (*Table 3.3*), in contrast to studies of drug burden in the existing literature which do not report antiepileptic medication as a significant contributor to drug burden (146, 150-155, 210, 212, 223). In addition to causing anticholinergic and sedative effects, antiepileptic medications also require careful monitoring and have the potential to introduce other clinical implications,

including drug-drug interactions (271). Multiple antipsychotic use is prevalent in this population and anticholinergics such as biperiden are often co-prescribed for movement disorders [1] and these add significantly to the anticholinergic burden along with antidepressants and anxiolytics (Table 3.3). The concurrent use of antipsychotics and anticholinergics requires caution (272) and has been associated with constipation and laxative use [1] in an earlier wave of this cohort. Hypnotics and sedatives were the dominant component of the sedative burden (7.1% of population exposed) while anti-dementia drugs were less prevalent (3.4%). However, with drugs from 38 therapeutic classes (Table 3.3 and Supporting Information Table S 3.4) contributing to the DBI scores of the participants, the sources of the burden reflect the diverse range of drugs used in people with ID (100).

### 3.5.4 Potential adverse effects and drug burden

Although levels of daytime dozing were high (35%), it was not significantly associated with DBI score after adjusting for confounding factors (DBI 0 > 1,  $p = 0.764$ ; DBI  $\geq 1$ ,  $p = 0.094$ , Table 3.4). The effect of medications on sleep in adults with ID not clear cut. It has been reported that the circadian sleep-wake rhythm in older adults with ID is less stable and more fragmented than older adults without ID. Higher age, dementia, depression and epilepsy have been associated with this disturbed sleep cycle, while no independent association was found with taking antiepileptic, antidepressant, antipsychotic or benzodiazepine medications (72). In contrast, a systematic review of sleep disturbance in ID identified a number of studies which found associations between medication use and sleep problems (273). These studies, however, examined early morning waking, broken sleep, snoring and nocturnal incontinence rather than daytime dozing. As sleep patterns are different in this population and a number of different factors may be influencing levels of daytime sedation, and since the DBI combines sedative and anticholinergic measures, it is not surprising that a conclusive association was not found. Further investigation is required to examine associations between DBI, its sedative and anticholinergic components and other measures of sleep quality in this population.

After adjusting for confounders, we identified no association between chronic constipation and higher DBI scores (DBI 0 > 1,  $p = 0.486$ ; DBI  $\geq 1$ ,  $p = 0.102$ , Table 3.4). However, it is noteworthy that almost nine in ten of those reporting constipation were exposed to anticholinergic and/or sedative medication, and almost two-thirds had a DBI score of  $\geq 1$  (Supporting Information Table S 3.5). Overall there is a high prevalence of constipation among the population with ID (38%). Although the cause of constipation is multifactorial, it is acknowledged that medications with

anticholinergic action contribute to constipation in older people (119). It has been found that medications are strongly associated with the presence of constipation in older adults with ID, in particular antiepileptic medications and antipsychotic medications, due to slowing down the transit times of the large bowel as a result of their anticholinergic activity (103, 274). People reporting constipation generally also report lower health-related Quality of Life (275-277), thus the impact of the anticholinergic medication component of the DBI should not be underestimated in this area.

History of falls was not significant after multivariate regression in our population of older adults with ID (DBI 0 > 1,  $p = 0.168$ ; DBI  $\geq 1$ ,  $p = 0.731$ , *Table 3.4*), which is in contrast to the findings of DBI studies in older adults without ID (154, 223). It is possible that the susceptibility to falls from anticholinergic and sedative medications may be different in older adults with ID as the long-term use of these medications in this population may result in the absence of the “starting effect” which has been associated with falls in adults who commence these types of medications later in life (278). The susceptibility to anticholinergic and/or sedative effects may vary with age and with the cause of ID and pattern of multimorbidity in this cohort. In addition, seizure disorders have been identified as one of the major risk factors for falls in adults with ID (279, 280), thus antiepileptic medications, despite being anticholinergic and sedative in nature, may provide seizure control which could affect the relationship between DBI and rate of falls differently to that observed in the general population. Individuals with higher dependency and/or multimorbidity may be monitored more closely for falls and risk of falls, or may be immobile due to factors such as poor health and level of disability.

It is worth noting that confidence intervals across all the categories were quite wide, thereby indicating there was still wide variation remaining after adjusting for confounding factors.

### **3.5.5 Factors associated with drug burden and physical function measures**

Higher Drug Burden Index scores were significantly associated with higher levels of dependency in Barthel Index ADLs after adjusting for relevant confounders including level of ID in this study ( $p < 0.05$ , *Figure 3.3*). This is similar to the findings of a study of DBI and instrumental ADLs in older Australian men (151). Compared to older adults without ID, people with ID may have lower scores in the Barthel Index which in turn may further be affected by Drug Burden Index. However as this is a cross-sectional study it is not possible to establish causality, but with repeated assessments over several waves of the cohort further analysis will be possible.

### **3.5.6 Impact of findings on practice**

Difficulties in patient assessment, including, but not limited to, problems with communication, staff shortages and time constraints, can hinder care and leave individuals with ID vulnerable to prescribing that is not regularly reviewed, the “prescribing cascade” or initiation of inappropriate drugs (50). Devolving responsibility and fragmentation of care have been identified as barriers to de-prescribing anticholinergic and sedative medications in older adults without ID (281). This is particularly relevant to older people with ID, due to the variety of medical conditions experienced. Higher rates of epilepsy, as outlined above, require the attention of specialist care, but unless there is adequate multidisciplinary involvement in review, de-prescribing cannot take place, as general practitioners feel specialist prescribers must conduct the de-prescribing and vice versa (281, 282).

People with ID in older age profile may experience different susceptibility to certain adverse effects of anticholinergic and sedative medications compared to the general population. A recent study in the United Kingdom found people with ID are more likely to experience movement-related side effects from antipsychotic medications (109). The effect of the drug burden itself may compromise individuals who have difficulties expressing their symptoms and whose expression of adverse drug effects may be limited. This may make it more challenging for carers and clinicians to assess and monitor these patients effectively. Therefore, the DBI tool offers a valuable tool to review these medications regimens (283).

The association of drug burden with poor performance in Barthel Index ADLs indicates the potential impact this burden has on the quality of life of older adults with intellectual disabilities. Further longitudinal examination of this burden is necessary. Evidence here should encourage greater attention to reducing polypharmacy, selection of alternative treatment options and finding means to systematically reduce sedative and anticholinergic drug burden.

Recognition of the impact of anticholinergic and sedative medications on physical and cognitive function, collaboration between patients, carers and healthcare professionals and reaction to de-prescribing “triggers” have all been acknowledged as facilitators for optimising medication use in people without ID (281). Indeed, targeted de-prescribing of drugs with anticholinergic and sedative effects is already underway in the older age population without ID, guided by the DBI (284).

While regular medication reviews are part of good case management, this is a population for whom review is often inhibited by difficulties in communication, high levels of morbidity and polypharmacy and utilisation of numerous specialist and non-specialist prescribers. The DBI

could be a screening tool to trigger medication review for older adults with ID. It can alert the prescriber to the existing status of the individual, make them mindful of the current burden, trigger a more frequent review of medications, allow for possible rationalisation of therapy, and inform further prescribing.

The potential of the DBI tool as a trigger for de-prescribing, and an enabler for medication review of people with ID, who often cannot speak for themselves, should be investigated. Dissemination of the findings of this study, education of professionals, patients and carers in optimising the use of anticholinergics and sedatives, encouraging the identification of adverse effects from these medicines and recognising the absence of symptoms can contribute to the optimising of medication use in this population. Longitudinal follow-up is required to fully establish the association of DBI with this population, as this study provides only baseline data which may be further investigated in future waves of the study.

### **3.5.7 Strengths and limitations**

Our study has five important strengths. First, the use of a large, nationally representative sample of older adults with intellectual disabilities which was selected at random in Ireland allowed sufficient power for multivariate analysis and is representative of the older population with ID in Ireland. Second, comprehensive medication data was recorded for the majority of Wave 2 participants (95.6%) and this medication data was cross-checked by interviewers. While collection of medication data was carried out by non-pharmacists, the training provided by a pharmacist (MO'D) and design of the medication data section facilitated high quality data capture. Participants and/or their proxies received the medication data section in advance of the face-to-face interview, allowing time to consult medical files to accurately capture this information. Third, detailed assessment of health characteristics provided data on potential confounding factors for our analysis. Fourth, we used the Drug Burden Index, which is a score that has been validated across a number of studies internationally and is a robust measure of anticholinergic and sedative drug effects. It also takes into account the dose each participant is exposed to, which is useful as adverse effects may often be dose-related. A comprehensive approach was utilised to create the Drug Burden Index inventory for use in an Irish population, and this list was both developed and approved by consensus of three pharmacists. Fifth, objective measures of physical performance were selected for examining physical function outcomes.

There are a number of limitations; as this is a cross-sectional observational study, we can only describe the associations between Drug Burden Index scores, potential adverse effects and physical function outcomes. This correlation does not imply causality, particularly with respect to physical function. While it is not possible to establish the effect of DBI scores on functional decline at present, this study offers the scope for further longitudinal analysis of data from IDS-TILDA by identifying the baseline levels of exposure and function in this population.

Although bias was removed where possible in our multivariate analysis by making adjustment for confounders, residual confounding factors may remain.

With respect to the multivariate regression and Barthel Index measure of dependency, it should be noted that the numbers of participants with all information available is restricted to 70% of the overall population due to missing data of participants who were unable to complete these elements of the interview. Thus, interpretation of this data should be conservative as it may not be fully representative of the entire population. The highest rates of missing data were observed in those with mild/moderate level of ID and those living independently or in community group homes.

In conclusion, this study has highlighted extensive use of medications with both anticholinergic and sedative properties in older adults with intellectual disabilities. This is the first time a study has examined the combined anticholinergic and sedative exposure of a cohort of people with ID. In addition, this high burden has been shown to have an association with higher dependency in Barthel Index ADLs. Use of the Drug Burden Index as a tool for clinicians could help guide prescribing practice and multidisciplinary involvement would be essential for the development of optimal medicine regimens and improvement of health outcomes for older adults with ID.

## Supporting Information Description SD 3.1 Behaviours Which Challenge Measure

Behaviours which challenge (BWC) were defined as any behaviour which:

“(1) is a barrier to a person participating in and contributing to their community (including both active and passive behaviours); (2) undermines directly or indirectly a person’s rights, dignity or quality of life, and (3) poses a risk to the health and safety of a person and those with whom they live and work” (74)

The responses to two questions included in the Wave 2 Pre-Interview Questionnaire (PIQ) measured behaviours which challenge:

- (1) *“Do you ever become annoyed, frustrated or angry when things don’t work out the way you want them?”* The response options were yes, no or don’t know.

Participants who answered yes to this question were requested to answer a second question regarding BWC. (2) *“If yes, what do you do? Please tick ALL that apply.”*

| Response                 | Tick |
|--------------------------|------|
| Scream                   |      |
| Hit out                  |      |
| Throw things             |      |
| Self-injure              |      |
| Do nothing/do not react  |      |
| Other                    |      |
| If other, please tell us |      |

Responses were recoded and placed into one of five categories (1) verbal aggression (2) physical aggression, (3) destructive behaviour, (4) self-injurious behaviour or (5) “other” behaviour which challenges. “Scream” was recoded as verbal aggression, “hit out” was recoded as physical aggression, “throw things” was recoded as “destructive behaviour”, “self-injury” was recoded as self-injurious behaviour. Responses to the “other, please tell us” option were also recoded into one of these five categories where applicable.



Supporting Information Table S 3.1 Modified Barthel Index

| IDS-TILDA Question                                                                                                                                  | IDS-TILDA Codes       | Modified to: | Modified Barthel Index Codes |
|-----------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|--------------|------------------------------|
| <b>Mobility</b>                                                                                                                                     |                       |              |                              |
| Please indicate the level of difficulty, if any, you have with walking 100 yards                                                                    | 1=No difficulty       | →            | 3=Independent                |
|                                                                                                                                                     | 2=Some difficulty     | →            | 2=Walks with help            |
|                                                                                                                                                     | 3=A lot of difficulty | →            | 1=Wheelchair independent     |
|                                                                                                                                                     | 4=Cannot do at all    | →            | 0=Immobile                   |
| <b>Stairs</b>                                                                                                                                       |                       |              |                              |
| Please indicate the level of difficulty, if any, you have with climbing one flight of stairs without resting.                                       | 1=No difficulty       | →            | 2=Independent                |
|                                                                                                                                                     | 2=Some difficulty     | →            | 1=Needs help                 |
|                                                                                                                                                     | 3=A lot of difficulty | →            | 0=Unable                     |
|                                                                                                                                                     | 4=Cannot do at all    | →            |                              |
| <b>Dressing</b>                                                                                                                                     |                       |              |                              |
| Please indicate the level of difficulty, if any, you have with dressing, including putting on shoe and socks.                                       | 1=No difficulty       | →            | 2= Independent               |
|                                                                                                                                                     | 2=Some difficulty     | →            | 1= Needs help                |
|                                                                                                                                                     | 3=A lot of difficulty | →            | 0=Unable                     |
|                                                                                                                                                     | 4=Cannot do at all    | →            |                              |
| <b>Bathing</b>                                                                                                                                      |                       |              |                              |
| Please indicate the level of difficulty, if any, you have with bathing or showering.                                                                | 1=No difficulty       | →            | 1= Independent               |
|                                                                                                                                                     | 2=Some difficulty     | →            | 0= Dependent                 |
|                                                                                                                                                     | 3=A lot of difficulty | →            |                              |
|                                                                                                                                                     | 4=Cannot do at all    | →            |                              |
| <b>Grooming</b>                                                                                                                                     |                       |              |                              |
| Please indicate the level of difficulty, if any, you have with cleaning your teeth/taking care of your dentures.                                    | 1=No difficulty       | →            | 1= Independent               |
|                                                                                                                                                     | 2=Some difficulty     | →            | 0= Needs help                |
|                                                                                                                                                     | 3=A lot of difficulty | →            |                              |
|                                                                                                                                                     | 4=Cannot do at all    | →            |                              |
| <b>Feeding</b>                                                                                                                                      |                       |              |                              |
| Please indicate the level of difficulty, if any, you have with eating such as cutting up your food, use of utensils, drinking from a cup/glass etc? | 1=No difficulty       | →            | 2=Independent                |
|                                                                                                                                                     | 2=Some difficulty     | →            | 1=Needs help                 |
|                                                                                                                                                     | 3=A lot of difficulty | →            | 0= Dependent                 |
|                                                                                                                                                     | 4=Cannot do at all    | →            |                              |
| <b>Transfer</b>                                                                                                                                     |                       |              |                              |
| Please indicate the level of difficulty, if any, you have with getting in or out of bed.                                                            | 1=No difficulty       | →            | 3= Independent               |
|                                                                                                                                                     | 2=Some difficulty     | →            | 2=Minor Help                 |
|                                                                                                                                                     | 3=A lot of difficulty | →            | 1 =Major help                |
|                                                                                                                                                     | 4=Cannot do at all    | →            | 0=Unable                     |
| <b>Toileting</b>                                                                                                                                    |                       |              |                              |
| Please indicate the level of difficulty, if any, you have with using the toilet, including getting up or down.                                      | 1=No difficulty       | →            | 2=Independent                |
|                                                                                                                                                     | 2=Some difficulty     | →            | 1=Needs help                 |
|                                                                                                                                                     | 3=A lot of difficulty | →            | 0= Dependent                 |
|                                                                                                                                                     | 4=Cannot do at all    | →            |                              |
| <b>Bladder Continence</b>                                                                                                                           |                       |              |                              |
| During the last 12 months, have you lost any amount of urine beyond your control?                                                                   | Yes & Yes             | →            | 0=Incontinent                |
| Did this happen more than once during a 1-month period?                                                                                             | Yes & No              | →            | 1=Occasional (In last month) |
|                                                                                                                                                     | No                    | →            | Continent                    |
| <b>Bowel Continence</b>                                                                                                                             |                       |              |                              |
| During the last 12 months, have you lost any amount of faeces beyond your control?                                                                  | Yes & Yes             | →            | 0=Incontinent                |
| Did this happen more than once during a 1-month period?                                                                                             | Yes & No              | →            | 1=Occasional (In last month) |
|                                                                                                                                                     | No                    | →            | Continent                    |

Supporting Information Table S 3.2 Modified Functional Comorbidity Index

| FCI Item                                                                                                                                                                                                                                                                     | IDS-TILDA Variable                                                                                                                                                                                                                                                                                                                                                                              | Score                 |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| Arthritis (rheumatoid arthritis and osteoarthritis)                                                                                                                                                                                                                          | <i>Has arthritis (including osteoarthritis or rheumatism)</i>                                                                                                                                                                                                                                                                                                                                   | 1                     |
| Osteoporosis                                                                                                                                                                                                                                                                 | <i>Has Osteoporosis/thin or brittle bones</i><br><i>Has QUS evidence for Osteoporosis and Osteopenia</i><br><i>Has scoliosis (all participants with scoliosis had evidence of osteoporosis/osteopenia)</i>                                                                                                                                                                                      | 1                     |
| Asthma                                                                                                                                                                                                                                                                       | <i>Has Asthma</i>                                                                                                                                                                                                                                                                                                                                                                               | 1                     |
| Chronic obstructive pulmonary disease (COPD), acute respiratory distress syndrome (ARDS), emphysema                                                                                                                                                                          | <i>Has chronic lung disease</i>                                                                                                                                                                                                                                                                                                                                                                 | 1                     |
| Angina                                                                                                                                                                                                                                                                       | <i>Has had angina</i>                                                                                                                                                                                                                                                                                                                                                                           | 1                     |
| Congestive heart failure (or heart disease)                                                                                                                                                                                                                                  | <i>Has congestive heart failure</i><br><i>Has a heart murmur</i><br><i>Has an abnormal heart rhythm</i><br><i>Have had angioplasty or stent</i><br><i>Have ever had open heart surgery</i><br><i>Has other heart trouble</i>                                                                                                                                                                    | 1                     |
| Heart attack (myocardial infarction; MI)                                                                                                                                                                                                                                     | <i>Has had a heart attack</i>                                                                                                                                                                                                                                                                                                                                                                   | 1                     |
| Neurological disease (e.g. Multiple sclerosis (MS), Parkinson's)                                                                                                                                                                                                             | <i>Has Parkinson's disease/</i><br><i>Has Multiple sclerosis/</i><br><i>Has Alzheimer's disease/</i><br><i>Has Spina bifida/</i><br><i>Has dementia, organic brain syndrome or senility/</i><br><i>Has epilepsy/</i><br><i>Has Cerebral Palsy/</i><br><i>Has muscular dystrophy</i>                                                                                                             | 1                     |
| Stroke or transient ischaemic attack (TIA)                                                                                                                                                                                                                                   | <i>Has had stroke</i><br><i>Has had ministroke/TIA</i>                                                                                                                                                                                                                                                                                                                                          | 1                     |
| Peripheral vascular disease                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                 | Excluded <sup>a</sup> |
| Diabetes I or II                                                                                                                                                                                                                                                             | <i>Has diabetes</i><br><i>Diabetic diet</i>                                                                                                                                                                                                                                                                                                                                                     | 1                     |
| Upper gastrointestinal (GI) disease (e.g. ulcer, hernia, reflux)                                                                                                                                                                                                             | <i>Has Gastroesophageal reflux disease/</i><br><i>Has stomach ulcers</i>                                                                                                                                                                                                                                                                                                                        | 1                     |
| Depression                                                                                                                                                                                                                                                                   | <i>Has depression</i><br><i>Has manic depression</i>                                                                                                                                                                                                                                                                                                                                            | 1                     |
| Anxiety or panic disorder                                                                                                                                                                                                                                                    | <i>Has anxiety condition</i>                                                                                                                                                                                                                                                                                                                                                                    | 1                     |
| Visual impairment (e.g., cataracts, glaucoma, macular degeneration)                                                                                                                                                                                                          | <i>Has age related macular degeneration/</i><br><i>Has glaucoma/</i><br><i>Has cataracts/</i><br><i>Has had cataracts surgery</i><br><i>Has other eye disease/</i><br><i>Have you been prescribed glasses or contact lenses?</i>                                                                                                                                                                | 1                     |
| Hearing impairment (i.e. very hard of hearing, even with hearing aids)                                                                                                                                                                                                       | <i>Is your hearing (with or without a hearing aid)... fair/poor?</i><br><i>Use of: Hearing aid (all of the time)</i><br><i>Hearing aid (some of the time)</i><br><i>Phone messaging service</i><br><i>Amplifier</i>                                                                                                                                                                             | 1                     |
| Degenerative disc disease (e.g. back disease, spinal stenosis, or severe chronic back pain)                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                 | Excluded <sup>a</sup> |
| Overweight/Obese <sup>b</sup>                                                                                                                                                                                                                                                | <i>Aggregated score of objective measure of:</i> <ul style="list-style-type: none"> <li><i>BMI (calculated from height and weight)</i></li> <li><i>Weight and ulnar length to estimate height (where height could not be measured)</i></li> <li><i>Mid Upper Arm Circumference measure (where could not measure weight or height eg wheelchair user)</i></li> </ul> <i>Weight reducing diet</i> | 1                     |
| MAX SCORE=16                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                 |                       |
| <p>a. Excluded as there was inadequate participant data collected to capture this condition.</p> <p>b. These two categories were aggregated as the Mid Upper Arm Circumference measure yields only three categories of result: underweight, normal and overweight/obese.</p> |                                                                                                                                                                                                                                                                                                                                                                                                 |                       |

Supporting Information Table S 3.3 Description of Missing Physical Function Scores

|                                | <b>Missing FCI<br/>% (% CI) (n)</b> | <b>Missing Barthel Index<br/>% (% CI) (n)</b> |
|--------------------------------|-------------------------------------|-----------------------------------------------|
| <b>Gender</b>                  |                                     |                                               |
| Male (n = 297)                 | 26.3 (21.6 – 31.5) (n = 78)         | 7.4 (4.9 – 11.0) (n = 22)                     |
| Female (n = 380)               | 17.6 (14.1 – 21.8) (n = 67)         | 5.3 (3.4 – 8.0) (n = 20)                      |
| <b>Level of ID</b>             |                                     |                                               |
| Mild (n = 149)                 | 26.8 (20.8 – 34.5) (n = 40)         | 6.0 (3.2 – 11.1) (n = 9)                      |
| Moderate (n = 287)             | 19.5 (15.3 – 24.5) (n = 56)         | 7.0 (4.6 – 10.5) (n = 20)                     |
| Severe/Profound (n = 188)      | 18.1 (13.2 – 24.2) (n = 34)         | 4.3 (2.2 – 8.2) (n = 8)                       |
| <b>Type of Residence</b>       |                                     |                                               |
| Independent (n = 102)          | 32.4 (24.1 – 41.9) (n = 33)         | 3.9 (1.5 – 9.7) (n = 4)                       |
| Community Group Home (n = 298) | 23.2 (18.7 – 28.3) (n = 69)         | 7.7 (5.2 – 11.3) (n = 23)                     |
| Residential Care (n = 276)     | 15.2 (11.5 – 19.9) (n = 42)         | 5.1 (3.0 – 8.3) (n = 14)                      |
| <b>Age Range</b>               |                                     |                                               |
| 44 – 49 years (n = 187)        | 24.6 (19.0 – 31.2) (n = 46)         | 5.3 (2.9 – 9.6) (n = 10)                      |
| 50 – 64 years (n = 347)        | 19.3 (15.5 – 23.8) (n = 67)         | 5.8 (3.8 – 8.7) (n = 20)                      |
| 65+ years (n = 142)            | 21.8 (15.8 – 29.3) (n = 31)         | 7.7 (4.4 – 13.3) (n = 11)                     |

Supporting Information Table S 3.4 Other therapeutic classes reported by <5% in decreasing prevalence

**Other therapeutic classes reported by <5% in decreasing prevalence:** Urologicals (G04B), Antihypertensives (C02(A, C)), Beta Blockers (C07A), Antiemetics & Antinauseants (A04A), Opioids (N02A), Drugs for Functional Gastrointestinal Disorders (A03(A, B, F)), Muscle Relaxants (M03B), Drugs for Peptic Ulcer Disease & Gastro-Oesophageal Reflux Disease (A02B), ACE Inhibitors (C09A), Antipropulsives (A07D), Hormone Antagonists (LO2B), Lipid Modifying Agents (C10A), Antiinflammatory & Antirheumatic Products (M01A), Antithrombotic Agents (B01A), Corticosteroids for Systemic Use (H02A), Dopaminegic Agents (N04B), Cardiac Therapy (C01[A, B]), Immunosuppressants (L04A), Antiandrogens (G03H), Mydriatics & Cycloplegics (S01F), Direct Acting Antivirals (J05A), Drugs used in Diabetes (A10B), Macrolides (J01F), Other Analgesics & Antipyretics (N02B), Other Gynaecologicals (G02C), Other Nervous System Drugs (N07X), Progestogens (G03D), Cough Suppressants (R05D), Selective Calcium Channel Blockers (C08C)

Supporting Information Table S 3.5 Drug Burden Index Binary Table

| <b>Population Characteristics<br/>(n = 677)</b>                                                        | <b>DBI Score 0<br/>(n = 145)<br/>% (% CI) (n)</b>                                                                   | <b>DBI Score 0 &gt; 1<br/>(n = 165)<br/>% (% CI) (n)</b>                                                            | <b>DBI Score ≥ 1<br/>(n = 367)<br/>% (% CI) (n)</b>                                                                    | <b>p<sup>a</sup></b> |
|--------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|----------------------|
| <b>Gender (n = 677)</b><br>Male<br>Female                                                              | 25.6 (20.64 – 30.56) (n = 76)<br>18.2 (14.32 – 22.08) (n = 69)                                                      | 20.5 (15.91 – 25.09) (n = 61)<br>27.4 (22.92 – 31.88) (n = 104)                                                     | 53.9 (48.23 – 59.57) (n = 160)<br>54.5 (49.49 – 59.51) (n = 207)                                                       | <b>0.024</b>         |
| <b>Age (n = 676)</b><br>44 – 49 years<br>50 – 64 years<br>65 years +                                   | 28.3 (21.84 – 34.76) (n = 53)<br>21.0 (16.71 – 25.29) (n = 73)<br>13.4 (7.8 – 19.0) (n = 19)                        | 23.0 (16.97 – 29.03) (n = 43)<br>25.7 (21.1 – 30.3) (n = 89)<br>23.2 (16.26 – 30.14) (n = 33)                       | 48.7 (41.54 – 55.86) (n = 91)<br>53.3 (48.05 – 58.55) (n = 185)<br>63.4 (55.48 – 71.32) (n = 90)                       | <b>0.016</b>         |
| <b>Level of ID (n = 624)</b><br>Mild<br>Moderate<br>Severe/Profound                                    | 29.5 (22.18 – 36.82) (n = 44)<br>25.1 (20.08 – 30.12) (n = 72)<br>9.6 (5.39 – 13.81) (n = 18)                       | 20.1 (13.67 – 26.53) (n = 30)<br>22.7 (17.85 – 27.55) (n = 65)<br>26.6 (20.28 – 32.92) (n = 50)                     | 50.3 (42.27 – 58.33) (n = 75)<br>52.3 (46.52 – 58.08) (n = 150)<br>63.8 (56.93 – 70.67) (n = 120)                      | <b>0.001</b>         |
| <b>Type of Residence (n = 676)</b><br>Independent<br>Community Group Home<br>Residential Care          | 41.2 (31.65 – 50.75) (n = 42)<br>22.8 (18.04 – 27.56) (n = 68)<br>12.7 (8.77 – 16.63) (n = 35)                      | 26.5 (17.94 – 35.06) (n = 27)<br>26.9 (21.87 – 31.93) (n = 80)<br>21.0 (16.19 – 25.81) (n = 58)                     | 32.4 (23.32 – 41.48) (n = 33)<br>50.3 (44.62 – 55.98) (n = 150)<br>66.3 (60.72 – 71.88) (n = 183)                      | <b>&lt;0.001</b>     |
| <b>Barthel Index (n = 635)</b><br>No/Mild Dependence<br>Moderate Dependence<br>Severe/Total Dependence | 33.1 (25.88 – 40.32) (n=54)<br>21.9 (17.0 – 26.8) (n=60)<br>10.6 (6.31 – 14.89) (n=21)                              | 32.5 (25.31 – 39.69) (n=53)<br>24.1 (19.04 – 29.16) (n=66)<br>19.7(14.16 – 25.24) (n=39)                            | 34.4 (27.11 – 41.69) (n=56)<br>54.0 (48.1 – 59.9) (n=148)<br>69.7 (63.3 – 76.1)(n=138)                                 | <b>&lt;0.001</b>     |
| <b>Functional Comorbidity Index (n = 532)</b><br>0<br>1<br>2<br>3+                                     | 66.7 (28.99 – 104.41) (n=4)<br>17.1 (2.9 – 31.3) (n=7)<br>36.7 (27.16 – 46.24)(n=36)<br>15.5 (11.96 – 19.04) (n=62) | 16.7 (-13.14 – 46.54) (n=1)<br>17.1 (2.9 – 31.3) (n=7)<br>24.5 (15.98 – 33.02)(n=24)<br>24.9 (20.67 – 29.13)(n=100) | 16.7 (-13.14 – 46.54) (n=1)<br>65.9 (48.02 – 83.78) (n=13)<br>38.8 (29.15 – 48.45)(n=38)<br>59.6 (54.8 – 64.4) (n=239) | <b>&lt;0.001</b>     |
| <b>Neurological Disease (n = 641)</b><br>Yes<br>No                                                     | 5.7 (3.2 – 9.2) (n = 15)<br>31.0 (26.4 – 36.0) (n = 117)                                                            | 22.0 (17.1 – 27.5) (n = 58)<br>26.3 (21.9 – 31.0) (n = 99)                                                          | 72.3 (66.5 – 77.7) (n = 191)<br>42.7 (37.7 – 47.9) (n = 161)                                                           | <b>&lt;0.001</b>     |

| Population Characteristics<br>(n = 677)                                  | DBI Score 0<br>(n = 145)<br>% (% CI) (n) | DBI Score 0 > 1<br>(n = 165)<br>% (% CI) (n) | DBI Score ≥ 1<br>(n = 367)<br>% (% CI) (n) | p <sup>a</sup>   |
|--------------------------------------------------------------------------|------------------------------------------|----------------------------------------------|--------------------------------------------|------------------|
| <b>Depression (n = 673)</b>                                              |                                          |                                              |                                            | <b>&lt;0.001</b> |
| Yes                                                                      | 7.0 (3.2 – 12.8) (n = 9)                 | 12.4 (7.3 – 19.4) (n = 16)                   | 80.6 (72.7 – 87.0) (n = 104)               |                  |
| No                                                                       | 25.0 (21.4 – 28.9) (n = 136)             | 27.0 (23.3 – 31.0) (n = 147)                 | 48.0 (43.7 – 52.3) (n = 261)               |                  |
| <b>Anxiety (n = 673)</b>                                                 |                                          |                                              |                                            | <b>&lt;0.001</b> |
| Yes                                                                      | 7.3 (4.1 – 12.0) (n = 14)                | 20.9 (15.4 – 27.4) (n = 40)                  | 71.7 ( 64.8 – 78.0) (n = 137)              |                  |
| No                                                                       | 27.2 (23.3 – 31.4) (n = 131)             | 25.5 (21.7 – 29.7) (n = 123)                 | 47.3 (42.8 – 51.9) (n = 228)               |                  |
| <b>Behaviours that Challenge (n = 677)</b>                               |                                          |                                              |                                            | <b>&lt;0.001</b> |
| Yes                                                                      | 13.4 (9.84 – 16.96) (n = 47)             | 22.4 (18.04 – 26.76) (n = 79)                | 64.2 (59.19 – 69.21) (n = 226)             |                  |
| No                                                                       | 30.2 (25.21 – 35.19) (n = 98)            | 26.5 (21.7 – 31.3) (n = 86)                  | 43.4 (38.01 – 48.79) (n = 141)             |                  |
| <b>Daytime Dozing (n = 665)</b>                                          |                                          |                                              |                                            | <b>&lt;0.001</b> |
| Yes                                                                      | 13.8 (9.36 – 18.24) (n = 32)             | 21.6 (16.3 – 26.9) (n = 50)                  | 64.7 (58.55 – 70.85) (n = 150)             |                  |
| No                                                                       | 25.6 (21.49 – 29.71) (n = 111)           | 26.6 (22.44 – 30.76) (n = 115)               | 47.8 (43.1 – 52.5) (n = 207)               |                  |
| <b>Chronic Constipation (n = 669)</b>                                    |                                          |                                              |                                            | <b>&lt;0.001</b> |
| Yes                                                                      | 12.5 (8.46 – 16.54) (n = 32)             | 21.8 (16.75 – 26.85) (n = 56)                | 65.8 (60.0 – 71.6) (n = 169)               |                  |
| No                                                                       | 26.9 (22.62 – 31.18) (n = 111)           | 26.2 (21.95 – 30.45) (n = 108)               | 46.8 (41.98 – 51.62) (n = 193)             |                  |
| <b>Fall in the Previous 12 Months (n = 667)</b>                          |                                          |                                              |                                            | <b>0.011</b>     |
| Yes                                                                      | 18.4 (12.89 – 23.91) (n = 35)            | 18.4 (12.89 – 23.91) (n = 35)                | 63.2 (56.34 – 70.06) (n = 120)             |                  |
| No                                                                       | 22.9 (19.13 – 26.67) (n = 109)           | 26.6 (22.63 – 30.57) (n = 127)               | 50.5 (46.01 – 54.99) (n = 241)             |                  |
| <b>Polypharmacy (n = 677)</b>                                            |                                          |                                              |                                            | <b>&lt;0.001</b> |
| No polypharmacy                                                          | 46.1 (39.9 – 52.21) (n = 118)            | 31.6 (25.9 – 37.3) (n = 81)                  | 22.3 (17.2 – 27.4) (n = 57)                |                  |
| Polypharmacy                                                             | 8.9 (5.43 – 12.37) (n = 23)              | 27.1 (21.68 – 32.52) (n = 70)                | 64.0(58.14 – 69.86) (n = 165)              |                  |
| Excessive polypharmacy                                                   | 2.5 (0.1 – 4.9) (n = 4)                  | 8.6 (4.3 – 12.9) (n = 14)                    | 89.0 (84.2 – 93.8) (n = 145)               |                  |
| a. P<0.05 is statistically significant; all significant factors in bold. |                                          |                                              |                                            |                  |

Supporting Information Table S 3.6 Review of Existing Drug Burden Index Literature – Observational Studies

| Study                      | Status; Age; Number of Participants; Setting                                                                                                                                           | % Receiving DBI = 0                                                    | % Receiving DBI 0 > 1 | % Receiving DBI ≥1 | % Receiving Anticholinergic Medications | % Receiving Sedative Medications |
|----------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|-----------------------|--------------------|-----------------------------------------|----------------------------------|
| IDS-TILDA Study            | People with ID; ≥44 years; n = 677; Community-dwelling and residential facilities                                                                                                      | 21%                                                                    | 24%                   | 54%                | 51%                                     | 32%                              |
| Hilmer et al., 2007 (146)  | People with and without cognitive impairment; 70 – 79 years; n = 3075; Community-dwelling                                                                                              | Reported as a linear/continuous variable. DBI values were capped at 3. |                       |                    | 25%                                     | 14%                              |
| Hilmer et al., 2009 (219)  | As above (146), at 1-, 3-, 5- and 6-year intervals                                                                                                                                     | 52%                                                                    | 19%                   | 29%                | -                                       | -                                |
| Gnjidic et al, 2009 (151)  | People with and without cognitive impairment; ≥70 years; n = 1705; Community-dwelling (Australia)                                                                                      | Mean DBI score reported; 0.18 ±0.35                                    |                       |                    | 21%                                     | 13%                              |
| Gnjidic et al, 2012 (217)  | n = 155; Self-care retirement villages                                                                                                                                                 | 56.5%                                                                  | 43.5%                 |                    | 20%                                     | 24%                              |
| Wilson et al., 2011 (154)  | People with and without cognitive impairment; ≥70 years; n = 602; Residential Aged Care Facilities                                                                                     | 30%                                                                    | 44%                   | 26%                | 35%                                     | 42%                              |
| Bosboom et al, 2012 (211)  | People without ID with dementia; n = 351; Residential Aged Care Facilities                                                                                                             | 21%                                                                    | 79%                   |                    | 36%                                     | 43%                              |
| Gnjidic et al, 2014 (218)  | People with Alzheimer’s Disease (cases), people without Alzheimer’s Disease (controls); ≥65 years; Matched case-controls, n = 16,603 cases and n = 16,603 controls; Community-dwelling | Cases: 47%                                                             | 35%                   | 16%                | -                                       | -                                |
|                            |                                                                                                                                                                                        | Controls: 67%                                                          | 25%                   | 9%                 | -                                       | -                                |
| Nishtala et al, 2014 (223) | ≥65 years; n = 537,387; Data obtained from Pharmacy Claims Data Mart, New Zealand                                                                                                      | 57%                                                                    | 43%                   |                    | -                                       | -                                |
| Floroff et al, 2014 (215)  | ≥65 years; n = 112; Critically ill patients in neuroscience Intensive Care Unit                                                                                                        | Specified changes in median DBI scores                                 |                       |                    | -                                       | -                                |
| Gnjidic et al, 2012 (217)  | All individuals both cognitively intact or with a diagnosis of dementia or mild cognitive impairment (study group) and those cognitively intact only                                   | Study Group: 72%                                                       | 22%                   | 5%                 | -                                       | -                                |

| Study                        | Status; Age; Number of Participants; Setting                                                                                                                                                             | % Receiving DBI = 0                                     | % Receiving DBI 0 > 1               | % Receiving DBI ≥1                 | % Receiving Anticholinergic Medications | % Receiving Sedative Medications |
|------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------|-------------------------------------|------------------------------------|-----------------------------------------|----------------------------------|
|                              | (cognitively intact subgroup); n = 987 study group and n = 887 cognitively intact subgroup; Concord Health and Ageing in Men Project (CHAMP) Study, Community-dwelling                                   | Subgroup: 74%                                           | 22%                                 | 5%                                 | -                                       | -                                |
| Lonnroos et al, 2012 (220)   | People without ID, with and without cognitive impairment; ≥75 years; n = 339; Community-dwelling                                                                                                         | 62%                                                     | 27%                                 | 11%                                | -                                       | -                                |
| Best et al, 2013 (210)       | People with and without dementia; ≥65 years; n = 329; Geriatric medical or rehabilitation team                                                                                                           | 51%                                                     | 34%                                 | 16%                                | -                                       | -                                |
| Narayan et al, 2013 (221)    | People with Pharmacy Claims Data and people dispensed donepezil (ie people with dementia); ≥65 years; n = 537,387 with Pharmacy Claims Data, n = 4,258 dispensed donepezil (dementia group); New Zealand | -                                                       | -                                   | -                                  | 31.8%                                   | -                                |
| Dauphinot et al, 2016 (214)  | People with and without dementia; ≥65 years; n = 337; Inpatient multicentre cohort                                                                                                                       | Mean scores                                             |                                     |                                    | -                                       | -                                |
| Dauphinot et al, 2014 (213)  | People with and without dementia; ≥65 years; n = 337; Inpatient multicentre cohort                                                                                                                       | Admission: 35%                                          | Admission: 65%                      | -                                  | -                                       | -                                |
|                              |                                                                                                                                                                                                          | Mean scores at admission and discharge or fall or death |                                     |                                    |                                         |                                  |
| Jansen et al, 2016 (196)     | Men with and without cognitive impairment; ≥70 years; n = 1705; CHAMP Study, community-dwelling                                                                                                          | -                                                       | 27.7 – 31.3%                        |                                    | -                                       | -                                |
| Pont et al, 2015 (224)       | Men with and without cognitive impairment; ≥70 years; n = 1696; CHAMP Study, community-dwelling                                                                                                          | 81% (Anticholinergic exposure only)                     | 17% (Anticholinergic exposure only) | 1% (Anticholinergic exposure only) | 18%                                     | -                                |
| Salahudeen et al, 2015 (225) | People with Pharmacy Claims Data; ≥65 years; n = 537,387; Pharmacy Claims Data Mart, New Zealand                                                                                                         | -                                                       | -                                   | -                                  | 32%                                     | -                                |
| Gnjidic et al, 2012 (164)    | People with and without cognitive impairment; ≥75 years; = 700; Community-dwelling (Finland)                                                                                                             | 63%                                                     | 24%                                 | 13%                                | -                                       | -                                |



## Chapter 4

# Association of Drug Burden Index with Physical Function Measures in Older Adults with Intellectual Disabilities: An Observational Cross-Sectional Study

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UNDER PEER REVIEW IN BMC GERIATRICS

**KEYWORDS:** AGEING; INTELLECTUAL DISABILITY; DRUG BURDEN INDEX; ANTICHOLINERGIC; SEDATIVE; MEDICATION; PHYSICAL FUNCTION; GRIP STRENGTH; TIMED UP AND GO; BARTHEL INDEX.

## 4.1 Abstract

**Background:** Drug Burden Index (DBI), a measure of exposure to medications with anticholinergic and sedative activity, has been associated with poorer physical function in older adults in the general population. While extensive study has been conducted on associations between DBI and physical function in older adults in the general population, little is known about associations in older adults with intellectual disabilities (ID). This is the first study which aims to examine the association between DBI score and its two sub-scores, anticholinergic and sedative burden, with two objective measures of physical performance, grip strength and timed up and go, and a measure of dependency, Barthel Index activities of daily living (ADLs), in older adults with ID.

**Methods:** Data from Wave 2 (2013/2014) of the Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing (IDS-TILDA) was analysed. Analysis of Covariance (ANCOVA) was used to detect associations and produce adjusted means for the physical function and dependency measures with respect to categorical DBI scores and the anticholinergic and sedative sub-scores (DBA and DBS).

**Results:** After adjusting for confounders (age, level of ID, history of falls, comorbidities and number of non-DBI medications, Down syndrome (grip strength only) and gender (timed up and go and Barthel Index)), neither grip strength nor timed up and go were significantly associated with DBI, DBA or DBS score  $> 0$  ( $p > 0.05$ ). Higher dependency in Barthel Index was associated with high DBS exposure ( $p < 0.001$ ).

**Conclusions:** DBI, DBA or DBS scores were not significantly associated with grip strength or timed up and go. This could be as a result of established limitations in physical function in this cohort, long-term exposure to these types of medications or lifelong sedentary lifestyles. Higher dependency in Barthel Index ADLs was associated with sedative drug burden, which is an area which can be examined further for review.

## 4.2 Introduction

Intellectual disability (ID) is a neurodevelopmental disorder which manifests early in life and is characterised by impairments of general mental abilities that affect adaptive functioning (1). Historically, people with ID had greatly reduced life expectancy compared to those without ID (10); however, in recent years the life expectancy among this group has increased and people with ID are living into middle and old age (10, 21). This success is derived from numerous factors, including better access to medical intervention and improved health status (285). However, people with ID still experience premature mortality. The Confidential Inquiry into premature deaths of people with ID, commissioned by the Department of Health in England, identified that there was a higher probability of preventable deaths of people with ID, owing to untreated health problems and deficiencies in healthcare provision for this population (26).

It has been reported that seven out of ten adults with ID over 40 years old experience multimorbidity, with mental illness, neurological disease, gastrointestinal disease and eye disease among the most prevalent conditions (57). Higher rates of cardiac abnormalities, musculoskeletal disorders, hypothyroidism, early menopause, epilepsy, dementia and hearing and visual impairments are observed in adults with ID as they age compared to the general population (286). Older adults with ID face different challenges as compared to older adults without ID. The trend of deinstitutionalisation for adults with ID, while important to enabling better quality of life and social connectedness, may also result in reduced access to services required to meet the needs of adults ageing with an ID. Health practitioners in primary care may fail to identify special and unique problems experienced by people with ID who are ageing (286).

In the absence of appropriate alternative interventions older adults with ID may have increased risk of experience of high levels of exposure to multiple medicines, including those with anticholinergic and sedative effects (101, 103). These types of medications have well-documented adverse effects on older adults in the general population, such as falls, frailty, fracture liability, and physical and cognitive impairment (161, 168, 244-250). Studies of the adverse effects of these types of medication on older adults with ID are limited, though existing research has found that use of anticholinergic medications in older adults with ID is associated with daytime drowsiness and chronic constipation (103). Sedative Load, a model which measures exposure to regular sedative medications, has been found to be associated with frailty, pre-frailty and frailty deficit index in older adults without ID (161). The prevalence of frailty in older adults with ID aged 50 – 64 has been found to be as high as in the general

population aged 65 and older (190), but neither Sedative Load nor its effect on frailty have been measured in this population.

The Drug Burden Index (DBI) has been developed as a tool to measure the exposure of an individual to anticholinergic and sedative medications (146). It has been internationally validated and has been associated with impairment of physical function in older people without ID, including poorer performance in measures such as walking speed, balance, grip strength, timed up and go (TUG) and the Short Physical Performance Battery (150, 151, 164, 166). DBI has also been found to be associated with a greater risk of transitioning from the robust state to the pre-frail state in community-dwelling men aged 70 and older (196). DBI has recently been analysed in older adults with ID, and it has been found that DBI scores are much higher in this population than those reported in older adults without ID, with 54% older adults with ID having a high DBI score ( $\geq 1$ ) compared to between 5 and 29% of older adults without ID (*Chapter 3*; (287)). In particular, exposure to medications with anticholinergic effects is much more frequent in older adults with ID (*Chapter 3*; (103, 287)). In addition, high DBI score has been found to be significantly associated with increased dependency in Barthel Index ADLs in older adults with ID (287).

Physical performance is an important marker of functional independence in older adults (164). Physical fitness measurements have only in recent years been assessed in older adults with ID. Hilgenkamp et al (181, 182) have examined the feasibility and reliability of physical function measures in this group and concluded that grip strength and walking speed were appropriate methods of measuring function in this group.

The association between performance in physical function measures and DBI has been examined in a number of studies of older adults without ID. However, there is a lack of research in the area of the association of drug burden on physical function in older adults with ID. To our knowledge, this is the first study to examine physical function measurements in relation to DBI in older adults with ID.

The aim of this study is to examine the association between Drug Burden Index and performance in two physical function measures, grip strength and TUG, and a measure of dependency, Barthel Index, in a cohort of older adults with ID at a cross-sectional level to establish if similar exposure in people with ID leads to the same functional effects as has been reported in the general population.

More specifically, the objectives were to identify associations and adjusted means for:

- a. Grip strength
- b. Timed up and go
- c. Barthel Index

with respect to exposure to DBI medications, DBI medications with anticholinergic activity (DBA) and DBI medications with sedative activity (DBS) and three-level, dose-related categorical DBI, DBA and DBS scores.

## 4.3 Methods

### 4.3.1 Design

Data for this study was obtained from older adults with ID enrolled in Wave 2 (2013/2014) of the Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing (IDS-TILDA), an observational, cross-sectional study, and has been described in detail elsewhere (287). IDS-TILDA is a large scale, nationally representative longitudinal study which examines the ageing of people with ID (52, 205).

### 4.3.2 Participants

The sampling frame for Wave 1 of this study was the National Intellectual Disability Database (NIDD). NIDD collects information to define the specific health services in use or required by people with ID in the Republic of Ireland. Staff at NIDD randomly selected 1,800 personal identification numbers (PINs) and an invitation pack with a consent form was sent to each potential participant. Participants signed written informed consent independently or, if this was not possible, a family member/guardian signed a letter of agreement for their family member to participate. At Wave 1 of the study (2009/2011), 753 people aged  $\geq 40$  years participated. Ethical approval for the study was granted by the Faculty of Health Sciences Research Ethics Committee in Trinity College Dublin. In addition, local and/or regional ethical committee approval was granted from each service provider ( $n = 138$ ).

All living Wave 1 participants ( $n = 719$ ) were invited to participate in Wave 2. The study population with available medication data was 677 (95.6%) (*Figure 4.1*).

Data was gathered by three means.

- Firstly, participants were provided with a pre-interview questionnaire (PIQ) one week in advance of the face-to-face interview. The PIQ captured data in a number of areas, including physical health and medication data. In the majority of cases (92.8%;  $n = 628$ ), the PIQ was completed by proxy (a key worker or family member known to participants for at least six months). It was provided in advance of the interview in order to allow adequate time for completion, which involved accessing medical records.
- Secondly, a computer assisted personal interview (CAPI) was used by field researchers in the face-to-face interview with participants. Three different interview techniques were employed to facilitate the needs of participants – (1) participants completed

interview independently, (2) participants completed interview with assistance from a proxy or (3) interview with a proxy only on behalf of the participant.

- Thirdly, a registered nurse in intellectual disability (RNID) carried out a health assessment which included the objective measures of physical function – grip strength and timed up and go (TUG). In addition, body mass index (BMI) and Lunar Achilles GE Quantitative Ultrasound (QUS) were assessed in order to collect data on overweight/obesity and osteoporosis/osteopenia (52). Adaptable and accessible materials and methods were developed to assist participants who partook in the health assessment. This component has been described in detail elsewhere, for further details see Burke et al, 2014, 2016a & 2016b (52, 240, 259).

*Figure 4.1* displays the flow chart of the study.

The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guidelines for cross-sectional studies were used (260, 261).

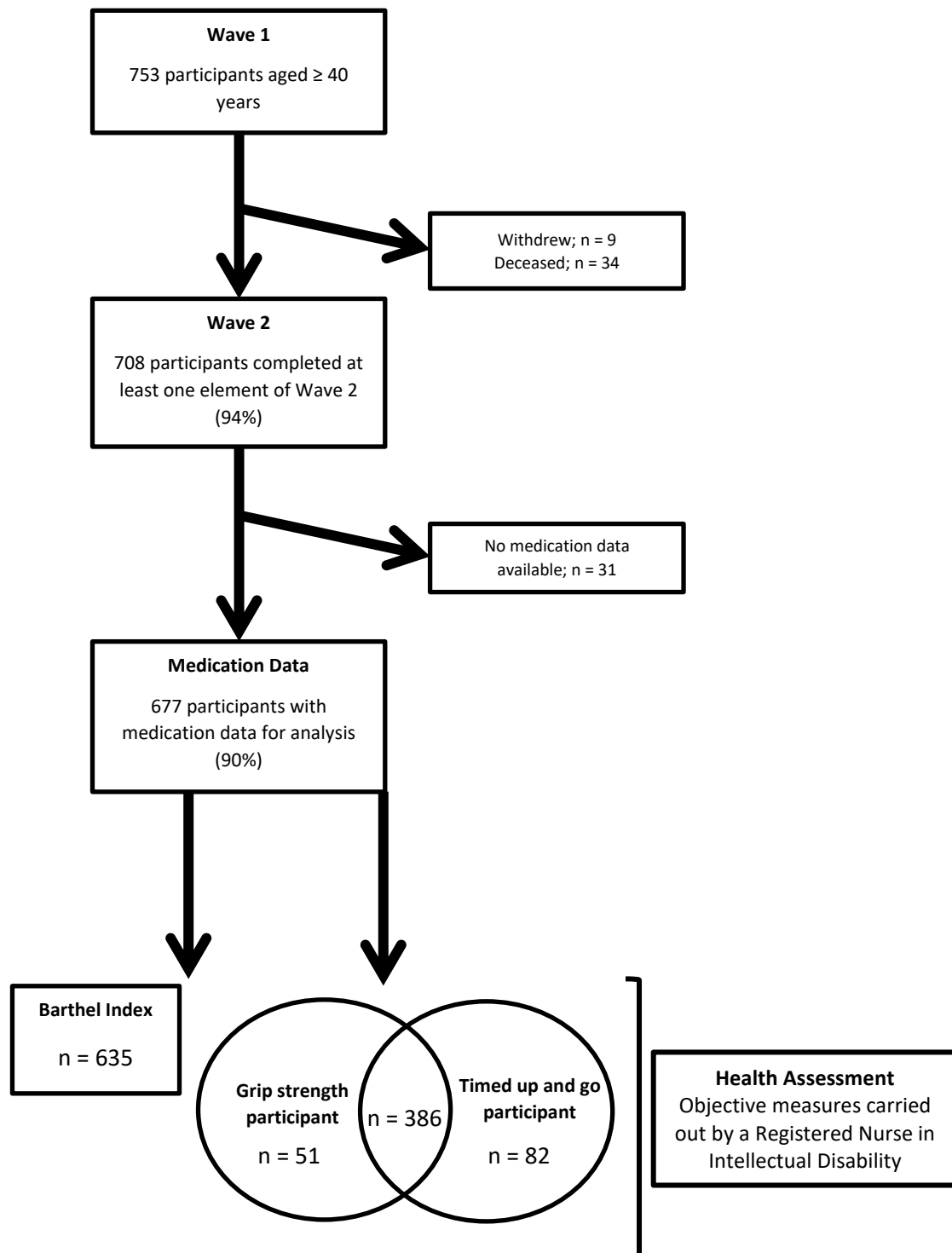


Figure 4.1 Flow Chart for IDS-TILDA



### 4.3.3 Drug Burden Index

Medication data was collected by asking participants/proxies to complete the medication section of the Pre-Interview Questionnaire (PIQ). Participants/proxies were asked “Can you tell me what medications (including prescribed or over the counter (OTC)) and supplements you take on a regular basis (like every day or every week)?”

Medication data was recorded by brand name/International Non-Proprietary Name (INN), dose, frequency, route of administration and date on which medicine was initiated in the PIQ.

The Anatomical Therapeutic Chemical Classification System (ATC) was used to code medications and data was verified by two pharmacists. Medications which were topical, inhaled, “as required” or recorded for use which was not regular (eg pre-dental/medical procedures; acute seizure control) were excluded from analysis. The only exception was atropine eye drops (ATC code S01FA01), which are considered to have clinically significant systemic effects (262). Prochlorperazine was recoded from ATC code N05AB04 (Antipsychotics) to A04A (Antiemetics and Antinauseants) as the dosages reported in the IDS-TILDA population fell within the dosage range used for treatment of Meniere’s syndrome, nausea and vomiting (10 – 40mg daily) as opposed to schizophrenia and other psychotic disorders (75 – 100mg daily) (288).

The DBI score for each participant was calculated using the following formula:

$$Drug\ Burden\ Index = \sum \frac{D}{\delta + D}$$

where D is the daily dose and  $\delta$  is the Minimum Daily Dose (MDD). The MDD is used as an estimate for the DR<sub>50</sub>, the daily dose to achieve 50% of the maximum of anticholinergic and/or sedative effect. Medications were identified as having clinically significant anticholinergic and/or sedative effects by referring to relevant studies (103, 143, 146, 152, 161) and the Irish medicinal product literature (Summary of Product Characteristics, SmPC), available from the Health Products Regulatory Authority (HPRA) (227) Medications with both anticholinergic and sedative effects were classified primarily as anticholinergic as per previous studies. MDDs were identified as the lowest effective daily dose listed in the Irish medicinal product licenses from the HPRA (227). This medication inventory and the DBI tool for this cohort has been described in more detail elsewhere (*Chapter 3*; (287)).

#### **4.3.4 Physical Function Measures**

Two measures of physical function were completed: grip strength and timed up and go. Grip strength is a measure of maximum voluntary force of the hand (235) and has been found to be a valid and reliable instrument for measuring hand strength (236). Three pre-assessment skills processes were conducted by a registered nurse in intellectual disability. Initially the person was asked to sign their consent and the researcher noted the hand used for signing. Then the person was asked which was their dominant hand (strongest or which one they used for doing most things). Dominance may be a challenging concept for people with ID to determine. If there remained a difficulty the researcher got the participant to squeeze two of her fingers on each hand and noted which side appeared stronger. Grip strength was measured using a Jamar Hydraulic Dynamometer (two measurements on each hand), a valid and reliable instrument for measuring hand strength (237). Grip strength is reported as a continuous variable (in kg) and as a categorical variable, stratified by age and gender according to the manufacturer's instructions (240). . Four grip strength readings were obtained, two from the right hand and two from the left, and all results were recorded.

TUG was used as a means of assessing the proximal muscle strength, balance and executive function of participants (239). A standard chair was placed against a wall to provide secure support. This chair measured 45cm from the floor to the top of the armrest. A tape measure was used to measure a distance three meters from the chair and high visibility tape was used to mark this point. Participants were instructed to get up from a sitting position in the chair, walk to the marked point, turn around, walk back to the chair and sit down. The procedure was timed and recorded in seconds with a Seca stopwatch (240).

Prior to assessment, participants were offered the opportunity to practice for the grip strength measurement by squeezing a rubber ball and were offered a practice run of the TUG.

#### **4.3.5 Barthel Index**

The Barthel Index measures the level of dependence of an individual in ten instrumental activities of daily living (mobility, using stairs, dressing, bathing, grooming, feeding, transfer, toileting and bladder and bowel continence). It consists of an ordinal scale with range 0 – 20 (170, 263). A modified form of Barthel Index ADLs was created for this population (*Supporting Information Table S 3.1, Chapter 3*). Lower scores indicated poorer physical function.

As per a previous study, participants with two or more missing values were excluded from the Barthel Index evaluation (n = 42) (196, 287).

#### 4.3.6 Representativeness of Sample

Pearson chi-square tests were used to identify bias in participation in the health assessment. Univariate analysis was used to compare participants (n = 437 for grip strength; n = 468 for TUG) with the total population with medication data available (n = 677) on demographics (gender (male/female), age range (44 – 49 years/50 – 64 years/65+ years), level of ID (mild/moderate/severe and profound), type of residence (independent/community group home/residential care), Down syndrome (yes/no), physical activity level (low/moderate/high) and exposure to medications). This reflected the method used in a previous study of physical fitness measures in adults with ID (289).

#### 4.3.7 Covariates

*Demographic variables:* Gender (male/female), age range (44 – 49 years; 50 – 64 years; 65+ years), level of ID (mild; moderate; severe/profound) and type of residence (independent, community group home, residential care) were included as covariates.

Level of ID is based on reported intelligence quotient (IQ) scores as follows; mild (50 – 55 to approx. 70), moderate (35 – 40 to 50 – 55) and severe/profound (below 35 - 40) (1). Participant case notes were used to identify correct classification. Those with unverified level of ID (n = 53) were excluded from analysis.

Community group homes were defined as homes with small groups of people with ID (<10), based in a community setting with staff support. Residential settings were defined where ten or more people share a single living unit or where the living arrangements are campus based.

*Physical activity level:* Participants/proxies were asked how many days they had been involved in physical activity in the previous week. The answers were classified into the three categories (low, moderate and high) based on the International Physical Activity Questionnaire (IPAQ) (290).

*History of falls:* Participants/proxies were asked “in the past year have you had any fall including a slip or trip in which you lost your balance and landed on the floor or ground or lower level?” to which they answered “yes”, “no” or “don’t know”. Those who answered “don’t know” were excluded from the analyses (n = 10).

*Functional Comorbidity Index:* A modified version of the Functional Comorbidity Index (FCI) was utilised to adjust for comorbidities in the analyses (*Supporting Information Table S 3.2, Chapter*

3). The FCI was calculated by summing the presence of a reported doctor's diagnosis of the following conditions: arthritis; osteoporosis/osteopenia; asthma; lung disease; angina; congestive heart failure (or heart disease); myocardial infarction; neurological disease; stroke or transient ischaemic attack; diabetes mellitus type I or II; upper gastrointestinal disease (e.g. ulcer, hernia, reflux); depression (unipolar or bipolar); anxiety or panic disorder; visual impairment (e.g., cataracts, glaucoma, macular degeneration); hearing impairment; and overweight/obese to produce a continuous score between 0 and 16. Data on osteoporosis/osteopenia and overweight/obese were also supplemented with objective data from the health assessment. Previously, a number of DBI studies have used modified versions of the FCI. Where participants were missing data on two or more conditions ( $n = 145$ ), they were excluded from the FCI score evaluation, reflecting the method used previously (146, 150, 153, 164, 166, 196, 220).

#### **4.3.8 Statistical Analysis**

Calculation of DBI scores was performed using Microsoft Excel 2010 (Microsoft Corporation). Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) version 21.0 (IBM Corporation). Statistical significance was set at  $p < 0.05$ .

The characteristics of the study population were described using descriptive analyses (percentages and 95% confidence intervals (CI's). Medians and interquartile range (IQR) are reported as the data was not normally distributed.

Analysis of covariance (ANCOVA), adjusted for comorbidities, level of ID, Down syndrome and falls, was used to assess the effect of age on mean grip strength for males and females separately. ANCOVA, adjusted for gender, comorbidities, level of ID, and falls, was used to assess the effect of age on TUG.

ANCOVA was also selected to detect associations between drug burden and physical function. This reflects the method of analysis used elsewhere for assessment of association between DBI and physical function measures (151). Continuous grip strength scores were separated by gender and analysed individually for males and females because of the reported inherent differences in grip strength depending on gender, (291) and because the underlying assumption of Normality for ANCOVA was violated when grip strength was analysed for both males and females together. TUG scores were reciprocal transformed in order to achieve a Normal distribution and homogeneity of error variances across all groups (292, 293).

ANCOVA was carried out to identify associations between performance in physical function measures and DBI score of  $> 0$ , anticholinergic only exposure (DBA  $> 0$ ), and sedative only exposure (DBS  $> 0$ ). The reference category was set as those with DBI score = 0. The model was adjusted for demographic variables – age, gender (TUG and Barthel Index), level of ID, history of falls, comorbidities (FCI) and number of non-DBI medicines; grip strength was also adjusted for Down syndrome as a result of the well-documented inferior muscular strength and hypotonia in individuals with Down syndrome (294).

A second ANCOVA was used to compare adjusted means of grip strength, TUG and Barthel Index between participants exposed to three different levels of Drug Burden Index ranges (DBI = 0, DBI 0.1  $> 1$  and DBI  $\geq 1$ ), three levels of anticholinergic exposure (DBA = 0, DBA 0.1  $> 1$  and DBA  $\geq 1$ ) and three levels of sedative exposure (DBS = 0, DBS 0.1  $> 1$  and DBS  $\geq 1$ ). Reciprocal TUG scores were back-transformed after analysis. While use of the anticholinergic and sedative sub-scores of the DBI has not been validated, these have been used previously in order to examine in greater detail associations between DBI and physical function (151). Giving consideration to the different medication exposure patterns (i.e., higher anticholinergic burden) in older adults with ID, further justified the method of analysis.

Variance Inflation Factors (VIF) and Spearman's correlation coefficients were used to test independent variables for multicollinearity. All VIFs were  $< 2$ , therefore there was no collinearity of concern between variables. Dancy and Reidy's categorisation (269) was used to interpret Spearman's correlation coefficients. All correlation coefficient values were  $< 0.4$ , indicating only weak correlations existed between variables which were again not of concern.

Power calculations were performed using G\*Power (version 3.1.9.2)(295). To detect a medium effect size (Cohen's  $f = 0.25$ )(296), for three-level analysis (DBI/DBA/DBS 0, 0.1  $> 1$ ,  $\geq 1$ ) with 6 covariates, a sample size of 133 for males achieved a power of 0.72 and a sample size of 199 for females achieved a power of 0.89 with  $\alpha = 0.05$  (grip strength assessment). For three-level analysis with 6 covariates, a sample size of 383 achieved a power of 0.995 with  $\alpha = 0.05$  (TUG assessment) and a sample size of 464 achieved a power of 0.999 with  $\alpha = 0.05$  (Barthel Index assessment).

For two-level analysis (DBI/DBA/DBS 0 or  $> 0$ ) with six covariates, a sample size of 133 for males achieved a power of 0.82 and a sample size of 199 for females achieved a power of 0.94 with  $\alpha = 0.05$  (grip strength assessment). For two-level analysis with 6 covariates, a sample size of 383 achieved a power of 0.998 with  $\alpha = 0.05$  (TUG assessment) and a sample size of 464 achieved a power of 0.999 with  $\alpha = 0.05$  (Barthel Index assessment).

## 4.4 Results

*Table 4.1* displays descriptive statistics of the characteristics of the IDS-TILDA population and the grip strength and TUG sub-populations.

Of the 677 individuals who took part in Wave 2 of IDS-TILDA, 56.1% (n = 380) were female and 51.3% (n = 347) were aged between 50 and 64 years. Of the 624 individuals with data available on level of ID, 44% (n = 287) of participants had moderate level of ID; 44% (n = 298) of the 676 participants with data on type of residence reported lived in a community group home. Almost three-quarters (73.5%; n = 491) of participants reported low level of physical activity. 644 participants (95.1%) reported taking medication and 78.6% (n = 532) were exposed to medication with anticholinergic and/or sedative activity (DBI medications). 21.4% (n = 145) of individuals were not exposed to DBI medicines (DBI = 0), 24.4% (n = 165) had a DBI score of 0.1 > 1 and 54.2% (n = 367) had a DBI score  $\geq 1$ . On sub-score analysis, 31.9% (n = 216) of participants were exposed to no anticholinergic medicines (DBA = 0), 33.5% (n = 227) had a DBA score of 0.1 > 1 and 34.6% (n = 234) had a DBA score  $\geq 1$ . 50.2% (n = 340) of participants were exposed to no sedative medicines (DBS = 0), 30.6% (n = 207) had a DBS score of 0.1 > 1 and 19.2% (n = 130) had a DBS score  $\geq 1$  (*Table 4.1*).

*Table 4.1* presents univariate analysis of demographic and clinical characteristics and participation in grip strength and TUG measurements. Level of ID, type of residence and physical activity level were significantly associated with participation in both measures ( $p < 0.05$ ). In addition, age range was significantly associated with participation in TUG ( $p = 0.040$ ). Those with mild and moderate ID were over-represented compared to those with severe/profound level of ID in both measures (IDS-TILDA 67.9% for mild/moderate, 30.1% for severe/profound; grip strength 83.5% for mild/moderate, 16.6% for severe/profound,  $p < 0.001$ ; TUG 75.9% for mild/moderate, 24.1% for severe/profound,  $p < 0.001$ ), and those living in residential care were under-represented in both measures (IDS-TILDA 40.8%; grip strength 34.8%,  $p < 0.001$ ; TUG 36.3%,  $p = 0.001$ ). Drug Burden Index exposure was significantly different for grip strength participants ( $p = 0.017$ ) but not for TUG participants ( $p = 0.062$ ) when compared to the overall population. DBS scores were statistically significantly different for grip strength and TUG participants when compared to the overall population, and those with high ( $\geq 1$ ) DBS score were underrepresented. Gender (male/female), Down syndrome (yes/no), medication exposure and DBA scores were not statistically significantly different with regards to participation in either grip strength or TUG ( $p > 0.05$ ).

Table 4.1 Descriptive of characteristics of IDS-TILDA participants (n = 677) and of the two physical function measures (grip strength n = 437; TUG n = 468) and

| Characteristics                                                                                                                           | IDS-TILDA<br>% (95% CI) (n)  | Grip strength<br>% (95% CI) (n)           |                   | TUG<br>% (95% CI) (n)                     |                   |
|-------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|-------------------------------------------|-------------------|-------------------------------------------|-------------------|
| <b>Total N</b>                                                                                                                            | 677                          | 437                                       | <i>p</i>          | 468                                       | <i>p</i>          |
| <b>Gender</b>                                                                                                                             | n = 677                      | n = 437                                   | 0.355             | n = 468                                   | 0.432             |
| Male                                                                                                                                      | 43.9 (40.2 – 47.6) (n = 297) | 42.6 (37.9 – 47.4) (n = 186)              |                   | 44.9 (40.3 – 49.5) (n = 210)              |                   |
| Female                                                                                                                                    | 56.1 (52.4 – 59.8) (n = 380) | 57.4 (52.6 – 62.1) (n = 251)              |                   | 55.1 (50.5 – 59.7) (n = 258)              |                   |
| <b>Age range</b>                                                                                                                          | n = 676                      | n = 437                                   | 0.498             | n = 468                                   | <b>0.040*</b>     |
| 44 – 49 years                                                                                                                             | 27.6 (24.2 – 31.0) (n = 187) | 26.5 (22.5 – 30.9) (n = 116)              |                   | 28.2 (24.2 – 32.5) (n = 132)              |                   |
| 50 – 64 years                                                                                                                             | 51.3 (47.5 – 55.1) (n = 347) | 51.3 (46.5 – 56.0) (n = 224)              |                   | 53.4 (48.8 – 58.0) (n = 250)              |                   |
| 65 years +                                                                                                                                | 21.0 (17.9 – 24.1) (n = 142) | 22.2 (18.4 – 26.4) (n = 97)               |                   | 18.4 (15.0 – 22.2) (n = 86)               |                   |
| <b>Level of ID</b>                                                                                                                        | n = 624                      | n = 398                                   | <b>&lt;0.001*</b> | n = 432                                   | <b>&lt;0.001*</b> |
| Mild                                                                                                                                      | 23.9 (20.6 – 27.3) (n = 149) | 30.2 (25.7 – 34.9) (n = 120) <sup>a</sup> |                   | 26.4 (22.3 – 30.8) (n = 114)              |                   |
| Moderate                                                                                                                                  | 44.0 (40.1 – 47.9) (n = 287) | 53.3 (48.2 – 58.3) (n = 212) <sup>a</sup> |                   | 49.5 (44.7 – 54.4) (n = 214) <sup>a</sup> |                   |
| Severe/Profound                                                                                                                           | 30.1 (26.5 – 33.7) (n = 188) | 16.6 (13.1 – 20.6) (n = 66) <sup>b</sup>  |                   | 24.1 (20.1 – 28.4) (n = 104) <sup>b</sup> |                   |
| <b>Type of residence</b>                                                                                                                  | n = 676                      | n = 437                                   | <b>&lt;0.001*</b> | n = 468                                   | <b>0.001*</b>     |
| Independent                                                                                                                               | 15.0 (12.3 – 17.7) (n = 102) | 17.6 (14.2 – 21.5) (n = 77)               |                   | 15.8 (12.6 – 19.4) (n = 74)               |                   |
| Community Group Home                                                                                                                      | 44.1 (40.4 – 47.8) (n = 298) | 47.6 (42.8 – 52.4) (n = 208)              |                   | 47.9 (43.3 – 52.5) (n = 224) <sup>a</sup> |                   |
| Residential Care                                                                                                                          | 40.8 (37.1 – 44.5) (n = 276) | 34.8 (30.3 – 39.5) (n = 152) <sup>b</sup> |                   | 36.3 (32.0 – 40.9) (n = 170) <sup>b</sup> |                   |
| <b>Down syndrome</b>                                                                                                                      | n = 663                      | n = 437                                   | 0.087             | n = 468                                   | 0.388             |
| Yes                                                                                                                                       | 19.2 (16.2 – 22.4) (n = 127) | 16.7 (13.3 – 20.5) (n = 73)               |                   | 17.3 (14.0 – 21.0) (n = 81)               |                   |
| No                                                                                                                                        | 80.8 (77.6 – 83.8) (n = 536) | 81.5 (77.5 – 85.0) (n = 356)              |                   | 81.0 (77.1 – 84.4) (n = 379)              |                   |
| <b>Physical activity level</b>                                                                                                            | n = 668                      | n = 432                                   | <b>0.043*</b>     | n = 462                                   | <b>0.002*</b>     |
| Low                                                                                                                                       | 73.5 (70.0 – 76.8) (n = 491) | 70.6 (66.1 – 74.9) (n = 305)              |                   | 69.5 (65.1 – 73.7) (n = 321) <sup>b</sup> |                   |
| Moderate                                                                                                                                  | 24.3 (21.0 – 27.7) (n = 162) | 27.3 (23.2 – 31.8) (n = 118)              |                   | 28.1 (24.1 – 32.5) (n = 130) <sup>a</sup> |                   |
| High                                                                                                                                      | 2.2 (1.3 – 3.7) (n = 15)     | 2.1 (1.0 – 3.9) (n = 9)                   |                   | 2.4 (1.2 – 4.2) (n = 11)                  |                   |
| <sup>a</sup> Over-represented <sup>b</sup> Under-represented<br>Statistically significant results are marked in bold with an asterisk (*) |                              |                                           |                   |                                           |                   |

representativeness

Table 4.1 Descriptive of characteristics of IDS-TILDA participants (n = 677) and of the two physical function measures (grip strength n = 437; TUG n = 468) and

| Characteristics                    | IDS-TILDA<br>% (95% CI) (n)  | Grip strength<br>% (95% CI) (n)           |               | TUG<br>% (95% CI) (n)                    |               |
|------------------------------------|------------------------------|-------------------------------------------|---------------|------------------------------------------|---------------|
| <b>Total N</b>                     | 677                          | 437                                       | <i>p</i>      | 468                                      | <i>p</i>      |
| <b>Exposure to any medications</b> | 95.1 (93.5 – 96.7) (n = 644) | 93.8 (91.1 – 95.9) (n = 410)              | 0.249         | 94.2 (91.7 – 96.2) (n = 441)             | 0.475         |
| <b>Exposure to DBI medications</b> | 78.6 (75.5 – 81.7) (n = 532) | 75.3 (71.0 – 79.3) (n = 329) <sup>b</sup> | <b>0.003*</b> | 76.7 (72.6 – 80.5) (n = 359)             | <b>0.045*</b> |
| <b>DBI score</b>                   | n = 677                      | n = 437                                   | <b>0.017*</b> | n = 468                                  | 0.062         |
| 0                                  | 21.4 (18.3 – 24.5) (n = 145) | 24.7 (20.7 – 29.0) (n = 108) <sup>a</sup> |               | 23.3 (19.5 – 27.4) (n = 109)             |               |
| 0.1 > 1                            | 24.4 (21.2 – 27.6) (n = 165) | 23.8 (19.9 – 28.1) (n = 104)              |               | 25.4 (21.5 – 29.6) (n = 119)             |               |
| ≥ 1                                | 54.2 (50.5 – 58.0) (n = 367) | 51.5 (46.7 – 56.3) (n = 225)              |               | 51.3 (46.7 – 55.9) (n = 240)             |               |
| <b>DBA score</b>                   | n = 677                      | n = 437                                   | 0.197         | n = 468                                  | 0.685         |
| 0                                  | 31.9 (28.4 – 35.6) (n = 216) | 33.9 (29.4 – 38.5) (n = 148)              |               | 32.5 (28.3 – 36.9) (n = 152)             |               |
| 0.1 > 1                            | 33.5 (30.0 – 37.2) (n = 227) | 31.4 (27.0 – 35.9) (n = 137)              |               | 32.5 (28.3 – 36.9) (n = 152)             |               |
| ≥ 1                                | 34.6 (31.0 – 38.3) (n = 234) | 34.8 (30.3 – 39.5) (n = 152)              |               | 35.0 (30.7 – 39.6) (n = 164)             |               |
| <b>DBS score</b>                   | n = 677                      | n = 437                                   | <b>0.039*</b> | n = 468                                  | <b>0.001*</b> |
| 0                                  | 50.2 (46.4 – 54.1) (n = 340) | 53.8 (49.0 – 58.5) (n = 235)              |               | 54.1 (49.4 – 58.6) (n = 253)             |               |
| 0.1 > 1                            | 30.6 (27.1 – 34.2) (n = 207) | 27.9 (23.8 – 32.4) (n = 122)              |               | 30.1 (26.0 – 34.5) (n = 141)             |               |
| ≥ 1                                | 19.2 (16.2 – 22.2) (n = 130) | 18.3 (14.8 – 22.3) (n = 80)               |               | 15.8 (12.6 – 19.4) (n = 74) <sup>b</sup> |               |

<sup>a</sup>Over-represented <sup>b</sup>Under-represented

Statistically significant results are marked in bold with an asterisk (\*)

representativeness (continued)



The mean score for grip strength for women was 16.9kg (Standard Deviation (SD)  $\pm 7.0$ kg) and for men was 24.5kg (SD  $\pm 10.6$ kg). Mean TUG was 16.8 seconds (SD  $\pm 10.3$  seconds). Mean Barthel Index was 13.7. The range of scores for grip strength was 1 – 54kg, for TUG was 5.9 – 89.8 seconds and for Barthel Index was 0 – 20. Median and interquartile ranges (IQR) are also reported (grip strength for women median score 17kg, IQR 9kg; grip strength for men 24kg, IQR 16.25kg; TUG median score 13.6 seconds, IQR 7.1 seconds; Barthel Index median score 16.0, IQR 9.0) (*Table 4.2*).

Table 4.2 Data for Grip Strength, TUG and Barthel Index

| Health Measure                         | Mean | $\pm$ SD | Range<br>(min – max) | Median | Interquartile<br>Range |
|----------------------------------------|------|----------|----------------------|--------|------------------------|
| Grip strength (females) (kg) (n = 251) | 16.9 | 7.0      | 2.0 – 36.0           | 17.0   | 9.0                    |
| Grip strength (males) (kg) (n = 186)   | 24.5 | 10.6     | 1.0 – 54.0           | 24.0   | 16.25                  |
| TUG (seconds) (n = 468)                | 16.8 | 10.3     | 5.9 – 89.8           | 13.6   | 7.1                    |
| Barthel Index (n = 635)                | 13.7 | 6.2      | 0.0 – 20.0           | 16.0   | 9.0                    |

Table 4.3 Categorical Data for Grip Strength (n=437)

| Grip Strength (n = 437) | % of Participants (95% CI) |
|-------------------------|----------------------------|
| Above Normal (n = 14)   | 3.2 (1.8 – 5.3)            |
| Normal (n = 15)         | 3.4 (1.9 – 5.6)            |
| Below Normal (n = 408)  | 93.4 (90.6 – 95.5)         |

Grip strength data was categorised by age and gender according to the manufacturer's instructions (*Table 4.3*). 408 participants (93.4%) were categorised as having “Below Normal” grip strength, 15 (3.4%) had “Normal” grip strength and 14 (3.2%) had “Above Normal” grip strength.

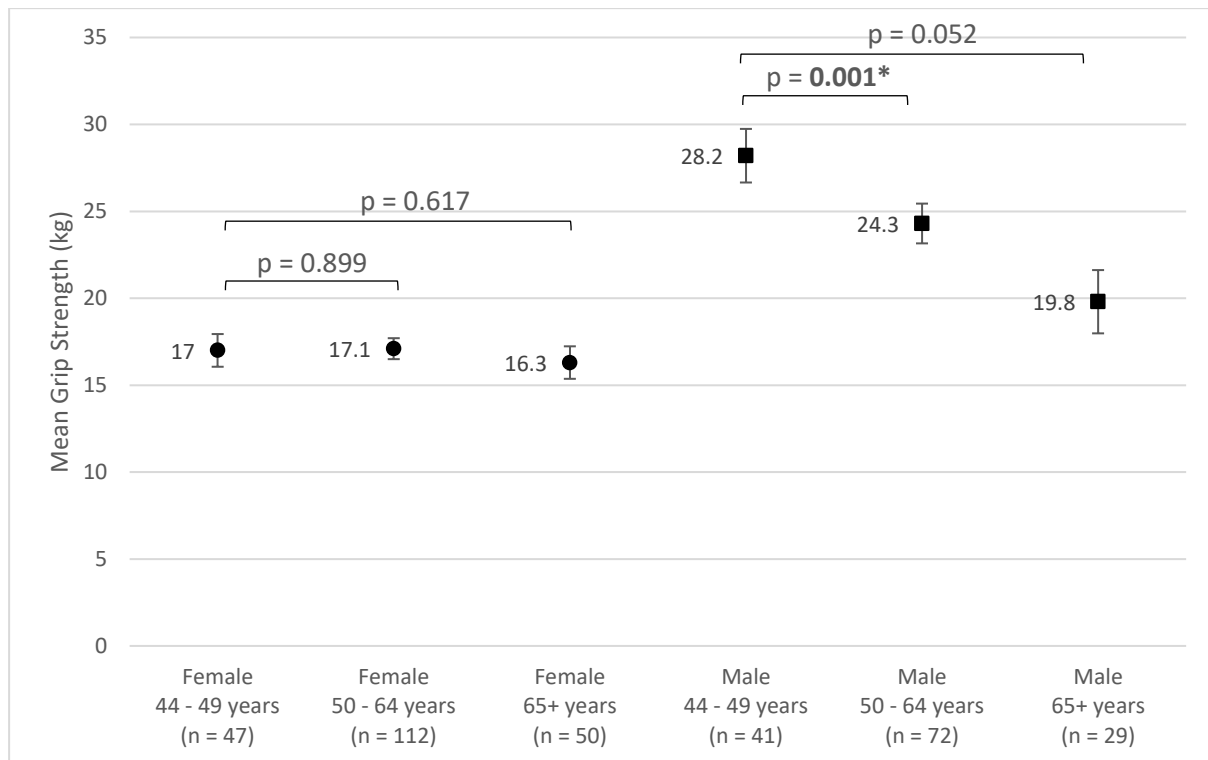


Figure 4.2 Grip Strength by Age and Gender (n = 351)

For women, there was no significant association of age with grip strength after adjusting for confounders (comorbidities, level of ID, Down syndrome and falls),  $p > 0.05$ , *Figure 4.2*.

For men, there was a highly significant association of age with grip strength, with mean grip strength decreasing from 28.2kg at 44 – 49 years to 24.3kg at 50 – 64 years ( $p = 0.001$ ) to 19.8kg at 65+ years ( $p = 0.052$ ) (*Figure 4.2*).

There was no significant association of age with increased TUG score from age range 44 – 49 years to 50 – 64 years after adjusting for confounders (gender, comorbidities, level of ID and falls),  $p > 0.05$ , *Figure 4.3*. However, there is a statistically significant association of age range with increased TUG between the youngest and oldest age ranges (44 – 49 years and 65+ years), with mean TUG increasing from 12.7 seconds at 44 – 49 years to 16.7 seconds at 65+ years ( $p = 0.004$ ) (*Figure 4.3*).

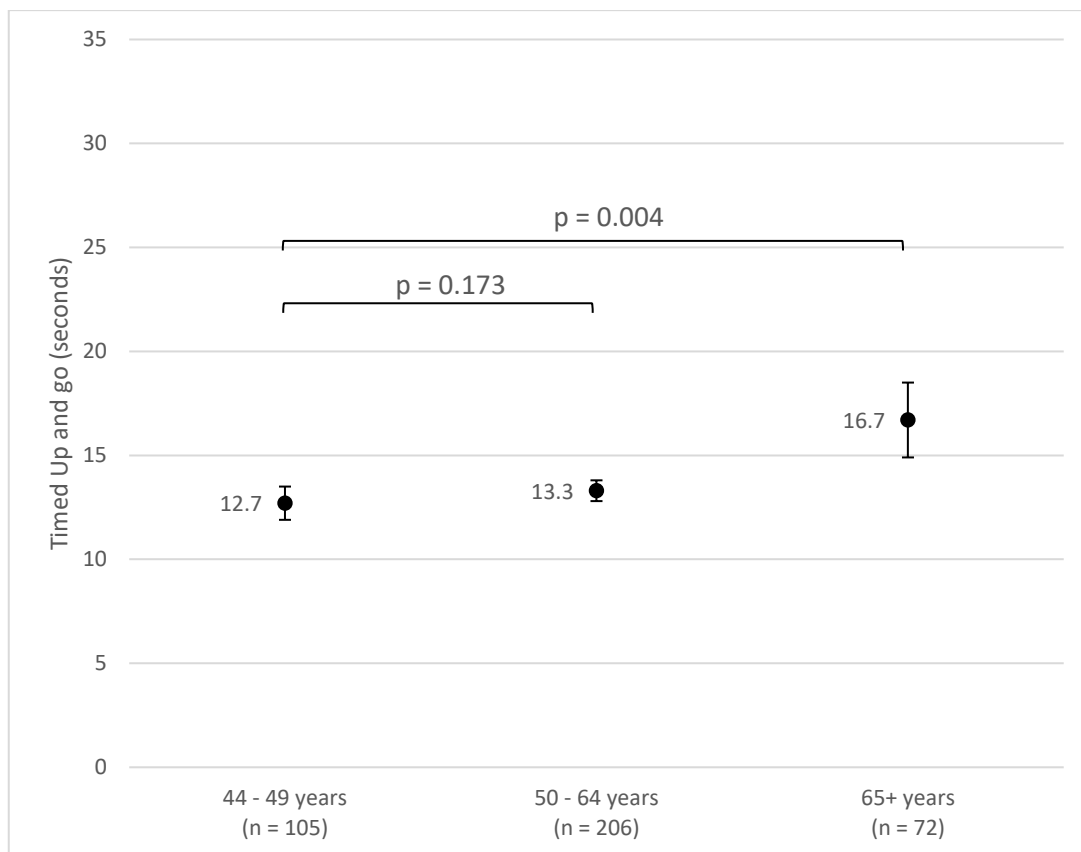


Figure 4.3 Timed Up and Go by Age (n = 383)

Table 4.4 Analysis of Covariance between DBI, DBA, DBS and Grip Strength, Reciprocal TUG and Barthel Index

|                                | DBI > 0                 |                   |     | DBA > 0                 |                   |     | DBS > 0                 |                   |     |
|--------------------------------|-------------------------|-------------------|-----|-------------------------|-------------------|-----|-------------------------|-------------------|-----|
|                                | B (95% CI)              | p                 | n   | B (95% CI)              | p                 | n   | B (95% CI)              | p                 | n   |
| <b>Grip strength (females)</b> |                         |                   |     |                         |                   |     |                         |                   |     |
| n = 251                        | -0.937 (-3.083; 1.209)  | 0.391             | 198 | -0.252 (-2.122; 1.618)  | 0.791             | 169 | -2.048 (-3.784; -0.313) | <b>0.021*</b>     | 125 |
| n = 209*                       | 0.998 (-1.240; 3.235)   | 0.380             | 162 | 1.224 (-0.720; 3.168)   | 0.216             | 139 | -0.557 (-2.418; 1.303)  | 0.555             | 108 |
| <b>Grip strength (males)</b>   |                         |                   |     |                         |                   |     |                         |                   |     |
| n = 186                        | -2.062 (-5.418; 1.295)  | 0.227             | 131 | -1.358 (-4.566; 1.850)  | 0.405             | 120 | 1.126 (-1.992; 4.244)   | 0.477             | 77  |
| n = 142*                       | 0.465 (-3.470; 4.400)   | 0.816             | 102 | 1.430 (-2.251; 5.111)   | 0.444             | 94  | 3.064 (-0.512; 6.641)   | 0.092             | 60  |
| <b>Reciprocal TUG</b>          |                         |                   |     |                         |                   |     |                         |                   |     |
| n = 468                        | -0.008 (-0.014; -0.002) | <b>0.010*</b>     | 359 | -0.007 (-0.013; -0.001) | <b>0.016*</b>     | 316 | -0.009 (-0.014; -0.004) | <b>0.001*</b>     | 215 |
| n = 383*                       | 0.002 (-0.004; 0.009)   | 0.517             | 295 | 0.002 (-0.004; 0.008)   | 0.512             | 261 | -0.003 (-0.009; 0.002)  | 0.241             | 184 |
| <b>Barthel Index</b>           |                         |                   |     |                         |                   |     |                         |                   |     |
| n = 635                        | -3.561 (-4.705; -2.417) | <b>&lt;0.001*</b> | 500 | -2.467 (-3.487; -1.447) | <b>&lt;0.001*</b> | 436 | -3.275 (-4.204; -2.346) | <b>&lt;0.001*</b> | 315 |
| n = 464*                       | -1.060 (-2.285; 0.165)  | 0.090             | 369 | -0.782 (-1.837; 0.273)  | 0.146             | 323 | -1.438 (-2.435; -0.440) | <b>0.005*</b>     | 238 |

\*For each end-point the first row represents unadjusted model and second row adjusted model for age, level of ID, history of falls, Functional Comorbidity Index, number of non-DBI medicines. Grip strength is also adjusted for Down syndrome. TUG and Barthel Index are adjusted for gender. B, parameter estimate; CI, confidence interval; DBI, Drug Burden Index; DBA, anticholinergic component of Drug Burden Index; DBS, sedative component of Drug Burden Index; p, significance; n, number exposed to anticholinergic and/or sedative drugs. n first row, number of subjects completing each test; n second row represents available data on subjects after controlling for confounders.

*Table 4.4* displays results from unadjusted and adjusted ANCOVA models for grip strength, TUG and Barthel Index in those exposed to DBI, DBA and DBS medications ( $> 0$ ) versus those not exposed ( $= 0$ ). Adjusted grip strength scores for females or males were not significantly associated with DBI, DBA or DBS exposure ( $p > 0.05$  in all cases). Unadjusted reciprocal TUG scores were significantly associated with DBI, DBA and DBS scores  $> 0$  (DBI  $> 0$ ,  $p = 0.010$ ; DBA  $> 0$ ,  $p = 0.016$ ; DBS  $> 0$ ,  $p = 0.001$ ). However, after adjusting for confounding factors, this association was no longer observed ( $p > 0.05$  in all three analyses). Unadjusted Barthel Index was significantly associated with DBI, DBA and DBS scores  $> 0$  ( $p < 0.001$  in all three cases). After adjusting for confounders, Barthel Index remained significantly associated with DBS  $> 0$  ( $p = 0.005$ ).

*Figure 4.4* displays the adjusted mean scores for female grip strength across the three types of exposure ( $= 0$ ,  $0.1 > 1$ ,  $\geq 1$ ) for DBI, DBA and DBS. There was no significant association between exposure levels and grip strength scores ( $p > 0.05$ ). Similarly, *Figure 4.5* displays adjusted mean scores for male grip strength, which were also not significantly associated with exposure level ( $p > 0.05$ ). Adjusted reciprocal TUG scores were back transformed after analysis and there was no significant association between exposure levels and scores ( $p > 0.05$ , *Figure 4.6*).

Increased dependency in Barthel Index ADLs was not significantly associated with DBA exposure after adjusting for confounders ( $p > 0.05$ ), but increased dependency was significantly associated with DBS exposure when high DBS score ( $\geq 1$ ) was compared to no exposure ( $p < 0.001$  for DBS = 0 vs DBS  $\geq 1$ , *Figure 4.7*)

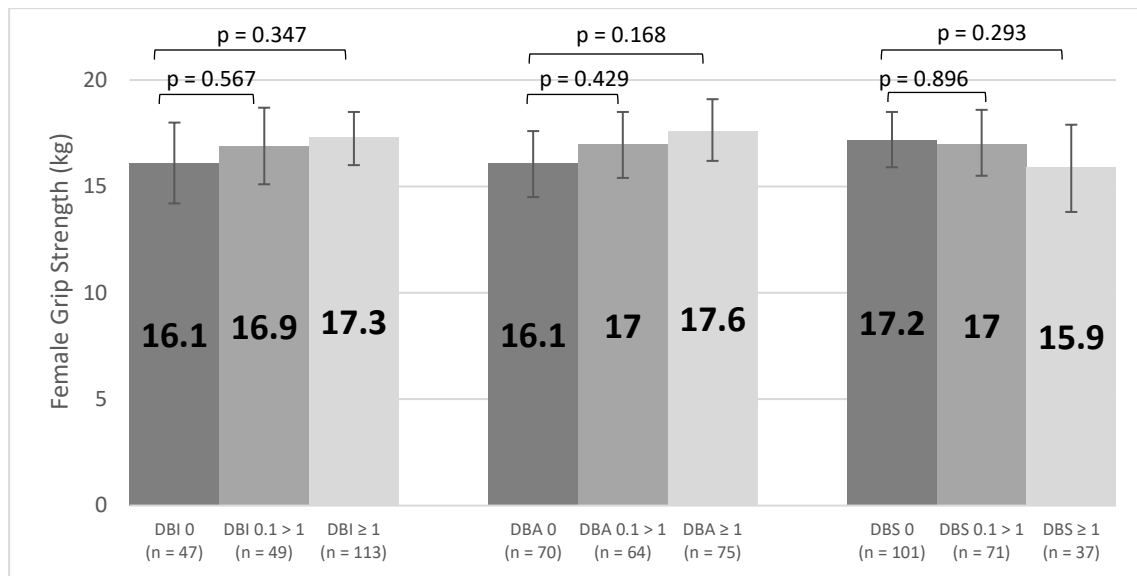


Figure 4.4 Adjusted Mean Scores for Female Grip Strength

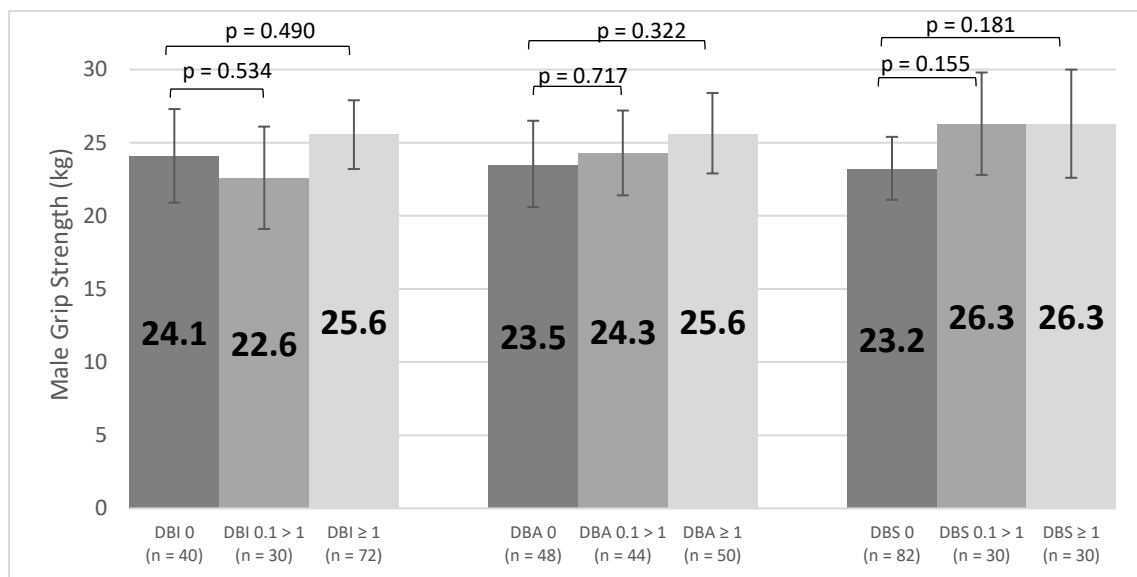


Figure 4.5 Adjusted Mean Scores for Male Grip Strength

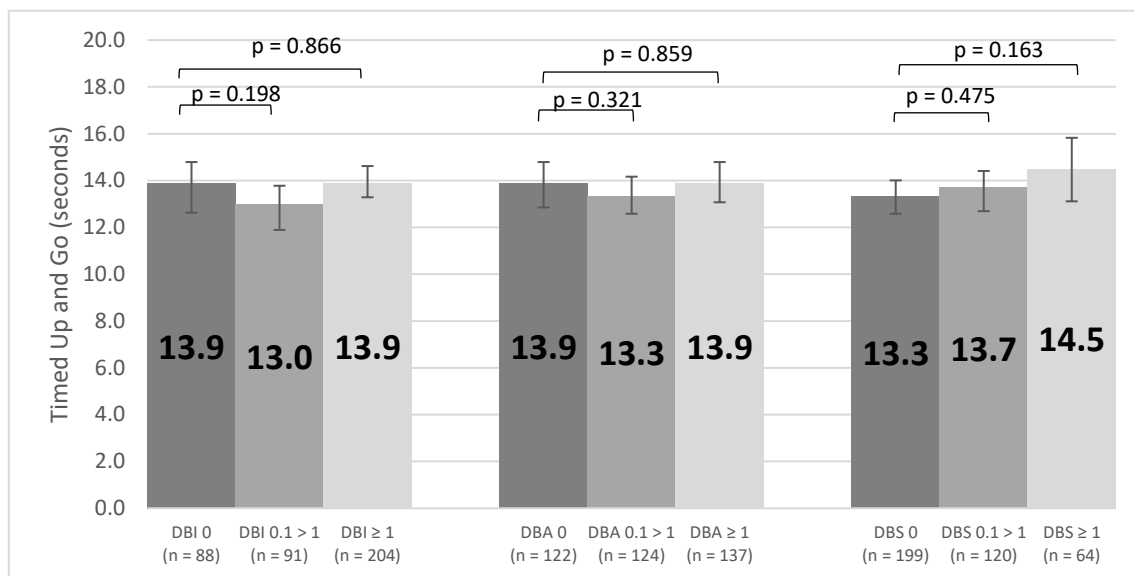


Figure 4.6 Adjusted Mean Scores for Timed Up and Go

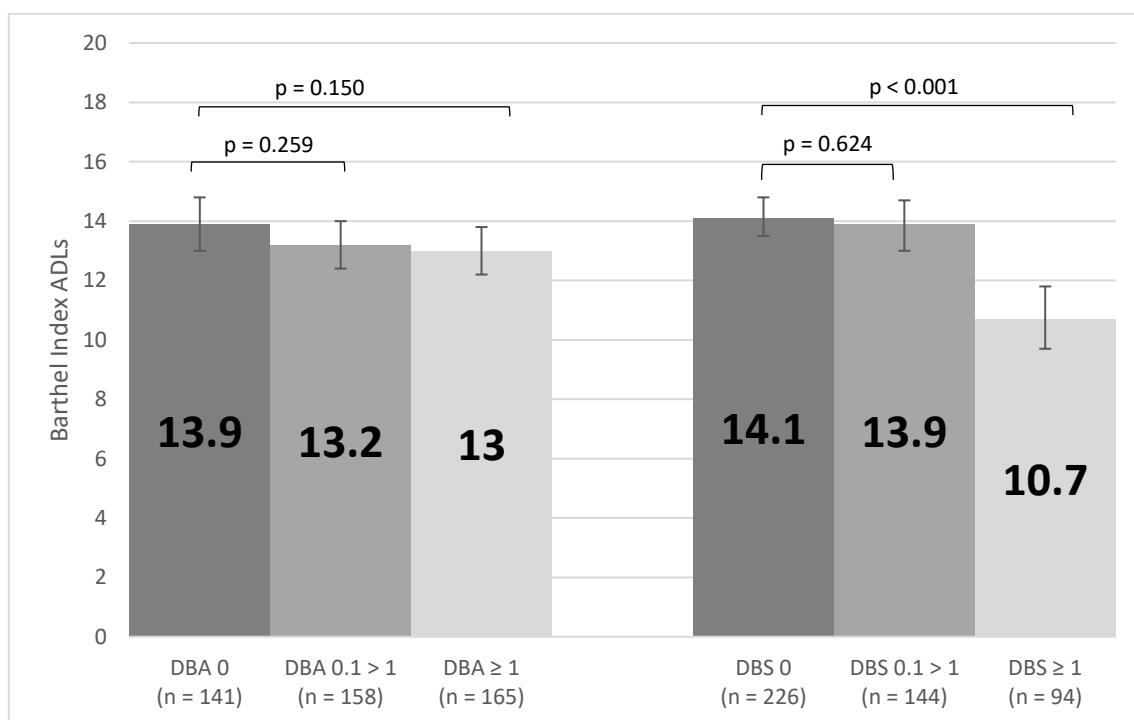


Figure 4.7 Adjusted Mean Scores for Barthel Index

## 4.5 Discussion

### 4.5.1 Key Findings

Drug Burden Index was not associated with poorer performance in two measures of physical function, grip strength and TUG, in analysis of covariance after adjusting for confounding factors in this cross-sectional study in older adults with ID. On sub-score analysis, the anticholinergic only and sedative only components of the DBI were also not associated with poorer performance in these measures. This is in contrast to other studies of DBI exposure and performance in measures of physical function in older adults without ID, where higher DBI has been found to be associated with grip weakness and slower TUG scores among 1,705 community-dwelling older men aged 70 and over (151) and slower TUG among 700 community-dwelling older adults aged 75 and over (164). Typically, among older adults without ID, associations with physical performance and function were stronger for the sedative than for the anticholinergic component of the DBI (151). The key findings of this study suggest that other factors may impact upon physical performance in people with ID, and these may potentially occur earlier in the life of a person with ID than in the general population.

### 4.5.2 Grip Strength

Grip strength scores were lower in the IDS-TILDA population than in the Dutch cross-sectional study “Healthy ageing and intellectual disabilities” (HA-ID), which included participants aged 50 years and over living primarily in residential care in the Netherlands (n = 1050, of which 725 completed grip strength assessment) (289, 297). In particular, grip strength scores for women in all age groups were lower than their counterparts in HA-ID (*Supporting Information Table S 4.1*) (289). Variation of grip strength scores was also large, with scores ranging from 2.0kg to 36.0kg (*Table 4.2*). It is important to consider that 9 out of 10 participants were categorised as having “Below Normal” grip strength. This finding is not surprising - Hilgenkamp et al (289) compared reference values for grip strength by gender in the general population with scores from older adults with intellectual disabilities living primarily in residential care settings. They found that 76.5% of men and 67.3% of women with ID had below average grip strength scores, compared to 2.5% of older adults in the general population.

It has been suggested that grip strength may be too low at baseline in this population to be able to find predictive relationships with measures including daily functioning (289, 298).



Female grip strength was significantly associated with exposure to DBS medications in the unadjusted model ( $p = 0.021$ , *Table 4.4*). However, after adjusting for confounding factors, this association was no longer statistically significant ( $p > 0.05$ ). DBI, DBA and DBS were not significantly associated with grip strength in the other unadjusted or adjusted models (*Table 4.4*).

#### **4.5.3 Timed Up and Go**

TUG scores in IDS-TILDA were comparable to other studies of older adults with ID. The mean TUG score in a Dutch observational feasibility study of 76 adults aged 50 years and over with mild to moderate ID was also 17 seconds, although this study excluded individuals with severe/profound ID and those with epilepsy from the analysis (299). There was large variation in scores across the population in IDS-TILDA for TUG, with a range of values between 5.9 and 89.8 seconds.

Our study findings revealed that while there was a significant association between timed up and go scores and exposure to DBI, DBA and DBS medications in the unadjusted models ( $p = 0.010$ ,  $0.016$  and  $0.001$ , respectively, *Table 4.4*), after adjusting for confounding factors this association was no longer statistically significant ( $p > 0.05$ ).

#### **4.5.4 Barthel Index Activities of Daily Living**

Previously, DBI exposure was found to be significantly associated a dose-related decline in Barthel Index score in this cohort (287). The current study provides a more in-depth analysis of the two components of DBI, and found that after adjusting for confounding factors, high sedative drug burden was significantly associated with increased dependence in Barthel Index ADLs ( $p < 0.001$ , *Figure 4.7*), but anticholinergic drug burden was not significantly associated with Barthel Index scores ( $p > 0.05$ , *Figure 4.7*).

#### **4.5.5 Comparison with Other Studies**

Grip strength scores were lower than findings from The Irish Longitudinal Study on Ageing (TILDA), which follows community-dwelling older adults without ID aged 50 years and over ( $n = 5897$ , of which 5819 completed grip strength assessment) (289, 297, 300) (*Supporting Information Table S 4.1* and *Supporting Information Table S 4.2*).

Similarly, TUG scores in IDS-TILDA (n = 5791) were also poorer than those observed in older adults without ID. TILDA reported mean TUG scores of 10 seconds (301), while in IDS-TILDA, the unadjusted mean score was 17 seconds (*Table 4.2* and *Supporting Information Table S 4.3*). There was greater variation in scores (reflected by standard deviation) for both physical function measures in IDS-TILDA when compared to TILDA, and this type of variation is similar to that seen in the HA-ID population (289, 300).

An association between higher DBI scores and lower grip strength has been reported in older adults without ID elsewhere (150, 151). The existing evidence in the literature suggests there is an association between higher DBI scores and slower TUG in older adults without ID (164).

A number of factors could be influencing the physical function scores of older adults with ID; ageing, gender, physical activity level, medication burden and the presence of the intellectual disability itself.

The effect of ageing, which is more pronounced at a younger age in people with ID, combined with the long-term reduced activity levels, could be overpowering the effect of drug burden alone. Decline in grip strength is significantly associated with age for men in this cohort, with mean grip strength decreasing across the three age ranges after adjusting for confounding factors ( $p \leq 0.05$ ); however, there is no significant association between decline in grip strength and age range for women ( $p > 0.05$ , *Figure 4.2*).

This also suggests that gender is an important factor when examining decline in grip strength, as men appear to be more susceptible to decline as they age, while women, though producing lower scores overall, maintain their function in this area.

Almost three quarters of the IDS-TILDA cohort have reported low levels of physical activity (*Table 4.1*), and this may be contributing to the reduced muscle strength and balance observed in this study. The low physical fitness level may be a result of lifelong sedentary lifestyle (289). It is well-established that adults with ID are less physically active than their counterparts without ID, and this lower level of activity is evident across all age ranges (302-304). It has been suggested that a lack of adequate physical activity choices in day services and residential care settings prevents adults with ID from meeting recommendations for physical activity (305). However, improvements in physical activity, such as cardiovascular training and balance and weight-bearing exercises lead to better performance in tests of muscle strength and improvement in measures of balance and executive function, including TUG (302). This suggests that physical activity levels play a substantial role in the extent of physical function, and that long-term inactivity impacts greatly on performance in tests of function.

Adults with ID generally take medications with anticholinergic and sedative effects throughout their lifetime, while older adults in the general population may only begin to take these classes of medications later in life (278). People with ID are exposed to higher proportions of these medications for a longer duration of time. Therefore, the effect on performance for older adults without ID is more pronounced from these types of medications. In previous DBI studies of older adults without ID, sedative medications contributed more to the overall Drug Burden Index score than anticholinergic medications, while in recently published research in the IDS-TILDA cohort, scores were considerably higher and anticholinergic medications contributed more to the burden (287). The association with physical function has been found to be stronger for the sedative sub-score of the DBI than the anticholinergic sub-score in older adults without ID (151). Interestingly, neither number of medications nor use of psychotropic medication were associated with any of the balance and gait tests carried out in a study of older adults with mild to moderate ID in the Netherlands (299). Older adults with ID also differ from those without ID because they have higher levels of polypharmacy even in the youngest age group (100, 101) and the evidence in the literature suggests that this higher level of drug use begins much earlier (100, 104). If exposure to DBI medications makes a contribution, it may be much earlier in the life of people with ID.

It may also be that the onset of epilepsy, dementia and neurological impairment, which is more prevalent in adults with ID as they age (57, 82, 289), causes a rapid decline in physical functioning, and the response of carers to these changes and their influence on the possibilities for physical activity in the person with ID, would render drug effects small in comparison.

The association between sedative drug burden and increased dependency in Barthel Index ADLs is of particular interest because the association remained even after correcting for the factors which may be having a strong influence on physical function, such as age and gender. It has been suggested that association of total DBI, anticholinergic-only Drug Burden and sedative-only Drug Burden with poorer Barthel Index is independent of established determinants of poorer physical function and the magnitude of the associations were similar to that of these determinants (169). Targeting sedative medications for review and re-assessing Barthel Index scores could potentially identify an area for clinical intervention that may improve quality of life in older adults with ID.

#### **4.5.6 Strengths and Limitations**

There are four main strengths in this study. First, this study uses data from a large, nationally representative sample of older adults with ID. Second, comprehensive medication data was collected for this cohort. Third, the Drug Burden Index was used, which is an internationally validated, robust measure of anticholinergic and sedative drug effects. Fourth, objective measures of physical performance were measured.

However, there are also several limitations to this study. This is a cross-sectional observational study so it is only possible to describe association, not causality. Another possible limitation of this study is that it under-represents those with severe/profound level of ID. It has been suggested that the higher drop-off rate from participants with severe/profound level of ID in grip strength measurements is as a result of difficulty in adaptation to grasping for this group (306). There is also no baseline/pre-exposure data, as these adults have typically been taking medications with anticholinergic and/or sedative effects long-term. The use of sub-score analysis of anticholinergic-only burden and sedative-only burden scores has not been validated in relation to physical function measures in any population. Finally, some of the data obtained is based on reported rather than measured data, and this may be a limitation to the accuracy of some data.

#### **4.5.7 Conclusions**

The current study findings suggest that the DBI tool may not be useful at identifying the effect of these medications on physical function in older adults with ID. However, the adverse effects of these medications are well established. It is highly probable that these medications are indeed affecting function to a degree in this cohort, but that this effect occurs earlier in life in these individuals. It is likely that the DBI tool is useful for detecting changes in physical function in older adults without ID that commence anticholinergic and/or sedative medications later in life. Regular medication review should be carried out for older adults with ID, alongside appropriate de-prescribing, due to the well-established adverse effects and interaction potential for these types of medications. The higher morbidity in this population also suggests that they are more likely to be exposed to these medications, and while the reference category of those with DBI = 0 have, at this point in time, no exposure to these medications, it does not necessarily mean they were never exposed, and it is not possible to ascertain prior exposure and duration of treatment from the current study design.

Considering the substantial number of participants who did not wish to, or were not able to complete the tests, this cohort of older adults with ID appear less active and physically weaker than older adults without ID. This also poses challenges to determining if there is a further decline in their physical functioning associated with drug use because of the low level of physical function they have attained already.

While DBI may be associated with other outcomes in older adults with ID, including higher dependence in Barthel Index ADLs (287), it was not significantly associated with the two objective measures of physical function in this study. Further study is needed to investigate associations between DBI and physical function in adults with ID, potentially by following a younger cohort, aged 40 – 50 years, over a longer period of time.

Supporting Information Table S 4.1 Female Grip Strength Comparison

| Age Range | IDS-TILDA Female (n = 251) |                                | HA-ID Female (n = 355) |                                | TILDA Female < 160cm |                                | TILDA Female ≥ 160cm |                                |
|-----------|----------------------------|--------------------------------|------------------------|--------------------------------|----------------------|--------------------------------|----------------------|--------------------------------|
|           | <i>n</i>                   | <i>Mean Grip Strength (kg)</i> | <i>n</i>               | <i>Mean Grip Strength (kg)</i> | <i>Age</i>           | <i>Mean Grip Strength (kg)</i> | <i>Age</i>           | <i>Mean Grip Strength (kg)</i> |
| 44 – 49   | 60                         | 16.60 ± 8.3                    | 0                      | N/A                            | N/A                  | N/A                            | N/A                  | N/A                            |
| 50 – 54   | 53                         | 19.49 ± 5.8                    | 82                     | 21.34 ± 8.83                   | 50                   | 23.0 ± 4.6                     | 50                   | 25.5 ± 5.1                     |
| 55 – 59   | 48                         | 17.67 ± 6.7                    | 90                     | 20.23 ± 7.97                   | 55                   | 21.3 ± 4.7                     | 55                   | 23.7 ± 5.2                     |
| 60 – 64   | 29                         | 14.27 ± 6.64                   | 65                     | 20.08 ± 7.13                   | 60                   | 20.7 ± 4.5                     | 60                   | 23.2 ± 5.0                     |
| 65 – 69   | 35                         | 16.23 ± 5.7                    | 47                     | 21.34 ± 5.58                   | 65                   | 20.3 ± 4.2                     | 65                   | 22.7 ± 4.6                     |
| 70 – 74   | 14                         | 16.64 ± 8.4                    | 38                     | 17.92 ± 6.47                   | 70                   | 19.1 ± 3.9                     | 70                   | 21.6 ± 4.4                     |
| 75 – 79   | 8                          | 14.63 ± 4.8                    | 23                     | 18.91 ± 7.33                   | 75                   | 17.9 ± 3.9                     | 75                   | 20.4 ± 4.4                     |
| 80 – 84   | 4                          | 10.75 ± 8.0                    | 5                      | 17.4 ± 6.11                    | 80                   | 16.8 ± 4.1                     | 80                   | 19.2 ± 4.7                     |
| 85 – 89   | 0                          | N/A                            | 5                      | 14.8 ± 5.72                    | 85                   | 15.7 ± 4.5                     | 85                   | 18.2 ± 5.2                     |

Supporting Information Table S 4.2 Male Grip Strength Comparison

| Age Range                                                                                                            | IDS-TILDA Male (n = 186) |                                | HA-ID Male (n = 370) |                                | TILDA Male < 173cm |                                | TILDA Male ≥ 173cm |                                |
|----------------------------------------------------------------------------------------------------------------------|--------------------------|--------------------------------|----------------------|--------------------------------|--------------------|--------------------------------|--------------------|--------------------------------|
|                                                                                                                      | <i>n</i>                 | <i>Mean Grip Strength (kg)</i> | <i>n</i>             | <i>Mean Grip Strength (kg)</i> | <i>Age</i>         | <i>Mean Grip Strength (kg)</i> | <i>Age</i>         | <i>Mean Grip Strength (kg)</i> |
| 44 – 49                                                                                                              | 56                       | 25.98 ± 10.4                   | 0                    | N/A                            | N/A                | N/A                            | N/A                | N/A                            |
| 50 – 54                                                                                                              | 40                       | 23.83 ± 10.3                   | 72                   | 29.43 ± 12.23                  | 50                 | 38.4 ± 7.5                     | 50                 | 42.7 ± 7.8                     |
| 55 – 59                                                                                                              | 35                       | 24.43 ± 10.8                   | 92                   | 28.78 ± 10.32                  | 55                 | 36.4 ± 7.4                     | 55                 | 40.7 ± 7.7                     |
| 60 – 64                                                                                                              | 19                       | 28.63 ± 9.9                    | 87                   | 29.69 ± 10.45                  | 60                 | 35.3 ± 7.2                     | 60                 | 39.7 ± 7.6                     |
| 65 – 69                                                                                                              | 19                       | 21.2 ± 10.5                    | 57                   | 29.28 ± 8.71                   | 65                 | 34.0 ± 7.0                     | 65                 | 38.4 ± 7.4                     |
| 70 – 74                                                                                                              | 6                        | 25.5 ± 14.8                    | 35                   | 27.69 ± 9.82                   | 70                 | 31.8 ± 6.7                     | 70                 | 36.1 ± 7.1                     |
| 75 – 79                                                                                                              | 5                        | 19.6 ± 5.7                     | 22                   | 24.86 ± 6.69                   | 75                 | 29.2 ± 6.5                     | 75                 | 33.6 ± 7.0                     |
| 80 – 84                                                                                                              | 3                        | 18.33 ± 2.1                    | 2                    | 26 ± 8.49                      | 80                 | 26.6 ± 6.3                     | 80                 | 30.9 ± 6.8                     |
| 85 – 89*                                                                                                             | 3                        | 11.33 ± 12.9                   | 3                    | 18.33 ± 10.21                  | 85                 | 23.8 ± 6.1                     | 85                 | 28.2 ± 6.7                     |
| *One participant was aged 90+ but was merged into previous category (85 – 89) as performed in a previous study (289) |                          |                                |                      |                                |                    |                                |                    |                                |

Supporting Information Table S 4.3 Timed Up and Go Comparison

| Age Range | IDS-TILDA (n = 251) |                       | TILDA Female < 160cm |                       | TILDA Female ≥ 160cm |                       | TILDA Male < 173cm |                       | TILDA Male ≥ 173cm |                       |
|-----------|---------------------|-----------------------|----------------------|-----------------------|----------------------|-----------------------|--------------------|-----------------------|--------------------|-----------------------|
|           | <i>n</i>            | <i>Mean TUG (sec)</i> | <i>Age</i>           | <i>Mean TUG (sec)</i> | <i>Age</i>           | <i>Mean TUG (sec)</i> | <i>Age</i>         | <i>Mean TUG (sec)</i> | <i>Age</i>         | <i>Mean TUG (sec)</i> |
| 44 – 49   | 132                 | 14.7 ± 7.5            | N/A                  |                       | N/A                  |                       | N/A                |                       | N/A                |                       |
| 50 – 54   | 100                 | 16 ± 10.0             | 50                   | 8.1 ± 3.2             | 50                   | 7.9 ± 1.6             | 50                 | 7.9 ± 1.8             | 50                 | 7.8 ± 1.3             |
| 55 – 59   | 92                  | 17.6 ± 12.5           | 55                   | 8.3 ± 2.9             | 55                   | 8.1 ± 1.6             | 55                 | 8.2 ± 2.1             | 55                 | 8 ± 1.4               |
| 60 – 64   | 58                  | 17.6 ± 12.0           | 60                   | 8.6 ± 2.9             | 60                   | 8.4 ± 1.7             | 60                 | 8.6 ± 2.5             | 60                 | 8.3 ± 1.6             |
| 65 – 69   | 49                  | 17.5 ± 8.4            | 65                   | 9.1 ± 3.4             | 65                   | 8.8 ± 1.8             | 65                 | 9.1 ± 3.4             | 65                 | 8.8 ± 1.8             |
| 70 – 74   | 19                  | 18.7 ± 6.7            | 70                   | 10.0 ± 4.7            | 70                   | 9.4 ± 2.2             | 70                 | 10 ± 5.1              | 70                 | 9.4 ± 2.3             |
| 75 – 79   | 10                  | 24.4 ± 15.6           | 75                   | 11.4 ± 7.4            | 75                   | 10.3 ± 3.2            | 75                 | 11.5 ± 8.1            | 75                 | 10.3 ± 3.5            |
| 80 – 84   | 6                   | 30.0 ± 16.8           | 80                   | 13.9 ± 12.1           | 80                   | 11.5 ± 5.8            | 80                 | 14.1 ± 12.6           | 80                 | 11.6 ± 6.2            |
| 85 – 89   | 2                   | 14.6 ± 8.6            | 85                   | 18.4 ± 18.9           | 85                   | 13.3 ± 12.0           | 85                 | 18.4 ± 18.9           | 85                 | 13.3 ± 11.9           |



## Chapter 5

# Association of Medication Burden with Frailty in Older Adults with Intellectual Disability: An Observational Cross-Sectional Study

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**KEYWORDS:** AGEING; FRAILITY; INTELLECTUAL DISABILITY; POLYPHARMACY; DRUG BURDEN INDEX; ANTICHOLINERGIC COGNITIVE BURDEN; SEDATIVE LOAD MODEL; MEDICATION.

## 5.1 Abstract

**Background:** Adults with intellectual disability (ID) are living longer than before. Frailty is a syndrome associated with ageing which includes a decline in functioning and increased dependency and vulnerability. Recently, efforts have been made to quantify frailty among older adults with ID. However, little research has been performed in relation to the association between medication exposure and frailty among older adults with ID, despite known the association between anticholinergic and sedative exposure with frailty among older adults without ID. The aim of this study was to examine the association between frailty and medication exposure, including anticholinergic and sedative medication exposure.

**Methods:** The data for this study was drawn from Wave 2 (2013/2014) of the Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing (IDS-TILDA), an observational study of ageing in people with ID in Ireland. A modified Fried's frailty phenotype was constructed and analysed for associations with Barthel Index activities of daily living (ADLs) and Functional Comorbidity Index (FCI) scores using Analysis of Covariance. Medication burden was measured by polypharmacy, Drug Burden Index (DBI), Anticholinergic Cognitive Burden (ACB) and Sedative Load model. Multinomial logistic regression was carried out to identify associations between frailty and drug burden.

**Results:** Frailty was found to be significantly associated with Barthel Index ADLs, and significant multicollinearity was identified between these measures. Frailty was also found to be significantly associated with number of comorbidities as measured by FCI. Frailty status was significantly associated with excessive polypharmacy, but not with DBI, ACB or Sedative Load score.

**Conclusions:** This is the first study to examine frailty and its association with anticholinergic and sedative medication burden among older adults with ID. There was a significant association between frailty and excessive polypharmacy but no significant association between frailty status and anticholinergic or sedative medication exposure. This could be because the frailty is caused by multiple different factors in people with ID, and anticholinergic and sedative medications may not be a dominant factor. Further research is required to investigate frailty as measured by other frailty models in relation to anticholinergic and a sedative medication burden.

## 5.2 Introduction

Intellectual disability (ID) is a lifelong condition characterised by deficits in cognitive functioning and skills acquisition. ID occurs with a frequency of around 1.5% of the population in Western countries (2, 75). Many people with ID, particularly those over 40 years of age, experience multiple disability and multi-morbidity (57, 75) and subsequently experience high levels of medication exposure (101). Prescribing rates of psychotropic medications have historically been much higher than those observed in the general population, despite the absence of diagnosed psychiatric disorders (75). Polypharmacy is not restricted to psychotropic medications, however, with this group reporting high levels of laxatives, analgesics, anticholinergics and drugs for peptic ulcer disease and gastro-oesophageal reflux (101, 103, 287, 307). Healthcare utilisation is also higher in this group (308). Much of the existing literature on medication use among people with ID focuses on antipsychotic use. However, recently attention has been directed to a greater breadth of medication burden, in particular anticholinergic and sedative medication use.

Average life expectancy among people with ID has increased substantially over the last few decades (21, 285, 309). While this life expectancy has not yet reached that observed in the general population, with improved population health status, access to quality medical care earlier in life and the trend of deinstitutionalisation, it is thought that life expectancy for adults with ID will reach that of the general population in due course (285). Nonetheless, there is still inequity in health and early death due to avoidable healthcare issues among people with ID (26). The concept of an ageing population which now includes people with ID further prompts study of frailty in this group.

Drug Burden Index (DBI) is a dose-dependent measure of anticholinergic and sedative burden on an individual. It has recently been examined in older adults with ID, and it has been identified that this population experiences higher levels of DBI exposure than older adults in the general population, and that this burden is associated with greater dependence in Barthel Index activities of daily living (ADLs) (*Chapter 3*; (287)). However, no association was found between DBI and two objective measures of physical function, grip strength and timed up and go (*Chapter 4*), in contrast to studies of older adults without ID (150, 151, 164, 166). It has been hypothesised that this is as a result of lifelong physical inactivity, long-term exposure to medications with anticholinergic and sedative effects and neurological impairments inherent to the ID itself (*Chapter 4*).

The Anticholinergic Cognitive Burden (ACB) is used to calculate the burden of medications with anticholinergic effects which have a negative impact on cognitive ability. Drugs with no

anticholinergic effects are given a score of 0, drugs with possible anticholinergic effects are given a score of 1 based on Serum Anticholinergic Activity (SAA) or *in vitro* affinity to muscarinic receptors lab tests but no evidence of clinically relevant cognitive effects, and drugs with definite clinical anticholinergic effects based on the degree of permeability to the blood-brain barrier and development of delirium are given a score of 2 or 3 (moderate or severe) (116, 140). The ACB scale has been studied in older adults with ID, and was found to be higher than that observed in the general population, in addition to being associated with daytime drowsiness, chronic constipation and laxative use (103, 120).

The original Sedative Load model drugs list was published in 2003 and was revised in 2011 (143, 144). Drugs are categorised according to sedative effect – primary sedatives (score 2) and drugs with a sedating component (score 1). Scores from regular medications are summed to give a cumulative non-dose related measure of sedative drug burden on an individual.

Frailty is a common term used to describe a syndrome typically associated with ageing which includes a decline in functioning and increased dependency and vulnerability (310). Common clinical presentations of frailty include extreme fatigue, unexplained weight loss, frequent infections, balance and gait impairment causing falls, delirium and fluctuating disability (184). Traditional frailty measures, such as the Cardiovascular Health Study criteria (Fried's frailty phenotype) (189) tend to be based exclusively on biological function (185), may be highly influenced by low mobility (311) and long term disability and may incorrectly identify individuals with ID as frail due to the strong emphasis placed on the physical domain of function (192). As a result, several attempts have been made to identify a frailty measure suitable for use in a population of older adults with ID, such as the Vienna Frailty Questionnaire, which was developed to measure frailty in individuals with ID and includes measures in the social, physiological, cognitive and psychological domains (191); the Tilburg Frailty Indicator, a multidimensional operational definition of frailty (185); and the accumulation of deficits, or Frailty Index, approach, which infers relative frailty on the basis of counting health- and age-related deficits such as symptoms, signs, disabilities, diseases, and laboratory measurements (185, 188). The Dutch "Healthy Ageing and Intellectual Disability" (HA-ID) study developed a 51-item frailty index (192) based on the criteria of Rockwood and Mitniski (188) and found frailty to be significantly associated with mortality (193) and disabilities in daily functioning independent of baseline demographics, ADLs or mobility (194) in older adults with ID.

Frail older adults report polypharmacy more frequently than non-frail older adults (152, 312). Gnjjidic et al, 2012 (152) found that polypharmacy, excessive polypharmacy and exposure to

anticholinergic and sedative medications as measured by DBI were significantly associated with frailty in an Australian cohort of community-dwelling older men ( $\geq 70$  years). A study of Australian inpatients reported that while polypharmacy was not found to be an independent predictor for adverse outcomes, examination of frailty status within polypharmacy category revealed there was a greater number of adverse events in frail participants with excessive polypharmacy than robust patients with excessive polypharmacy. This suggests use of a frailty measure in conjunction with polypharmacy provides a better assessment of risk than examining polypharmacy status alone (200). Several other studies have found frailty to be associated with polypharmacy among different patient groups (195, 198, 199). Exposure to anticholinergic medications as measured by the Anticholinergic Drug Scale was also found to be significantly associated with frailty (197). High Sedative Load has been found to be associated with frailty, pre-frailty and frailty index in older adults in the general population (161). In addition, number of medications has been found to be associated with frailty transitions, with one study finding each additional medication a participant was exposed to was associated with a 22% greater risk of transitioning from robust to death, and each unit increase in DBI score was associated with a 73% greater risk of transitioning from non-frail to prefrail (196). The majority of studies of medication exposure and frailty use Fried's frailty phenotype (152, 195-199), while Poudel et al, 2016 (200) used an accumulation of deficits frailty index and Peklar et al, 2015 (161) used both the phenotype and frailty index approach to measuring frailty.

In spite of the known associations between polypharmacy, anticholinergic and sedative exposure with frailty in older adults without ID, and the high levels of exposure to these amongst people with ID, little research has been performed to assess the association between frailty by any measure with medication exposure in older adults with ID. For this reason, a modified Fried's frailty phenotype, similar to that which was examined in HA-ID, will be examined for associations with medication exposure.

The aim of this study is to describe frailty and examine the cross-sectional association between anticholinergic and sedative medication exposure using four tools (polypharmacy, Drug Burden Index, Anticholinergic Cognitive Burden and Sedative Load) with frailty in a cohort of older adults with intellectual disabilities.

More specifically, the objectives were:

- d) To describe frailty by creating a modified version of the Fried's Frailty Phenotype and examine its association with performance in Barthel Index ADLs and comorbidities as measured by the Functional Comorbidity Index;

- e) To update an existing inventory and scoring system for measuring anticholinergic burden (Anticholinergic Cognitive Burden) and sedative burden (Sedative Load);
- f) To identify associations between polypharmacy, Drug Burden Index, Anticholinergic Cognitive Burden and Sedative Load model with frailty as measured by frailty phenotype.

## 5.3 Methods

### 5.3.1 Design

This study used data from Wave 2 (2013/2014) of the Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing (IDS-TILDA), a nationally representative, observational, cross-sectional study of older adults with intellectual disabilities in Ireland (52, 205). This study has been described in detail elsewhere (*Chapter 2, 3 and 4; (287)*). Ethical approval for the study was granted by the Faculty of Health Sciences Research Ethics Committee in Trinity College Dublin and local and/or regional ethical committee approval was granted from each service provider (n = 138).

All living Wave 1 participants (n = 719) were invited to participate in Wave 2. The study population with available medication data was 677 (95.6%)

Data was gathered by three means.

- A pre-interview questionnaire (PIQ) was sent to each participant one week prior to interview. For the most part (92.8%; n = 628), a proxy (family member or key worker known to participants for at least six months) completed the PIQ, which involved consultation of medical records.
- Field researchers conducted a face-to-face computer assisted personal interview (CAPI) with participants. Three different interview techniques were employed to facilitate the needs of participants – participants completed interview independently, participants completed interview with assistance from a proxy or a proxy completed interview on behalf of the participant, with or without the participant present.
- Thirdly, a registered nurse in intellectual disability (RNID) carried out a health assessment which included the objective measures of physical function – grip strength and timed up and go (TUG). In addition, body mass index (BMI) and Lunar Achilles GE Quantitative Ultrasound (QUS) were assessed in order to collect data on overweight/obesity and osteoporosis/osteopenia [29]. Adaptable and accessible

materials and methods were developed to assist participants who partook in the health assessment. This component has been described in detail elsewhere, for further details see Burke et al, 2014, 2016a & 2016b [29, 31, 32].

The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guidelines for cross-sectional studies were used in this study (260, 261).

### 5.3.2 Medication Data

The PIQ included the question “Can you tell me what medications (including prescribed or over the counter (OTC)) and supplements you take on a regular basis (like every day or every week)?” and participants/proxies filled in this medication data in the PIQ. Medication data was recorded by brand name/International Non-Proprietary Name (INN), dose, frequency, route of administration and date on which medicine was initiated. Medications were coded by the Anatomical Therapeutic Chemical Classification System (ATC) (228) and two pharmacists verified this data.

### 5.3.3 Polypharmacy

No polypharmacy was defined as exposure to 0 – 4 medications; polypharmacy was defined as exposure to 5 – 9 medications; excessive polypharmacy was defined as exposure to 10 or more medications. This categorisation was used previously in the IDS-TILDA study and in other epidemiological studies (*Chapter 3*; (101, 287)).

### 5.3.4 Drug Burden Index

Medications which were topical, inhaled, “as required” or recorded for use which was not regular (e.g. pre-dental/medical procedures; acute seizure control) were excluded from analysis. The only exception was atropine eye drops (ATC code S01FA01), which are considered to have clinically significant systemic effects (262). Prochlorperazine was recoded from ATC code N05AB04 (Antipsychotics) to A04A (Antiemetics and Antinauseants) as the dosages reported in the IDS-TILDA population fell within the dosage range used for treatment of Meniere’s syndrome, nausea and vomiting (10 – 40mg daily) as opposed to schizophrenia and other psychotic disorders (75 – 100mg daily)(288).

The DBI score for each participant was calculated using the following formula:

$$Drug\ Burden\ Index = \sum \frac{D}{\delta + D}$$

where  $D$  is the daily dose and  $\delta$  is the Minimum Daily Dose (MDD). The MDD is used as an estimate for the  $DR_{50}$ , the daily dose to achieve 50% of the maximum of anticholinergic and/or sedative effect. Medications were identified as having clinically significant anticholinergic and/or sedative effects by referring to relevant studies (103, 143, 146, 152, 161) and the Irish medicinal product literature (Summary of Product Characteristics, SmPC), available from the Health Products Regulatory Authority (HPRA) (227). Medications with both anticholinergic and sedative effects were classified primarily as anticholinergic as per previous studies. MDDs were identified as the lowest effective daily dose listed in the Irish medicinal product licenses from the HPRA [39]. This medication inventory and the DBI tool for this cohort has been described in more detail elsewhere (*Chapter 3*; (287)). Total cumulative DBI score was categorised as no exposure (DBI = 0), low exposure (DBI  $0.1 > 1$ ) and high exposure (DBI  $\geq 1$ ).

### 5.3.5 Anticholinergic Cognitive Burden

The reference medication inventory and associated scores for this study of the Anticholinergic Cognitive Burden (ACB) Scale is drawn from the one published in a study of the same cohort at Wave 1 of the IDS-TILDA study (2010/2011) (103). This list of anticholinergic medications was derived from the updated 2012 Anticholinergic Cognitive Burden Scale (140), and modified to include drugs possessing anticholinergic properties used by participants of the IDS-TILDA study which were not previously included in the updated ACB Scale (103). For one medication reported in the IDS-TILDA cohort, benztropine, no Irish or UK SmPC was available, so the New Zealand Datasheet was utilised for information on anticholinergic activity (230).

Medications were defined as having absent (ACB Score 0), possible (ACB score 1) or definite anticholinergic properties (ACB score 2 or 3).

In order to identify other anticholinergic medications which may not have been included in this version of the ACB scale, a recent systematic review of anticholinergic risk scales in older adults was consulted (141). This review examined the medications included in seven anticholinergic risk scales but did not include the ACB scale. The scales included were the Anticholinergic Drug Scale, Anticholinergic Burden Classification, Chew et al, 2008, Clinical-rated Anticholinergic Score, Anticholinergic Risk Scale, Anticholinergic Activity Scale and Anticholinergic Loading Scale (133-139). Thirty-seven additional medications were included in this review. Of these medications, one (fexofenadine) was automatically excluded because the 2012 update of the ACB scale explicitly stated it was reviewed for inclusion but not added (140). Of the remaining



36 medicines, 12 were reported in the IDS-TILDA cohort. The SmPCs for these medications were examined for statements with regard to anticholinergic activity (227). Three additional medications were found to possess anticholinergic properties from this review – dosulepin, morphine and oxycodone. Thus, these medications were added to the current ACB inventory. The scores for these additional medicines were assigned as 2, 1 and 1 respectively. These scores were derived from examining ACB scores for other drugs in the same class, examination of anticholinergic scores in other scales and, in the case of dosulepin, consultation of the Maudsley Prescribing Guidelines (231).

ACB score was calculated as the sum of the anticholinergic ratings at an individual level, for regularly used medications. ACB scores of 0, 1-4, and 5+ indicated no, low, and high ACB respectively.

*Appendix 6* lists the medications in the list and corresponding ACB scores.

### **5.3.6 Sedative Load Model**

The original Sedative Load model drugs list was published in 2003 and was revised in 2011 (143, 144). Drugs are categorised as follows:

- group 1: primary sedatives;
- group 2: drugs with sedation as a prominent side effect or preparations with a sedating component;
- group 3: drugs with sedation as a potential adverse effect; and
- group 4: drugs with no known sedation.

Drugs included in groups 1, 2, and 3-4 were assigned sedative ratings of 2, 1, and 0, respectively. In our study, the medication inventory was adapted from a study of Sedative Load of community-dwelling older adults in Ireland (161), which was derived from the original (2003) and updated (2011) Sedative Load model (143, 144), and modified to include other sedative medications in the IDS-TILDA population. Detailed examination of the SmPCs of medications was carried out as for the ACB scale development (227, 230, 232). The search terms used to identify sedative potential during review of the SmPC were “fatigue, asthenia, somnolence, sedation, lassitude, lethargy, tiredness and drowsiness”. The list of search terms which were used were modelled on those used in the original 2003 Sedative Load model: “sedating, sedative, drowsiness, sleepiness, lassitude, exhaustion, tiresome, fatigability.”(143). In addition, the Maudsley Prescribing Guidelines were consulted for the relative adverse effects of antipsychotic and antidepressant medications (231).

Sedative Load was calculated as the sum of the sedative ratings at an individual level, for regularly used drugs. Sedative Load scores of 0, 1 – 2, and 3 indicated no, low, and high Sedative Load respectively (161).

*Appendix 7* represents the list of medications not included in the reference list (Peklar et al, 2015 (161)) and proposed groups for each based on evidence from the original and updated Sedative Load model (143, 144) and relevant information on sedative severity from SmPCs and the Maudsley Prescribing Guidelines (231). *Appendix 8* represents the list of medications and proposed scores of medications which were included in the reference list, with the same additional information provided for medications on *Appendix 7*.

One pharmacist (JO'C) consulted, reviewed, and amended scores for the original updated list of drugs for both the ACB and Sedative Load inventories. A second pharmacist (NM) independently reviewed these inventories and scoring of medications. Disagreements were resolved by consensus with MH and MO'D. There was one disagreement with regard to the ACB inventory – dosulepin. This medication was initially categorised with score 3 on the basis of the scores assigned to other tricyclic antidepressants (exclusively 3 for all other medicines in the class). However, after discussion and examination of the Maudsley Prescribing Guidelines, which categorised dosulepin's anticholinergic effects as moderate rather than severe (231), and the systematic review conducted by Duran et al (2013) (141), which scored dosulepin as 2, the score for dosulepin was changed from 3 to 2.

There was one disagreement with regard to the Sedative Load inventory – clozapine. This medicine was initially categorised as Group 2 (drugs with sedation as a prominent side effect or preparations with a sedating component) as per two Sedative Load studies (143, 144). However, after consultation of the Maudsley Prescribing Guidelines, clozapine was found to have high incidence/severity of sedation (231) so it was recategorized to Group 1 (primary sedatives).

### **5.3.7 Modified Fried's Frailty Phenotype**

According to Fried's frailty phenotype, five criteria are used to assess frailty. Scores from these five measures are summed to give a total frailty score. Scores are then categorised as follows: 0 = robust; 1 – 2 = pre-frail;  $\geq 3$  = frail (189). This procedure was used in the current study.

The modified Fried's Frailty Phenotype was constructed for use in this study from five measures. The criteria were operationalised as follows:

1. Shrinking was defined by answering the following question:

“Within the last year, have you lost or gained ten pounds (4.5 kg) or more in weight when you weren't trying to?”

Answers were coded as follows:

- a. No, weight has remained the same = 0
- b. Yes, gained weight = 0
- c. Yes, gained and lost weight = 0
- d. Yes, lost weight = 1

This is consistent with the original Fried’s Frailty Phenotype variable on shrinking (189).

- 2. Weakness was defined as being in the lowest sample quintile (20%) for grip strength, adjusted for gender and BMI. The cut-offs identified are shown in *Table 5.1*.

Table 5.1 Grip strength cut-offs by gender and BMI

| <b>BMI Category</b> | <b>Male</b> | <b>Female</b> |
|---------------------|-------------|---------------|
| Underweight         | ≤1 kg       | ≤ 2 kg        |
| Normal              | ≤12.8 kg    | ≤10 kg        |
| Overweight/Obese    | ≤16.6 kg    | ≤ 12 kg       |

Where data on BMI was missing, grip strength scores were examined according to gender. If a score was above the highest cut-off (>16.6kg for males and >12kg for females), the participant scored 0 for this measure.

For one male participant missing BMI data, the score fell between two cut-offs (15kg). In this case (n = 1), and where data on grip strength were missing (n = 240), they were coded as missing for this subsection of the Fried’s Frailty Phenotype.

- 3. Poor endurance and exhaustion were measured by response to the following questions:
  - a. “How much of the time during the past 4 weeks did you feel worn out?”
  - b. “How much of the time during the past 4 weeks did you feel tired?”

Answers were coded as follows: All of the time/most of the time/a good bit of the time = 1; some of the time/a little bit of the time/none of the time = 0.

This method of measuring poor endurance and exhaustion follows a common modification which substitutes two questions from the Vitality Scale of the RAND Health Survey Tool for the original Fried’s frailty phenotype exhaustion criterion (313).

4. Slowness was defined as being in the lowest sample quintile (20%) for timed up and go, adjusted for gender and height. The cut-offs identified are shown in *Table 5.2*.

Table 5.2 Timed up and go cut-offs by gender and height

| Gender | Height               | Cut-off              |
|--------|----------------------|----------------------|
| Male   | Height $\leq$ 173 cm | $\geq$ 21.56 seconds |
|        | Height $>$ 173 cm    | $\geq$ 16.94 seconds |
| Female | Height $\leq$ 159 cm | $\geq$ 22.75 seconds |
|        | Height $>$ 159 cm    | $\geq$ 20.43 seconds |

To participate in the timed up and go assessment, participants were required to be able to walk alone without holding on to another person, using a walking stick or other walking aid. Therefore, wheelchair users, walking aid users, participants requiring assistance to walk across a room and those otherwise physically unable to participate in the assessment were assigned a score of 1 for this element of the frailty phenotype ( $n = 109$ ).

Where data on height was missing ( $n = 79$ ), timed up and go scores were examined according to gender. If a score was below the lowest cut-off ( $< 16.94$  seconds for males and  $< 20.43$  seconds for females), the participant scored 0 for this measure ( $n = 53$ ).

If a score was above the highest cut-off ( $\geq 21.56$  for males and  $\geq 22.75$  seconds for females), the participant scored 1 for this measure ( $n = 18$ ).

For one female participant and seven male participants, the score fell between the cut-offs (female: 21.75 seconds; males ranged from 17.19 to 21.13 seconds)

In these cases ( $n = 8$ ) and where data on timed up and go were missing ( $n = 100$ ), they were coded as missing for this subsection of the Fried's Frailty Phenotype.

5. Low physical activity was defined as no reported activity or some reported activity but not enough to meet moderate or high physical activity criteria as measured by the International Physical Activity Questionnaire – Short Form (IPAQ) (290, 314).

Moderate activity was defined as either of the following 3 criteria:

- a. 3 or more days of vigorous activity of at least 20 minutes per day or
- b. 5 or more days of moderate-intensity activity and/or walking of at least 30 minutes per day or
- c. 5 or more days of any combination of walking, moderate-intensity or vigorous intensity activities achieving a minimum of at least 600 metabolic equivalent (MET) minutes per week.

High activity was defined as either of the following 2 criteria:

- a. Vigorous-intensity activity on at least 3 days and accumulating at least 1500 MET minutes per week or
- b. 7 or more days of any combination of walking, moderate or vigorous intensity activities accumulating at least 3000 MET-minutes/week.

Low physical activity was scored as 1; moderate and high physical activity were both scored as 0.

Where an individual was missing data in two or more of the individual frailty components, they were excluded from analysis (n = 167). This reflects the method used in a similar study of frailty phenotype in older adults with ID, but is more conservative (HA-ID allowed a maximum of two criteria to be missing) (190).

### **5.3.8 Covariates**

*Demographic variables:* Gender (male/female), age range (44 – 59 years/60+ years), level of ID (mild; moderate; severe/profound) and type of residence (independent, community group home, residential care) were included as covariates.

Age range was categorised into two groups for regression analysis due to small numbers in the robust age 65+ group (n = 9). The categories selected were 44 – 59 years and 60+ years. These categories were selected due to the effects of ageing occurring in people with ID at a younger age than those without ID. Previous studies of medication exposure in relation to frailty status typically examined adults aged 70+ years (152, 198-200). In order to account for the premature effects of ageing in this population, the groups 44 – 59 and 60+ were selected. The four regression analyses were also performed with the standard age range categorisation employed across IDS-TILDA – age 44 – 49, age 50 – 64 and 65+ years (*Appendix 9*).

Level of ID is based on reported intelligence quotient (IQ) scores as follows; mild (50 – 55 to approx. 70), moderate (35 – 40 to 50 – 55) and severe/profound (below 35 - 40) (1). Participant case notes were used to identify correct classification. Those with unverified level of ID (n = 53) were excluded from analysis.

Independent residence referred to those living independently or with family. Community group homes were defined as homes with small groups of people with ID (< 10), based in a community setting with staff support. Residential settings were defined where ten or more people share a

single living unit or where the living arrangements are campus based. Type of residence was aggregated into two categories for regression analysis due to small numbers in the independent subgroup. Those living independently or with family (n = 102) were combined with those living in community group homes (n = 298).

Having Down syndrome or ID of another aetiology and reported doctor's diagnosis of Alzheimer's disease and/or dementia (yes/no) were examined as covariates because these were found to be significantly associated with prefrailty at univariate level using a modified Fried's frailty phenotype in a previous study of frailty in older adults with ID (HA-ID) (190).

*History of falls:* Participants/proxies were asked "in the past year have you had any fall including a slip or trip in which you lost your balance and landed on the floor or ground or lower level?" to which they answered "yes", "no" or "don't know". Those who answered "don't know" were excluded from the analyses (n = 10).

*Barthel Index ADLs:* Barthel Index ADLs include ten basic measures of daily activities (mobility, using stairs, dressing, bathing, grooming, feeding, transfer, toileting and bladder and bowel continence) and the degree of dependence reported for each (170, 263). A modified version of Barthel Index ADLs (*Supporting Information Table S 3.1, Chapter 3*) was developed and examined in the IDS-TILDA population. Each participant was assigned a score between 0 and 20 based on their self-/proxy-report of difficulty experienced with each activity. Lower scores indicated poorer physical function. Barthel Index scores were categorised as per Wade & Collin (1988) classifications: total dependence (0 – 4), severe dependence (5 – 12), moderate dependence (13 – 18), mild dependence (19) and total independence (20) (233). Barthel Index ADLs score was analysed as a continuous variable for its association with frailty status.

*Functional Comorbidity Index:* A modified version of the Functional Comorbidity Index (FCI) was examined in relation to frailty (*Supporting Information Table S 3.2, Chapter 3*). The FCI was calculated by summing the presence of a reported doctor's diagnosis of the following conditions: arthritis; osteoporosis/osteopenia; asthma; lung disease; angina; congestive heart failure (or heart disease); myocardial infarction; neurological disease; stroke or transient ischaemic attack; diabetes mellitus type I or II; upper gastrointestinal disease (e.g. ulcer, hernia, reflux); depression (unipolar or bipolar); anxiety or panic disorder; visual impairment (e.g., cataracts, glaucoma, macular degeneration); hearing impairment; and overweight/obese to produce a continuous score between 0 and 16. Data on osteoporosis/osteopenia and overweight/obese were also supplemented with objective data from the health assessment. Previously, a number

of DBI studies have used modified versions of the FCI. Where participants were missing data on two or more conditions ( $n = 145$ ), they were excluded from the FCI score evaluation, reflecting the method used previously (196).

### 5.3.9 Statistical Analysis

Calculation of ACB, Sedative Load and DBI scores was performed using Microsoft Excel 2010 (Microsoft Corporation). Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) version 25.0 (IBM Corporation). Statistical significance was set at  $p < 0.05$ .

Descriptive statistics were generated to provide percentages, and 95% confidence intervals.

Univariate analysis was performed to examine associations between frailty and demographic and clinical characteristics in addition to medication exposure as measured by DBI, ACB and Sedative Load. Chi-square tests for independence were used to test for significant associations between categorical variables. For one variable (Alzheimer's disease/dementia), one category had less than 5 participants, which can affect the assumptions of the Chi-square test. As a result, a Fisher's Exact Test was performed for a  $2 \times 2$  table – Alzheimer's disease/dementia (yes/no) and non-frail versus pre-frail and frail combined.

Two separate Analyses of Covariance (ANCOVAs) were performed to produce adjusted means for Barthel Index ADLs and comorbidities as measured by FCI.

Four separate multinomial logistic regressions were carried out to identify the association between frailty phenotype and medication exposure according to polypharmacy, DBI, ACB and Sedative Load. The reference category was those classified as robust. The model was adjusted for age, level of ID and type of residence. In addition, the Drug Burden Index regression was adjusted for number of non-DBI medicines; the Anticholinergic Cognitive Burden regression was adjusted for number of non-ACB medicines; and the Sedative Load regression was adjusted for number of non-Sedative Load medicines.

Four additional multinomial logistic regressions were performed with Alzheimer's disease/dementia included, with all other variables the same. The results of these regressions are included in *Appendix 10*.

Required sample size for the four multinomial logistic regressions was determined as follows according to the guideline of Peduzzi et al (270): for a minimum number of cases ( $n$ ) needed for the study,  $n = 10k/p$ , where  $p$  is the smallest of the proportions of negative or positive cases in

the population and  $k$  is the number of covariates. For the multinomial logistic regression, there were 6 covariates and the proportion of negative cases (Robust) was 0.179, therefore a minimum sample size of  $n = 353$  was needed, which our sample size ( $n = 528$ ) exceeded.

Power calculations for the ANCOVA were performed using G\*Power (version 3.1.9.2)(295). To detect a medium effect size (Cohen's  $f = 0.25$ )(296), for three-level analysis (Fried's frailty phenotype – robust, pre-frail and frail) with 4 covariates (age, type of residence, level of ID, polypharmacy), a sample size of 501 achieved a power of 0.99 with  $\alpha = 0.05$  (Barthel Index assessment) and a sample size of 464 achieved a power of 0.99 with  $\alpha = 0.05$  (FCI assessment).

Variance Inflation Factors (VIF) and Spearman's correlation coefficients were used to test variables for multicollinearity. All VIFs were  $<2$ , therefore there was no collinearity of concern between variables. Dancy and Reidy's categorisation (269) was used to interpret Spearman's correlation coefficients. All correlation coefficient values with the exception of Barthel Index ADLs were  $<0.4$ , indicating only weak correlations existed between variables which were again not of concern.



## 5.4 Results

### 5.4.1 Characteristics of the Study Population (n = 570)

Table 5.3 Univariate Analysis of Modified Fried's Frailty Phenotype

| Independent Variables                                                                                          | Fried's Frailty Phenotype Status (n = 570)<br>% (95% Confidence Interval (CI)) n   |                                                                                       |                                                                                   |                   |
|----------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|-------------------|
|                                                                                                                | Robust<br>17.9 (14.7 - 21) n = 102                                                 | Pre-Frail<br>64 (60.1 - 68) n = 365                                                   | Frail<br>18.1 (14.9 - 21.2) n = 103                                               | p value           |
| <b>Gender</b><br>Male (n = 237)<br>Female (n = 333)                                                            | 19.4 (14.4 - 24.4) n = 46<br>16.8 (12.8 - 20.8) n = 56                             | 66.7 (60.7 - 72.7) n = 158<br>62.2 (57 - 67.4) n = 207                                | 13.9 (9.5 - 18.3) n = 33<br>21 (16.6 - 25.4) n = 70                               | 0.090             |
| <b>Age</b><br>44 – 49 years (n = 158)<br>50 – 64 years (n = 291)<br>65+ years (n = 121)                        | 19 (12.9 - 25.1) n = 30<br>21.6 (16.9 - 26.4) n = 63<br>7.4 (2.8 - 12.1) n = 9     | 65.2 (57.8 - 72.6) n = 103<br>63.6 (58 - 69.1) n = 185<br>63.6 (55.1 - 72.2) n = 77   | 15.8 (10.1 - 21.5) n = 25<br>14.8 (10.7 - 18.9) n = 43<br>28.9 (20.8 - 37) n = 35 | <b>0.001*</b>     |
| <b>Age</b><br>44 – 59 years (n = 381)<br>60+ years (n = 189)                                                   | 21.5 (17.4 - 25.6) n = 82<br>10.6 (6.2 - 15) n = 20                                | 64.6 (59.8 - 69.4) n = 246<br>63 (56.1 - 69.8) n = 119                                | 13.9 (10.4 - 17.4) n = 53<br>26.5 (20.2 - 32.7) n = 50                            | <b>&lt;0.001*</b> |
| <b>Level of ID</b><br>Mild (n = 123)<br>Moderate (n = 252)<br>Severe/Profound (n = 153)                        | 28.5 (20.5 - 36.4) n = 35<br>16.7 (12.1 - 21.3) n = 42<br>11.1 (6.1 - 16.1) n = 17 | 65 (56.6 - 73.5) n = 80<br>63.5 (57.5 - 69.4) n = 160<br>62.7 (55.1 - 70.4) n = 96    | 6.5 (2.1 - 10.9) n = 8<br>19.8 (14.9 - 24.8) n = 50<br>26.1 (19.2 - 33.1) n = 40  | <b>&lt;0.001*</b> |
| <b>Type of Residence</b><br>Independent/Community Group Home (n = 327)<br>Residential Care (n = 243)           | 21.4 (17 - 25.9) n = 70<br>13.2 (8.9 - 17.4) n = 32                                | 66.1 (60.9 - 71.2) n = 216<br>61.3 (55.2 - 67.4) n = 149                              | 12.5 (8.9 - 16.1) n = 41<br>25.5 (20 - 31) n = 62                                 | <b>&lt;0.001*</b> |
| <b>Polypharmacy</b><br>No polypharmacy (n = 205)<br>Polypharmacy (n = 192)<br>Excessive polypharmacy (n = 113) | 26.3 (20.3 - 32.3) n = 55<br>16.2 (11.4 - 21.1) n = 36<br>7.9 (3.4 - 12.4) n = 11  | 65.1 (58.6 - 71.5) n = 136<br>65.3 (59.1 - 71.6) n = 145<br>60.4 (52.3 - 68.6) n = 84 | 8.6 (4.8 - 12.4) n = 18<br>18.5 (13.4 - 23.6) n = 41<br>31.7 (23.9 - 39.4) n = 44 | <b>&lt;0.001*</b> |

Table 5.3 Univariate Analysis of Modified Fried's Frailty Phenotype (continued)

| Independent Variables                                                                                              | Fried's Frailty Phenotype Status (n = 570)<br>% (95% Confidence Interval (CI)) n |                                     |                                     |                   |
|--------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|-------------------------------------|-------------------------------------|-------------------|
|                                                                                                                    | Robust<br>17.9 (14.7 - 21) n = 102                                               | Pre-Frail<br>64 (60.1 - 68) n = 365 | Frail<br>18.1 (14.9 - 21.2) n = 103 | p value           |
| <b>Cause of ID</b>                                                                                                 |                                                                                  |                                     |                                     | 0.135             |
| Down syndrome (n = 99)                                                                                             | 12.1 (5.7 - 18.6) n = 12                                                         | 64.6 (55.2 - 74.1) n = 64           | 23.2 (14.9 - 31.6) n = 23           |                   |
| Other (n = 471)                                                                                                    | 19.1 (15.6 - 22.7) n = 90                                                        | 63.9 (59.6 - 68.2) n = 301          | 17 (13.6 - 20.4) n = 80             |                   |
| <b>Alzheimer's Disease/Dementia</b>                                                                                |                                                                                  |                                     |                                     | <sup>a</sup>      |
| Yes (n = 38)                                                                                                       | 2.6 (-2.5 - 7.7) n = 1                                                           | 50 (34.1 - 65.9) n = 19             | 47.4 (31.5 - 63.2) n = 18           |                   |
| No (n = 499)                                                                                                       | 19.2 (15.8 - 22.7) n = 96                                                        | 65.7 (61.6 - 69.9) n = 328          | 15 (11.9 - 18.2) n = 75             |                   |
| <b>Fall in the previous 12 months</b>                                                                              |                                                                                  |                                     |                                     | 0.371             |
| Yes (n = 160)                                                                                                      | 14.4 (8.9 - 19.8) n = 23                                                         | 68.1 (60.9 - 75.3) n = 109          | 17.5 (11.6 - 23.4) n = 28           |                   |
| No (n = 406)                                                                                                       | 19 (15.2 - 22.8) n = 77                                                          | 62.6 (57.9 - 67.3) n = 254          | 18.5 (14.7 - 22.2) n = 75           |                   |
| <b>Barthel Index</b>                                                                                               |                                                                                  |                                     |                                     | <b>&lt;0.001*</b> |
| No / mild dependence (n = 137)                                                                                     | 29.9 (22.3 - 37.6) n = 41                                                        | 68.6 (60.8 - 76.4) n = 94           | 1.5 (-0.5 - 3.5) n = 2              |                   |
| Moderate dependence (n = 228)                                                                                      | 21.9 (16.6 - 27.3) n = 50                                                        | 68.9 (62.8 - 74.9) n = 157          | 9.2 (5.5 - 13) n = 21               |                   |
| Severe / total dependence (n = 176)                                                                                | 3.4 (0.7 - 6.1) n = 6                                                            | 53.4 (46 - 60.8) n = 94             | 43.2 (35.9 - 50.5) n = 76           |                   |
| <b>Drug Burden Index</b>                                                                                           |                                                                                  |                                     |                                     | <b>0.003*</b>     |
| No Exposure (n = 116)                                                                                              | 26.7 (18.7 - 34.8) n = 31                                                        | 63.8 (55 - 72.5) n = 74             | 9.5 (4.2 - 14.8) n = 11             |                   |
| Low Exposure (n = 141)                                                                                             | 19.1 (12.7 - 25.6) n = 27                                                        | 65.2 (57.4 - 73.1) n = 92           | 15.6 (9.6 - 21.6) n = 22            |                   |
| High Exposure (n = 313)                                                                                            | 14.1 (10.2 - 17.9) n = 44                                                        | 63.6 (58.2 - 68.9) n = 199          | 22.4 (17.7 - 27) n = 70             |                   |
| <b>Anticholinergic Cognitive Burden</b>                                                                            |                                                                                  |                                     |                                     | <b>0.029*</b>     |
| No Exposure (n = 169)                                                                                              | 22.5 (16.2 - 28.8) n = 38                                                        | 66.9 (59.8 - 74) n = 113            | 10.7 (6 - 15.3) n = 18              |                   |
| Low Exposure (n = 262)                                                                                             | 16.8 (12.3 - 21.3) n = 44                                                        | 62.2 (56.3 - 68.1) n = 163          | 21 (16.1 - 25.9) n = 55             |                   |
| High Exposure (n = 139)                                                                                            | 14.4 (8.6 - 20.2) n = 20                                                         | 64 (56.1 - 72) n = 89               | 21.6 (14.7 - 28.4) n = 30           |                   |
| <b>Sedative Load</b>                                                                                               |                                                                                  |                                     |                                     | <b>0.006*</b>     |
| No Exposure (n = 145)                                                                                              | 24.1 (17.2 - 31.1) n = 35                                                        | 66.9 (59.2 - 74.6) n = 97           | 9 (4.3 - 13.6) n = 13               |                   |
| Low Exposure (n = 169)                                                                                             | 17.2 (11.5 - 22.8) n = 29                                                        | 63.9 (56.7 - 71.1) n = 108          | 18.9 (13 - 24.8) n = 32             |                   |
| High Exposure (n = 256)                                                                                            | 14.8 (10.5 - 19.2) n = 38                                                        | 62.5 (56.6 - 68.4) n = 160          | 22.7 (17.5 - 27.8) n = 58           |                   |
| *Significant factors (p < 0.05) highlighted in bold                                                                |                                                                                  |                                     |                                     |                   |
| <sup>a</sup> Insufficient power to compute Chi-square test statistic – Fisher's Exact Test used as an alternative. |                                                                                  |                                     |                                     |                   |

Table 5.4 Fisher's Exact Test for Alzheimer's Disease/Dementia and Frailty Status

| Independent Variable                | Fried's Frailty Phenotype Status (n = 537)<br>% (95% Confidence Interval (CI)) n |                                                  | p value       |
|-------------------------------------|----------------------------------------------------------------------------------|--------------------------------------------------|---------------|
|                                     | Not Frail<br>18.1 (14.8 - 21.3) n = 97                                           | Pre-Frail or Frail<br>81.9 (78.7 - 85.2) n = 440 |               |
| <b>Alzheimer's Disease/Dementia</b> |                                                                                  |                                                  | <b>0.007*</b> |
| Yes (n = 38)                        | 2.6 (-2.5 - 7.7) n = 1                                                           | 97.4 (92.3 - 102.5) n = 37                       |               |
| No (n = 499)                        | 19.2 (15.8 - 22.7) n = 96                                                        | 80.8 (77.3 - 84.2) n = 403                       |               |

#### 5.4.2 Prevalence of Frailty

Of the 677 participants with medication data available, 570 (84.2%) provided sufficient data to assess their frailty status using the modified Fried's frailty phenotype. The prevalence of frailty in this sample was 18.1% (n = 103), 64.0% (n = 365) were pre-frail and 17.9% (n = 102) were robust. There was no statistically significant association between gender, cause of ID or history of falls with frailty status (p = 0.090, 0.135 and 0.371, respectively; *Table 5.3*). Frailty status was significantly associated with age using both categorisations (three-level p = 0.001; two-level p < 0.001; *Table 5.3*), level of ID (p < 0.001; *Table 5.3*), type of residence (p < 0.001; *Table 5.3*), polypharmacy (p < 0.001; *Table 5.3*) and Barthel Index (p < 0.001; *Table 5.3*). Alzheimer's disease or dementia was found to be statistically significantly associated with frailty status as a combined variable using Fisher's Exact Test (p = 0.007; *Table 5.4*) with an Odds Ratio (OR) of 0.113 (95% Confidence Interval (CI) 0.015 – 0.837).

#### 5.4.3 Medication Exposure

On univariate analysis, frailty status was found to be statistically significantly associated with DBI, ACB and Sedative Load model categories. Of those with both medication data and frailty data (n = 570), 79.6% (n = 454) were exposed to DBI medications, 70.3% (n = 401) were exposed to ACB medications and 74.6% (n = 425) were exposed to Sedative Load medications. Of those with no exposure to DBI, 26.7% (n = 31) were classified as robust, while only 14.1% (n = 44) with high DBI exposure were robust. Of those with no ACB exposure, 22.5% (n = 38) were robust, versus 14.4% (n = 20) of those with high exposure. Of those with no exposure to Sedative Load medications, 24.1% (n = 35) were categorised as robust, while 14.8% (n = 38) of those who had high exposure were robust.

#### 5.4.4 Frailty and Barthel Index ADLs

There was significant multicollinearity between the modified Fried's frailty phenotype category and Barthel Index ADLs score ( $p < 0.001$ ). This correlation was moderate (0.481). This correlation was moderate to strong (0.578) between modified Fried's frailty phenotype continuous score and Barthel Index score. This association was also statistically significant ( $p < 0.001$ ).

Adjusted means for Barthel Index ADLs from ANCOVA analysis, adjusted for confounding factors (age, type of residence, level of ID, polypharmacy, dementia) were found to be statistically significantly associated with frailty category. The adjusted mean for performance in Barthel Index ADLs for the pre-frail group was 14.1, while the adjusted mean for the frail group was 8.2, in comparison with the robust group, which had an adjusted mean score of 15.8 ( $p = 0.003$  for robust versus pre-frail;  $p < 0.001$  for robust versus frail) (Figure 5.1).

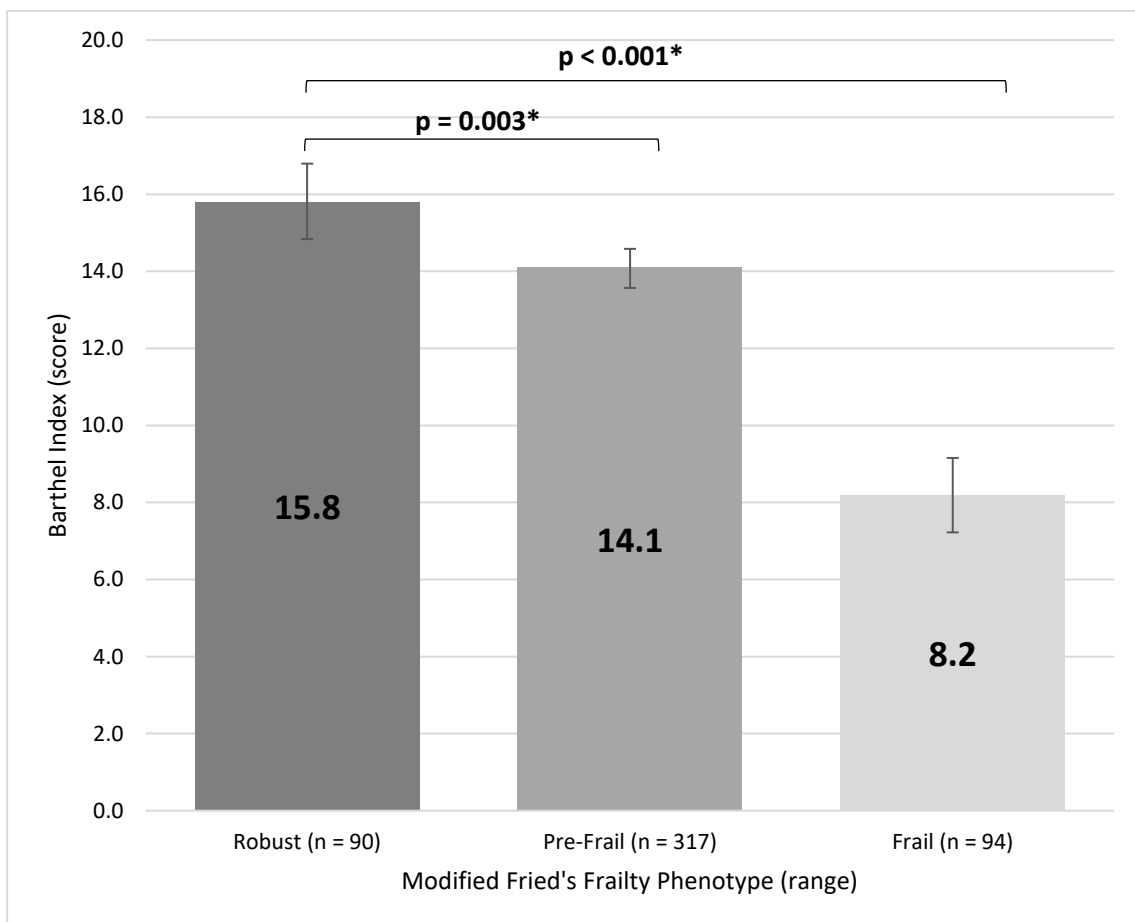


Figure 5.1 Adjusted Means for Barthel Index ADLs Score and Frailty (adjusted for age, type of residence, level of ID, polypharmacy)

#### 5.4.5 Frailty and Functional Comorbidity Index

Adjusted means for FCI score from ANCOVA, also adjusted for confounding factors (age, type of residence, level of ID, polypharmacy, dementia) were found to be statistically significantly associated with frailty category. Adjusted mean number of comorbidities as measured by FCI was 3.6 for the pre-frail group and 4.0 for the frail group, compared to 3.1 in the robust category ( $p = 0.006$  for robust versus pre-frail;  $p = 0.001$  for robust versus frail) (Figure 5.2).

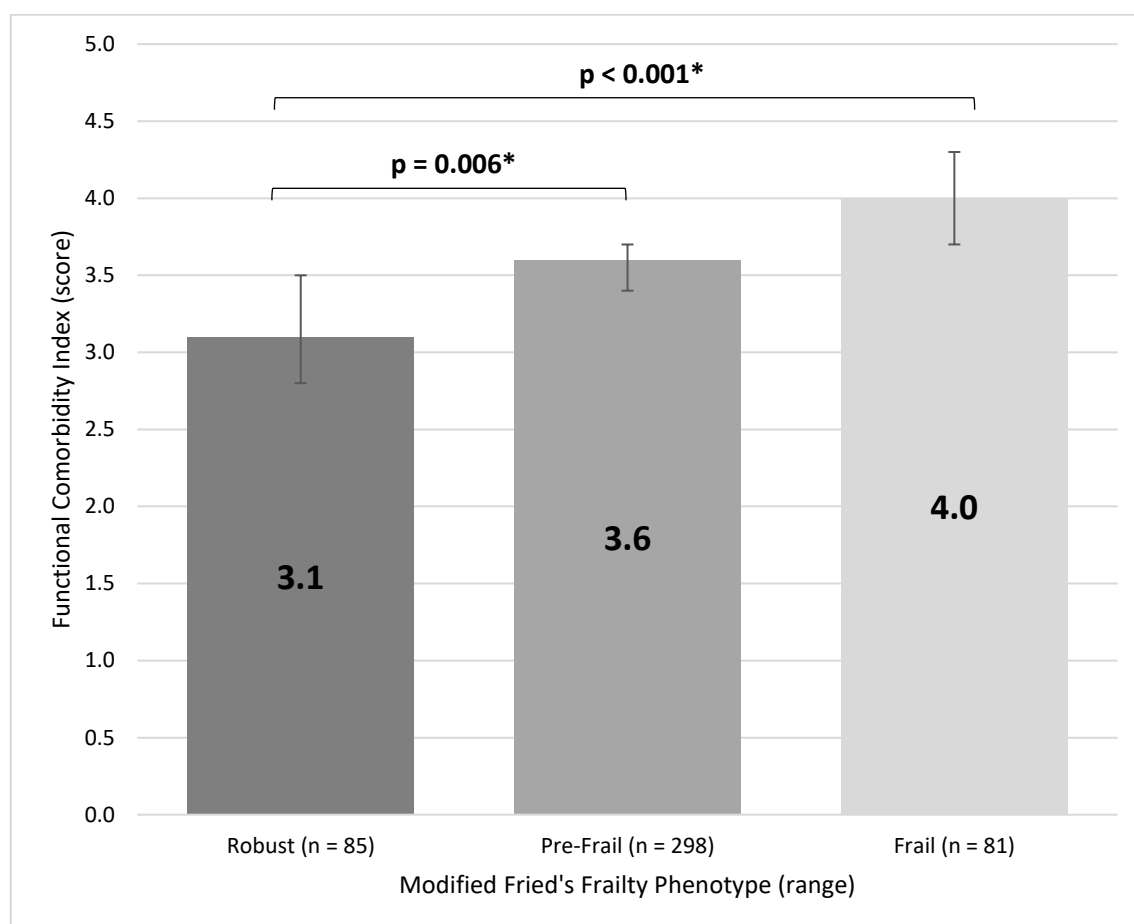


Figure 5.2 Adjusted Means for Comorbidities as measured by Functional Comorbidity Index and Frailty (adjusted for age, type of residence, level of ID, polypharmacy)

#### 5.4.6 Association between Frailty and Medication Exposure

On univariate analysis, polypharmacy was significantly associated with frailty status as determined by the modified Fried's frailty phenotype ( $p < 0.001$ ; Table 5.3). DBI exposure was significantly associated with frailty phenotype ( $p = 0.003$ ; Table 5.3). ACB exposure was significantly associated with frailty phenotype ( $p = 0.029$ ; Table 5.3). Sedative Load exposure was also significantly associated with frailty phenotype ( $p = 0.006$ ; Table 5.3)

On multivariate analysis, excessive polypharmacy was found to be significantly associated with being pre-frail ( $p = 0.017$ ; Odds Ratio (OR) 2.555; 95% Confidence Interval (CI) 1.186 – 5.502; *Table 5.5*) and frail ( $p < 0.001$ ; OR 7.133; 95% CI 2.808 – 18.119; *Table 5.5*). The other factor found to be significantly associated with pre-frailty was severe/profound level of ID ( $p = 0.026$ ; OR 2.235; 95% CI 1.103 – 4.530; *Table 5.5*). The factors significantly associated with frailty were age 60+ years ( $p < 0.001$ ; OR 3.649; 95% CI 1.791 – 7.435; *Table 5.5*), moderate level of ID ( $p = 0.001$ ; OR 4.707; 95% CI 1.892 – 11.708) and severe/profound level of ID ( $p < 0.001$ ; OR 7.523; 95% CI 2.668 – 21.219; *Table 5.5*).

There was no statistically significant association between DBI score categories with frailty status after adjusting for confounding factors. In the regression model, age 60+ ( $p = 0.018$ ; OR 2.077; 95% CI 1.135 – 3.801) and severe/profound level of ID ( $p = 0.031$ ; OR 2.185; 95% CI 1.075 – 4.441; *Table 5.6*) were found to be associated with pre-frailty, and age 60+ years ( $p < 0.001$ ; OR 3.573; 95% CI 1.761 – 7.249; *Table 5.6*), moderate level of ID ( $p = 0.001$ ; OR 4.628; 95% CI 1.864 – 11.487), severe/profound level of ID ( $p < 0.001$ ; OR 7.653; 95% CI 2.720 – 21.533; *Table 5.6*) were found to be significantly associated with frailty.

ACB score category was not found to be associated with frailty status after adjusting for confounding factors ( $p > 0.05$ ; *Table 5.7*). In this regression model, age 60+ ( $p = 0.012$ ; OR 2.166; 1.182 – 3.969) and severe/profound level of ID was found to be associated with pre-frailty ( $p = 0.028$ ; OR 2.208; 95% CI 1.088 – 4.480; *Table 5.7*), and age 60+ years ( $p < 0.001$ ; OR 3.704; 95% CI 1.821 – 7.535; *Table 5.7*), moderate level of ID ( $p = 0.001$ ; OR 4.503; 95% CI 1.809 – 11.210), severe/profound level of ID ( $p < 0.001$ ; OR 7.420; 95% CI 2.636 – 20.890; *Table 5.7*) were found to be significantly associated with frailty.

Sedative Load was not found to be associated with frailty status after adjusting for confounding factors ( $p > 0.05$ ; *Table 5.8*). As for the DBI and ACB regressions, the factor which was found to be statistically significantly associated with pre-frailty were age 60+ ( $p = 0.021$ ; OR 2.039; 95% CI 1.113 – 3.733) and severe/profound level of ID ( $p = 0.026$ ; OR 2.240; 95% CI 1.104 – 4.546; *Table 5.8*), and the factors significantly associated with frailty were age 60+ years ( $p < 0.001$ ; OR 3.523; 95% CI 1.735 – 7.155; *Table 5.8*), moderate level of ID ( $p = 0.001$ ; OR 4.548; 95% CI 1.833 – 11.282) and severe/profound level of ID ( $p < 0.001$ ; OR 7.629; 95% CI 2.721 – 21.389; *Table 5.8*).

When the four multinomial regressions were performed with three-level age range (44 – 49 years, 50 – 64 years and 65+ years), age 65+ was found to be associated with frailty in all four cases, and there was no significant association between age and pre-frailty.

Each of these four multinomial regressions were also performed with Alzheimer's disease/dementia included as a variable. The significant factors from the analyses remained the same as the model with Alzheimer's disease/dementia included. Alzheimer's disease/dementia was found to be significantly associated with frailty in all four models ( $p < 0.05$  in all cases, *Appendix 10*)

Table 5.5 Multivariate analysis of polypharmacy and frailty (n = 528)<sup>a</sup>

|                                                                                                                                      | Pre-Frail            |               | Frail                 |                   |
|--------------------------------------------------------------------------------------------------------------------------------------|----------------------|---------------|-----------------------|-------------------|
|                                                                                                                                      | OR (95% CI)          | <i>p</i>      | OR (95% CI)           | <i>p</i>          |
| <b>Polypharmacy</b>                                                                                                                  |                      |               |                       |                   |
| No Polypharmacy                                                                                                                      | 1 (reference)        |               | 1 (reference)         |                   |
| Polypharmacy                                                                                                                         | 1.365 (0.809; 2.304) | 0.244         | 2.076 (0.967; 4.454)  | 0.061             |
| Excessive Polypharmacy                                                                                                               | 2.555 (1.186; 5.502) | <b>0.017*</b> | 7.133 (2.808; 18.119) | <b>&lt;0.001*</b> |
| <b>Age</b>                                                                                                                           |                      |               |                       |                   |
| 44 – 59 years                                                                                                                        | 1 (reference)        |               | 1 (reference)         |                   |
| 60+ years                                                                                                                            | 2.150 (1.175; 3.932) | <b>0.013*</b> | 3.649 (1.791; 7.435)  | <b>&lt;0.001*</b> |
| <b>Level of ID</b>                                                                                                                   |                      |               |                       |                   |
| Mild                                                                                                                                 | 1 (reference)        |               | 1 (reference)         |                   |
| Moderate                                                                                                                             | 1.620 (0.947; 2.773) | 0.078         | 4.707 (1.892; 11.708) | <b>0.001</b>      |
| Severe/Profound                                                                                                                      | 2.235 (1.103; 4.530) | <b>0.026*</b> | 7.523 (2.668; 21.219) | <b>&lt;0.001*</b> |
| <b>Type of Residence</b>                                                                                                             |                      |               |                       |                   |
| Independent/Community                                                                                                                | 1 (reference)        |               | 1 (reference)         |                   |
| Group Home                                                                                                                           |                      |               |                       |                   |
| Residential Care                                                                                                                     | 0.989 (0.584; 1.674) | 0.967         | 1.262 (0.651; 2.444)  | 0.491             |
| <sup>a</sup> Reference category: Robust. Data are adjusted odds ratio (OR). Cox and Snell $r^2$ is 0.131; Nagelkerke $r^2$ is 0.157. |                      |               |                       |                   |

Table 5.6 Multivariate analysis of Drug Burden Index exposure and frailty (n = 528)<sup>a</sup>

|                          | Pre-Frail            |               | Frail                 |                   |
|--------------------------|----------------------|---------------|-----------------------|-------------------|
|                          | OR (95% CI)          | <i>p</i>      | OR (95% CI)           | <i>p</i>          |
| <b>Drug Burden Index</b> |                      |               |                       |                   |
| No Exposure              | 1 (reference)        |               | 1 (reference)         |                   |
| Low Exposure             | 1.063 (0.550; 2.056) | 0.856         | 1.359 (0.504; 3.666)  | 0.545             |
| High Exposure            | 1.270 (0.700; 2.304) | 0.432         | 2.159 (0.892; 5.228)  | 0.088             |
| <b>Age</b>               |                      |               |                       |                   |
| 44 – 59 years            | 1 (reference)        |               | 1 (reference)         |                   |
| 60+ years                | 2.077 (1.135; 3.801) | <b>0.018*</b> | 3.573 (1.761; 7.249)  | <b>&lt;0.001*</b> |
| <b>Level of ID</b>       |                      |               |                       |                   |
| Mild                     | 1 (reference)        |               | 1 (reference)         |                   |
| Moderate                 | 1.606 (0.934; 2.761) | 0.087         | 4.628 (1.864; 11.487) | <b>0.001</b>      |
| Severe/Profound          | 2.185 (1.075; 4.441) | <b>0.031*</b> | 7.653 (2.720; 21.533) | <b>&lt;0.001*</b> |
| <b>Type of Residence</b> |                      |               |                       |                   |
| Independent/Community    | 1 (reference)        |               | 1 (reference)         |                   |
| Group Home               |                      |               |                       |                   |
| Residential Care         | 0.969 (0.571; 1.643) | 0.906         | 1.297 (0.671; 2.505)  | 0.439             |

<sup>a</sup> Reference category: Robust. Data are adjusted odds ratio (OR). Model adjusted for number of non-DBI medicines; Cox and Snell  $r^2$  is 0.127; Nagelkerke  $r^2$  is 0.151.

Table 5.7 Multivariate analysis of Anticholinergic Cognitive Burden exposure and frailty (n = 528)<sup>a</sup>

|                                         | Pre-Frail            |               | Frail                 |                   |
|-----------------------------------------|----------------------|---------------|-----------------------|-------------------|
|                                         | OR (95% CI)          | <i>p</i>      | OR (95% CI)           | <i>p</i>          |
| <b>Anticholinergic Cognitive Burden</b> |                      |               |                       |                   |
| No Exposure                             | 1 (reference)        |               | 1 (reference)         |                   |
| Low Exposure                            | 0.893 (0.515; 1.549) | 0.688         | 1.614 (0.742; 3.512)  | 0.228             |
| High Exposure                           | 0.919 (0.464; 1.821) | 0.810         | 1.470 (0.596; 3.628)  | 0.403             |
| <b>Age</b>                              |                      |               |                       |                   |
| 44 – 59 years                           | 1 (reference)        |               | 1 (reference)         |                   |
| 60+ years                               | 2.166 (1.182; 3.969) | <b>0.012*</b> | 3.704 (1.821; 7.535)  | <b>&lt;0.001*</b> |
| <b>Level of ID</b>                      |                      |               |                       |                   |
| Mild                                    | 1 (reference)        |               | 1 (reference)         |                   |
| Moderate                                | 1.570 (0.914; 2.695) | 0.102         | 4.503 (1.809; 11.210) | <b>0.001</b>      |
| Severe/Profound                         | 2.208 (1.088; 4.480) | <b>0.028*</b> | 7.420 (2.636; 20.890) | <b>&lt;0.001*</b> |
| <b>Type of Residence</b>                |                      |               |                       |                   |
| Independent/Community                   | 1 (reference)        |               | 1 (reference)         |                   |
| Group Home                              |                      |               |                       |                   |
| Residential Care                        | 0.958 (0.562; 1.631) | 0.874         | 1.273 (0.655; 2.472)  | 0.476             |

<sup>a</sup> Reference category: Robust. Data are adjusted odds ratio (OR). Model adjusted for number of non-ACB medicines; Cox and Snell  $r^2$  is 0.139; Nagelkerke  $r^2$  is 0.166.



Table 5.8 Multivariate analysis of Sedative Load exposure and frailty (n = 528)<sup>a</sup>

|                                                                                                                                                                                                | Pre-Frail            |               | Frail                 |                   |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|---------------|-----------------------|-------------------|
|                                                                                                                                                                                                | OR (95% CI)          | <i>p</i>      | OR (95% CI)           | <i>p</i>          |
| <b>Sedative Load</b>                                                                                                                                                                           |                      |               |                       |                   |
| No Exposure                                                                                                                                                                                    | 1 (reference)        |               | 1 (reference)         |                   |
| Low Exposure                                                                                                                                                                                   | 0.898 (0.483; 1.669) | 0.734         | 1.533 (0.620; 3.790)  | 0.355             |
| High Exposure                                                                                                                                                                                  | 1.021 (0.564; 1.848) | 0.945         | 2.056 (0.880; 4.806)  | 0.096             |
| <b>Age</b>                                                                                                                                                                                     |                      |               |                       |                   |
| 44 – 59 years                                                                                                                                                                                  | 1 (reference)        |               | 1 (reference)         |                   |
| 60+ years                                                                                                                                                                                      | 2.039 (1.113; 3.733) | <b>0.021*</b> | 3.523 (1.735; 7.155)  | <b>&lt;0.001*</b> |
| <b>Level of ID</b>                                                                                                                                                                             |                      |               |                       |                   |
| Mild                                                                                                                                                                                           | 1 (reference)        |               | 1 (reference)         |                   |
| Moderate                                                                                                                                                                                       | 1.599 (0.932; 2.745) | 0.088         | 4.548 (1.833; 11.282) | <b>0.001*</b>     |
| Severe/Profound                                                                                                                                                                                | 2.240 (1.104; 4.546) | <b>0.026*</b> | 7.629 (2.721; 21.389) | <b>&lt;0.001*</b> |
| <b>Type of Residence</b>                                                                                                                                                                       |                      |               |                       |                   |
| Independent/Community                                                                                                                                                                          | 1 (reference)        |               | 1 (reference)         |                   |
| Group Home                                                                                                                                                                                     |                      |               |                       |                   |
| Residential Care                                                                                                                                                                               | 0.966 (0.567; 1.647) | 0.900         | 1.282 (0.662; 2.483)  | 0.461             |
| <sup>a</sup> Reference category: Robust. Data are adjusted odds ratio (OR). Model adjusted for number of non-Sedative Load medicines; Cox and Snell $r^2$ is 0.132; Nagelkerke $r^2$ is 0.158. |                      |               |                       |                   |

## 5.5 Discussion

### 5.5.1 Principal findings

Our findings in this study reveal that older people with ID have higher levels of frailty as measured by a modified Fried's frailty phenotype than older adults without ID. Frailty in the IDS-TILDA cohort was found to be 18.1%, compared to a weighted average prevalence of 9.9% in previous studies of older adults (15 studies; n = 44,894 participants) (184, 315). Pre-frailty was reported in 64.0% in IDS-TILDA (*Table 5.3*), while it was found to be 44.2% on average in other older populations (15 studies; n = 44,894 participants) (184, 315). Frailty status was significantly associated with performance in Barthel Index ADLs, after adjusting for confounding factors. There was significant moderate-to-strong correlation between frailty status and Barthel Index score. There was a statistically significant association between frailty and comorbidities as measured by the Functional Comorbidity Index. After adjusting for confounders, multivariate analysis identified that excessive polypharmacy was statistically significantly associated with pre-frailty and frailty (*Table 5.5*). However, adjusted multivariate analysis for DBI, ACB and Sedative Load revealed no statistically significant association between these measures of medication exposure and frailty (*Table 5.6*). From the multinomial regression it was found that those aged 60+ years and those with severe/profound level of ID were significantly more likely to be categorised as pre-frail, and those aged 60+ years, those with moderate level of ID and those with severe/profound level of ID were significantly more likely to be categorised as frail.

### 5.5.2 Frailty and Barthel Index ADLs

There was significant multicollinearity between frailty and Barthel Index ADLs score. Greater dependency in Barthel Index ADLs has previously been identified as a determinant of frailty (316). Adjusted mean Barthel Index scores decreased as level of frailty increased, an association which was found to be statistically significant, indicating greater dependency of those who were classified as pre-frail or frail compared to the robust group. Considering some of the concepts which are examined in Barthel Index overlap with the criteria examined in the modified Fried's frailty phenotype (for example, poor mobility in Barthel Index reflects results for slowness and low physical activity in the modified Fried's frailty phenotype), this high level of multicollinearity is expected between these variables. The HA-ID study previously found a strong overlap between motor disability and frailty (190), and considering both Barthel Index ADLs and frailty

as measured by a Fried's frailty phenotype are typically influenced by mobility (172, 192, 311), the findings from the current study correspond with existing evidence.

### **5.5.3 Frailty and Functional Comorbidity Index**

Frailty status was found to be statistically significantly associated with number of comorbidities as measured by the FCI (*Figure 5.2*). Pre-frail and frail older adults with ID appear to have a greater number of comorbidities than their robust counterparts. Considering that the FCI is a measure of comorbidities which are determined to impact on physical function (174), and the modified Fried's frailty phenotype is based on a number of measures of physical function, this is as expected. A number of the comorbidities included in the FCI have been identified as potential risk factors for frailty in older adults in the general population, in particular cardiovascular disease, diabetes, stroke, arthritis and chronic obstructive pulmonary disease (186), so the comorbidities included in the FCI are likely to be impacting upon functional ability, and the measure of frailty used in this study supports this.

### **5.5.4 Frailty and medication exposure in older adults with ID**

Despite the younger age profile of the adults in IDS-TILDA, high levels of frailty and pre-frailty were identified in this study, reflecting how age-related changes tend to occur earlier in the lives of people with ID (10).

Exposure to DBI medications has previously been described in this cohort, and was found to be higher than that observed in older adults without ID (*Chapter 3*; (287)). Exposure to ACB medications (65.1%) was higher than that observed in older adults without ID, where it has been reported that ACB exposure was between 34 and 61%, depending on the population studied (157-159). Community-dwelling and hospitalised older adults ( $\geq 65$  years) had the lowest prevalence of exposure to ACB medicines (36.5% (158) and 34.1% (159), respectively), while a UK study of hospitalised adults aged 90 years and older reported exposure to ACB medication of 61.1% (157).

Exposure to Sedative Load model medications (74.6%) was substantially higher than the exposure reported in a recent study of Sedative Load and frailty among older community-dwelling adults ( $\geq 65$  years) in Ireland (19%) (161) and a study of community-dwelling older adults ( $\geq 75$  years) in Finland, which reported exposure to sedative medications in 29% of the cohort (144).

The findings from this study reveal that while excessive polypharmacy is associated with pre-frailty and frailty as assessed by a modified Fried's frailty phenotype, DBI, ACB and Sedative Load exposure are not. Polypharmacy is a relatively crude measure of drug exposure, and as such it is very broad, while the DBI, ACB and Sedative Load models are specific to anticholinergic and sedative medications. It could be the case that anticholinergic and sedative medications are indeed having an effect on frailty in this population, but they are one of many factors. It is possible that the clinical risk of medication exposure on the older adult with ID may not be captured by these tools, because some high-risk drugs which are not included in these measures, such as antiplatelets, anticoagulants and hypoglycaemic agents, medicines which are known to cause hospitalisation due to adverse events (223, 317), could also be contributing to frailty. In a study by Gnjidic et al, 2012, exposure to high-risk medicines was significantly associated with the development of frailty over 2 years in a study of 1,662 community-dwelling frail older men  $\geq 70$  years of age (152). The cumulative exposure to medications over a lifetime in people with ID is not captured by this study because it is cross-sectional. This lifelong cumulative exposure may be also having an effect on the development of frailty, but it is not possible to measure this cumulative exposure in the current population. Frailty is also a dynamic process, and people can transition from one frailty state to another, including improvement in frailty, even within a short amount of time (318).

In addition, people with ID already experience differences in pharmacokinetics and pharmacodynamics of medications. This can be mediated through a number of pathways. Pharmacodynamically, people with ID have increased sensitivity to medication due to reduced neuronal tissue and reduced receptor number. With regard to pharmacokinetics, people with ID may have differences in body fat, which may influence volume of distribution of medications, renal abnormalities, which can affect elimination of medications, and differences in the expression of enzyme responsible for drug metabolism (111).

### **5.5.5 Normal ageing versus frailty**

Frailty in itself is a complex construct. Normal ageing involves reduction and deterioration of the body's functional properties (319). The ageing process can impact on the pharmacokinetics and pharmacodynamics of medications (312). Common manifestations of ageing include a reduction in hepatic volume and blood supply and decreased glomerular filtration, leading to decreased phase I metabolism and less efficient renal drug elimination. Reduction in the expression of cytochrome P450 enzymes as a result of ageing may also alter drug plasma concentrations (91).

These changes can lead to prolonged drug half-lives (90-92). Fewer target cell receptor sites also influence medication pharmacokinetics (91).

Frailty has many features in common with normal ageing. However, while ageing produces a loss of homeostasis generally, frailty is characterised by specific deficits in maintaining the homeostasis of energy metabolism and the neuromuscular system. Changes in physical function in frail older adults has been found to be different than those observed in those with normal ageing (319). In addition, frailty may produce different or more exaggerated effects on medication pharmacokinetics than normal ageing alone (320).

A hallmark of frailty is chronic inflammation which is hyper-responsive to external stressors (184, 312). This inflammation may cause reduced receptor function which in turn may exaggerate or reduce medication effects (312). Inflammation in the ageing brain may also lead to increased sensitivity to stressors, leading to further damage and neuronal death, and this may contribute to the development of delirium (184). These changes may further impact the body's inherent muscle homeostasis, leading to sarcopenia. Sarcopenia, one of the key components of frailty (184), leads to a loss of lean body mass and a relative increase in body fat. This can reduce the volume of distribution of water-soluble medications and increase the volume of distribution of lipid-soluble medications (312). Storage of lipophilic medications may temporarily shorten the medication effect, but later slow release from fat stores may result in significantly increased plasma levels. While albumin levels do not change in normal ageing, frail older people have significantly lower levels of serum albumin, and as a result, acidic medications, which typically bind to albumin, will be unbound, increasing availability in target sites and potentially causing toxicity, even though the drug levels may be normal. Certain enzymes involved in drug metabolism may be affected by frailty but not by normal ageing. Glucuronidation, sulphation and plasma esterase activity have been found to be lower in frail people (320).

Frailty has been found to be associated with a number of adverse outcomes, including falls, worsening disability, hospitalisation, care home admission and mortality (184). Frailty also increases the risk of adverse effects from medications (312). Cullinan et al (2016) (321) found that increasing frailty index score was significantly associated with experiencing an adverse drug reaction.

### **5.5.6 Frailty and Dementia**

It is widely recognised that there is an association between frailty and the development of Alzheimer's disease and dementia (184, 322, 323). Frailty has been identified as a risk factor for dementia among older adults without ID, even when the frailty index is constructed only from non-cognitive risk factors (323).

People with ID of aetiologies other than Down syndrome have been reported to have similar prevalence rates of dementia to the general population, while those with Down syndrome are more frequently affected by Alzheimer's disease and dementia (324-327). Individuals with Down syndrome tend to develop neurological evidence of these syndromes earlier in life than the older adults without ID (328, 329), although diagnosis may be difficult in this population (330). The higher rates of dementia among people with Down syndrome is hypothesised to be as a result of the trisomy of chromosome 21, one of the genetic links most widely speculated to be a causal mechanism for dementia, as production of the beta-amyloid precursor protein is mediated by one of the genes on chromosome 21 (331). Populations of older adults without ID but with Alzheimer's disease and dementia share similarities with people with ID. Dementia is characterised by a global deterioration of cognition and causes limitations in functional ability, such as impairments in the ability to identify objects, ability to comprehend or use language and impairments in abstract thinking, reasoning, insight or judgement (332). Patients with dementia may have difficulty with ordinary ADLs (332), such as those measured by Barthel Index.

### **5.5.7 Implications of Findings on Practice**

Since it appears that frailty is a predictor of incident Alzheimer's disease and dementia, this is an area which requires much attention in order to improve the quality of life and independence into old age for people with ID, especially considering the increased risk people with Down syndrome already carry for developing dementia (324-327).

There may be certain subpopulations of people with ID, such as those with Down syndrome and those with high medication exposure, which may be particularly susceptible to frailty. Although further research is required to establish if this is truly the case, this study highlights that special attention may need to be paid to people with ID with certain distinct risk factors for frailty, and these risk factors may be different to those identified in the general population.

Several factors applicable to this population may influence the pharmacokinetics and pharmacodynamics of medications. Normal ageing, frailty and the presence of the intellectual

disability itself can affect the way medications produce their effects and are processed by the body. For frail older adults with ID, they therefore may be susceptible to the combined effects of these pharmacodynamic and pharmacokinetic changes. This is why it is important to examine the association between medication exposure and frailty in this group.

Dosing based on renal impairment, hepatic impairment and older age are well-established considerations in prescribing. However, considering that frailty is distinct from normal ageing in a number of ways, the concept of dosing for frail patients as a separate category may be useful (320, 333). Commonly, frail older patients and people with ID are excluded from clinical trials. As a result, prescribing guidance for these groups is extrapolated from studies of robust patients with few co-morbidities (320) or, in the case of people with ID, from patient populations experiencing a mental health condition such as schizophrenia without other co-morbidities (106). This may not be appropriate, and as the population of older adults with ID grows, and the life expectancies continue to increase, it is essential to produce more specific, evidence-based prescribing guidelines for frail older adults with ID, taking into account the potential for increased sensitivity to medications and differences in the metabolism and elimination mechanisms among this population.

Polypharmacy is not always undesirable, and the concept of “appropriate polypharmacy” has begun to gain interest in recent years (334). It is possible that a patient requires a number of medications, but can receive appropriate therapeutic benefit from reduced doses due to the physiological changes brought about by their frail status. Nonetheless, it has been well-documented that people with ID receive a high number of psychotropic medications, often without a specific, licensed indication, and intraclass polypharmacy is particularly prevalent among older adults with ID (101). The association identified between pre-frailty and frailty with excessive polypharmacy requires further investigation, especially considering there may be classes of medications which are contributing to frailty which are not included in the DBI, ACB or Sedative Load models.

It is possible that as adults with ID become pre-frail and frail, more medications may be introduced to manage the manifestations of this frailty, including adverse effects from existing medications. They may also experience a greater number of comorbidities for which they receive medication. An issue which may arise subsequently could be that the reduced pharmacokinetic abilities of the pre-frail and frail body struggle to process an increased number of medications. As the pharmacokinetic mechanisms of drug metabolism and elimination are generalised, with many different types of medications being processed by the same metabolic

and clearance mechanisms, it may be the volume of medications rather than the pharmacological characteristics which become important in frailty.

#### **5.5.8 Strengths and limitations**

This study has four important strengths. Firstly, the sample of older adults with ID provided sufficient power for both the ANCOVA analyses of association with Barthel Index ADLs and FCI and the multivariate logistic regressions for association with polypharmacy, DBI, ACB and Sedative Load. Secondly, comprehensive medication data was available for Wave 2 of IDS-TILDA, and medication data was provided for the majority of participants (95.6%). Thirdly, the choice of medication exposure measures is a strength of the study. Polypharmacy has consistently been found to be associated with frailty as measured by Fried's frailty phenotype in older adults (152, 195, 196, 198, 199). The DBI is an internationally validated, robust measure of exposure to anticholinergic and sedative medications. The ACB model is the most frequently investigated model for measuring anticholinergic burden in relation to adverse effects among older adults (156). The Sedative Load model has been previously investigated for its association with frailty among a population of Irish older adults without ID (161). In addition, the DBI and the Sedative Load model allow measurement of exposure to drugs that cause sedation through multiple mechanisms rather than focusing on primary sedatives alone (121, 144). Fourthly, use of the Fried's frailty phenotype is clinically coherent, reproducible and identifies frailty as a wasting disorder (335, 336). It has been validated as a predictor of adverse outcomes in large epidemiological studies. It has been widely investigated and modification to individual study populations is very commonly performed (313).

This study also has several limitations. The cross-sectional design of this study only allows us to describe association and does not allow us to establish causality. Fried's frailty phenotype places a strong emphasis on the physical domain of function and may misclassify some older adults with ID as frail due to its reliance on mobility (192, 311). While the Fried's frailty phenotype is commonly modified, it has been recommended that authors consider how these modifications may influence their findings (313). A consideration in the study of frailty in older adults with ID is whether frailty is both measurable and clinically significant. No gold standard approach to measuring frailty has been developed. The cut-offs suggested by Fried et al, 2001 (189) are arbitrary, and among a population of older adults with ID these cut-offs may not be valid. A model of frailty specifically for use in a population of older adults with ID is currently under development in IDS-TILDA, and this measure may have utility. Alzheimer's disease and dementia



have been found to be associated with frailty in older adults without ID (184, 322, 323). However, due to the small number of participants with a diagnosis of Alzheimer's disease/dementia, and only one participant reporting dementia being classified as robust, it was not possible to include this variable in the regression model. The regression was carried out with this variable included (*Appendix 10*) as a comparison, but it did not have sufficient numbers to be included in the main regression analysis. The small numbers reporting Alzheimer's disease/dementia could be as a result of the difficulty in diagnosis of dementia in older adults with ID (337). The regression analyses performed do not include a number of potential factors which have been identified in previous studies of frailty in older adults without ID. Comorbidities were not adjusted for in the final model, nor was Alzheimer's disease, dementia or cognitive impairment (186). In addition, the Cox and Snell and Nagelkerke  $r^2$  values are low (typically 13 – 17%), indicating less than one-fifth of the variance in frailty is explained by the model.

#### **5.5.9 Conclusion**

Frailty as measured by a modified version of Fried's frailty phenotype was found to be higher among older adults with ID than observed in studies of the general population. Frailty status was found to be associated with higher dependency in Barthel Index ADLs and number of comorbidities as measured by FCI. Frailty status was significantly associated with excessive polypharmacy in multivariate logistic regression, but was not associated with anticholinergic and sedative medication burden as measured by DBI, ACB or Sedative Load. This could be because a number of factors are influencing frailty in this population, and anticholinergic and sedative medication use is not the dominant factor. It may still be contributing to frailty in this population to some extent. Further study should include measuring the impact on medication exposure on the advancement of frailty in people with ID, as it has been found that increased number of medications was associated with a higher risk of transitioning from the robust state to death, and increase in DBI has been found to be associated with transition from robust state to pre-frail state and to death in community-dwelling older men without ID (196). An accumulation of deficits frailty index constructed for this population may provide better insight into associations of frailty with medication use in this cohort.

## Chapter 6

### Discussion

## 6.1 Principal Findings

In *Chapter 1*, the following research question was presented:

*“How can we assess the complexity of medication burden among older adults with intellectual disabilities (ID), and how is this associated with potential adverse effects, functional limitations, physical function, and frailty?”*

In this thesis, the burden of anticholinergic and sedative medications in a representative population of older adults with ID was measured. This burden was measured using three distinct measures of drug burden – Drug Burden Index (DBI), Anticholinergic Cognitive Burden (ACB) and Sedative Load model. Findings indicated that older adults with ID had a high burden of anticholinergic and sedative medication use. This burden was compared to studies of medication burden in older adults without ID. Analyses on the association of this burden with specific outcome measures – adverse effects (daytime dozing, chronic constipation and falls), Barthel Index activities of daily living (ADLs), grip strength, timed up and go (TUG) and frailty – were performed. Medication burden was not significantly associated with adverse effects, grip strength or TUG in this population. DBI, in particular sedative exposure, was found to be significantly associated with higher dependence in Barthel Index ADLs. Excessive polypharmacy was found to be significantly associated with frailty as measured by a modified version of Fried’s Frailty Phenotype, but DBI, ACB and Sedative Load were not, after adjusting for confounding factors.

The studies included in this thesis are novel because they investigate the association between medication exposure based on pharmacological principles and physical function measures among older adults with ID. This is the first time that DBI has been evaluated in a cohort of older adults with ID, and investigated in relation to associations with adverse effects, physical function measures, including Barthel Index ADLs, grip strength and TUG among older people with ID. This is also the first time that a modified version of the Functional Comorbidity Index (FCI) (174) has been developed for use in a population of older adults with ID. It is the first time the Sedative Load model has been investigated in older adults with ID. It is also the first time that anticholinergic and sedative medication exposure has been investigated in relation to frailty among older adults with ID as measured by a modified Fried’s frailty phenotype. Existing measures of frailty among people with ID have not examined in detail the association of frailty with specific types of medication exposure. Indeed, only one study has previously investigated medication exposure in relation to frailty among older adults with ID, and this study focused on the relatively crude measure of number of medications (201).

Considering the evidence among the general population that anticholinergic and sedative medications can negatively impact on both cognitive and physical health (146, 150, 151, 153, 164, 166, 196, 220, 250, 338), and the lifelong exposure to these types of medications people with ID experience due to their unique patterns of morbidity, the research presented in this thesis was both timely and highly informative. It provides a baseline level of knowledge in this area which did not previously exist. This knowledge can further inform practice and have policy implications in the future, as well as highlighting important areas for improving the quality of life of people with ID as they age.

The DBI burden was higher than the burden reported by older adults without ID. It was also found that there was a greater variety of therapeutic classes of medications contributing to this burden than in older adults without ID – in total, medications from 38 therapeutic classes contributed to the DBI in this population, in comparison to 7 – 13 in other studies of older adults without ID (151, 166, 210, 216). The most commonly reported classes contributing to the burden were also different, and antipsychotic medications (44%), antiepileptics (42%), antidepressants (28%) were the highest contributors to anticholinergic burden, while sedatives and hypnotics (7.1%) were the highest contributor to sedative burden in the DBI calculations. This is in comparison to studies of older adults without ID, who most frequently reported exposure to antidepressants (8 – 19%), anxiolytics (4.5 – 28%) and benzodiazepines (5 – 9%) (151, 210, 216).

DBI was associated with poorer performance in Barthel Index ADLs, but was not significantly associated with adverse effects, grip strength or TUG. Analysis of the two component scores of DBI, anticholinergic-only drug burden (DBA) and sedative-only drug burden (DBS), was also performed with respect to grip strength, TUG and Barthel Index ADLs. While grip strength and TUG were still not significantly associated with DBI on sub-score analysis, high DBS score was found to be associated with poorer performance in Barthel Index ADLs. There was no association between DBA and performance in Barthel Index ADLs. These findings suggest that other factors may be influencing poorer physical performance in this group compared with older adults without ID.

ACB and Sedative Load model scores were also reported in this study. Similar to the findings of the DBI, older adults with ID had higher scores from these medications than older adults without ID. Exposure to ACB medications was found to be 65%, in comparison with studies of older adults without ID, which found ACB exposure to be between 34 and 61% (157-159). Sedative Load exposure was also high, at 75%, compared to studies of community-dwelling older adults which found exposure between 19 and 29% (144, 161). Excessive polypharmacy was found to be

significantly associated with pre-frailty and frailty as measured by a modified Fried's frailty phenotype, after adjusting for relevant confounders. However, DBI, ACB and Sedative Load were not significantly associated with frailty, after adjusting for confounding factors. This is the first time this type of medication burden has been investigated in older adults with ID in relation to frailty.

## **6.2 Aim 1**

*To investigate anticholinergic and sedative exposure using the Drug Burden Index tool in a cohort of older adults with intellectual disabilities, and to evaluate its association with demographic characteristics, dependency and potential adverse effects.*

The DBI is a suitable measure of drug burden in a population of older adults with ID for a number of reasons. Use of antipsychotic medications in particular is well known amongst people with ID and has been documented in this group as far back as the introduction of this class of medications to clinical use in the 1970s (339, 340). The prevalence of this drug class is high (44%) in this population (101, 104), and antipsychotics have anticholinergic and sedative effects due to their affinity for binding to muscarinic receptors, where they act as antagonists, and their antihistamine (H<sub>1</sub>) properties, especially chlorpromazine, clozapine, olanzapine and quetiapine (114). It is useful to adapt an existing tool which measures these particular drug characteristics in order to measure burden in this group. Similarly, antiepileptic medications have known sedative effects in particular due to their effect on GABA receptors. In addition, some antiepileptics (e.g. carbamazepine) also possess anticholinergic properties, which is thought to be related to how they are structurally similar to tricyclic antidepressants (341, 342). Considering the much higher prevalence of epilepsy and antiepileptic use among people with ID, using the DBI is well suited to capture exposure to these medications. The dose-dependency of the DBI is also a valuable component by estimating receptor occupancy of medicines with anticholinergic and sedative effects, a feature which is not present in earlier models of drug burden.

While use of polypharmacy as a measure of medication burden is also of great value, the high level of morbidity and associated medication use in this population allows the DBI to offer greater depth of understanding by bringing pharmacological principles of medication exposure into analysis.

Creation of an inventory for measuring the burden of medications with clinically significant anticholinergic and sedative activity was essential to accurately measure the DBI in the study population. Several inventories have been proposed in existing research, though none had previously been investigated in older people with ID. Other studies noted use of the DBI but did not specify medication inventory or minimum effective daily doses. While this did provide a challenge in terms of developing an inventory specific to an older population with ID, the DBI was designed to provide international flexibility in its use, due to the many varying formularies, indications and minimum effective daily doses for medications (149). Customising the inventory for the study setting was important in order to ensure all medications with potential anticholinergic and sedative effects were included in the study. The method used to define the inventory was thorough and systematic and relied on the consensus of three pharmacists.

The drug burden in older adults with ID as measured by the DBI is noticeably different from previous studies of older adults without ID. The two most commonly prescribed therapeutic classes contributing to DBI in the IDS-TILDA cohort, antipsychotics and antiepileptics, were typically infrequently reported among older adults without ID (0.6% - 13% and 0.9% - 9%, respectively (151, 154, 164, 178, 210, 212, 216, 226)). This reflects the much higher usage of these medications in people with ID. Regular antipsychotic use was reported at 44% in IDS-TILDA. People with ID receive antipsychotic medications for indications other than traditional treatment of mental health conditions (75, 105, 343). It has been reported that between 14 and 30% of people with ID receiving psychotropics medications are receiving them to manage problem behaviours such as aggression or self-injurious behaviour (75), in spite of the significant lack of evidence for the effectiveness of these medications for this purpose (79, 344-349). The trajectory of medication use may then follow the prescribing cascade, whereby anticholinergic agents such as biperiden are used in order to counteract the extrapyramidal side effects of the antipsychotic medications, especially typical agents (350).

Antiepileptic usage was reported at 42% in this study, while diagnosis of epilepsy was reported by 36% of the population. Epilepsy prevalence is higher than the pooled estimate from other studies (22%), though this may be accounted for by the fact that this is an older age group and epilepsy prevalence tends to increase with age, particularly among adults with Down syndrome (83). The discrepancy between diagnosis and antiepileptic use may be attributable to their use in mood stabilisation, as it has been reported that 29% of those prescribed antiepileptic medications have no diagnosis of epilepsy, and 78% of those reporting use of an antiepileptic medication without an epilepsy diagnosis reported a mental health condition (87). Antidepressant and anxiolytic use were high (27.8% and 11.5% respectively), reflecting the high

lifetime prevalence of depression (28.4%) and anxiety (19.2%) reported by people with ID in this study. Use of sedative only medications by 32% of older adults with ID in this study was higher than older adults without ID living in the community setting (13 – 24% (146, 151, 217, 219)) but lower than studies of older adults in residential aged care facilities (over 40% (154, 211)). Hypnotics and sedatives were reported by 7.1% of the population, while anti-dementia drugs were only used by 3.4%, despite evidence of the high prevalence of dementia in people with ID (6% after age 60), rising to between 50 and 70% in those aged 60 or older with Down syndrome (324-327). This may be due to the difficulty in diagnosis of dementia in people with ID, as the commonly used assessment tools such as the Mini Mental State Examination are not appropriate for use in people with ID (351).

The DBI separates medications into anticholinergic or sedative, and any which possess both properties are automatically classified as anticholinergic. Medications with primarily anticholinergic effects may also have sedative potential. Therefore, exposure to medication with a sedating effect is in fact higher than it may appear from our study findings. Sedative-only DBI medications were reported in just under 50% of the population using the DBI. In contrast, the Sedative Load model in *Chapter 5* identified that 75% of the population with data available on both medication use and frailty reported exposure to medications with sedative effects, because this tool only examines sedative effect, and as a result it includes many medications with both sedative and anticholinergic effects, including biperiden, carbamazepine, olanzapine and paroxetine, among others.

An additional consideration for evaluating the utility of the DBI is the potential for drug-drug interactions, limiting the usefulness of a single MDD, which only considers the drug use in isolation. For example, lamotrigine used concomitantly with inducers of lamotrigine glucuronidation, such as phenytoin, carbamazepine or phenobarbital, requires a higher daily dose to achieve its therapeutic effect than monotherapy (352). However, one MDD is selected for lamotrigine, therefore DBI score may be overestimated as interacting substances are not considered. This may not have the same consequences in measurement in the general population due to the lower incidence of epilepsy among this population, but it may be an important factor in the study of people with ID. Similarly, theophylline clearance is reduced by medications like cimetidine and clarithromycin and is increased by carbamazepine and phenytoin, leading to a requirement to reduce or increase the dosage in these cases (353). Thus, the therapeutic effect (and adverse effects) may be similar between two people taking very different doses depending on concomitant medication use. Renal and hepatic impairment also

influence the posology of medications, as often dose adjustment is required to achieve appropriate therapeutic benefit in these populations.

The potential adverse effects which were examined (daytime dosing, constipation and falls) were selected due to the existing evidence around recognised adverse effects attributed to sedative medications (daytime dosing and falls (122)) and anticholinergic medications (daytime dosing and chronic constipation (103)) and studies of DBI exposure and falls in older adults (154, 213, 223).

Univariate analysis revealed that daytime dosing was significantly associated with DBI exposure (*Supporting Information Table S 3.5, Chapter 3*). However, after adjusting for confounding factors, this association no longer remained significant. Much of the literature around sleep in ID is based on sleep in children with ID rather than older adults (354). Some more recent studies which examined anticholinergic burden and psychotropic use in older adults with ID found daytime dosing was significantly associated with anticholinergic drug exposure and sleep problems were significantly associated with psychotropic polypharmacy (103, 104)

Disturbed sleep and sleep problems are issues affecting older adults both with and without ID. The circadian rhythm is controlled by a group of cells in the hypothalamus called the suprachiasmatic nucleus (the “circadian pacemaker”). The intrinsic circadian rhythm is slightly longer than 24 hours, and as a result, exposure to external stimuli including light are vital to establish a regular sleep-wake rhythm (72). However, people with ID regularly experience visual and hearing impairments, which can affect their perception of environmental cues in relation to sleep (355). With ageing, the circadian pacemaker cells degenerate, and older adults in the general population experience more fragmented sleep patterns and early morning waking. In addition to the effect of ageing on the circadian pacemaker, the neurological dysfunction associated with the presence of the ID can also impact on the efficacy of the circadian pacemaker cells (72). Mental health conditions such as depression can also disturb the circadian rhythm in older adults (72).

People with ID often live in groups with other people, and this can also impact on the quality of their sleep, due to ambient noise and light (72). Excessive daytime sleepiness appears to be characteristic of some aetiologies of ID, especially Prader Willi syndrome (356). Difficulties settling, anxiety about sleep and fear of the dark, night-time waking due to noise, nocturia, urinary incontinence, epilepsy, and parasomnias (teeth grinding, nightmares, sleepwalking) have all been documented as sleep problems in adults with ID (354). Older people with ID, therefore, often have numerous factors impacting on their sleep.



One of the first surveys of sleep behaviours in adults with ID in a community setting (Brylewski et al, 1998 (354)) found 34.6% of individuals reported occasional irresistible urges to sleep during the day – similar to the 34.8% of individuals in IDS-TILDA reporting daytime dozing (*Supporting Information Table S 3.5, Chapter 3*). The daytime dozing may be as a result of a number of different influential factors combined – night-time sleep disturbance could lead to daytime dozing, which itself perpetuates a cycle of night-time sleeplessness; comorbidities may impact on sleep quality; lack of physical activity and reduced social participation in certain settings may result in boredom and napping (357); aetiological factors such as Prader-Willi may leave an individual predisposed to daytime somnolence; and use of long-acting hypnotics, anxiolytics, or drugs with sedative side effects can combine with these other factors to result in the relatively high levels of daytime dozing reported in IDS-TILDA.

Univariate analysis of Drug Burden Index in relation to reported doctor's diagnosis of constipation found a statistically significant association between DBI exposure and diagnosis (*Supporting Information Table S 3.5, Chapter 3*). This mirrors the findings of O'Dwyer et al in relation to ACB exposure, which found that reported doctor's diagnosis of chronic constipation was reported more frequently (26.6%) among those with a high ACB score (ACB score of 5 or higher) in contrast to those with an ACB score of 0 (7.5%), which was a statistically significant association (103). However, after adjusting for confounding factors in the DBI study, we found that this association no longer remained statistically significant.

Rather than suggesting that the effect of medication is not important, we hypothesise that this may be because the cause of constipation in people with ID, much like other populations, is multifactorial. It has been identified that constipation may be primary or secondary. Primary constipation may be caused by low-fibre diet, slow gastrointestinal transit due to neurological disorder or functional abnormalities. Secondary constipation may be as a result of obstruction, psychiatric disorder, neurological disorders, metabolic conditions or medication use (358).

Lack of physical activity, communication difficulties, multimorbidity, behaviours that challenge, neurological health conditions and immobility all contribute to the development of constipation (359). Depression is highly prevalent among older adults with ID, and could contribute to secondary constipation. Hirschsprung's disease, a neurological disorder that causes constipation, is most frequently associated with Down syndrome. Hirschsprung's disease occurs as a result of absent nerve ganglia along the intestine, leading to functional intestinal obstruction (360). Even after corrective surgery, patients may still experience lifelong constipation (361). Metabolic disorders, such as hypothyroidism (commonly observed in people with Down

syndrome) and diabetes mellitus with autonomic neuropathy can lead to constipation (361, 362).

Constipation may be caused or worsened by a number of different types of medications. Anticholinergic medications (particularly anti-Parkinson drugs, antipsychotics, antihistamines and tricyclic antidepressants) produce reduced gastrointestinal motility and secretions as a result of decreased acetylcholine mediated stimulation of M<sub>2</sub> receptors; opioids increase tone, decrease peristalsis, enhance non-propulsive contractions and reduce motility through interaction with  $\mu$  and  $\sigma$  opioid receptors; calcium channel blockers reduce motility and promote intestinal electrolyte and water absorption; clonidine also promotes absorption and inhibits secretion of fluid and electrolytes in the bowel as well as interacting with enteric neuro-receptors and enterocytes to increase gastrointestinal transit time; iron causes constipation by possibly influencing intestinal bacterial flora, and sympathomimetic agents cause smooth muscle relaxation through interaction with  $\beta_2$  receptors (114, 363).

Consequently, although statistically following multivariate regression the association between DBI and constipation was non-significant, from a clinical and therapeutic point of view, medication exposure remains an important factor to address in older people with ID when considering causes of constipation, especially chronic constipation. Also, as this was a cross-sectional study, it is also not possible to assess causal relationships.

The reported prevalence of falls in the previous 12 months in Wave 2 of IDS-TILDA (28%) was consistent with other studies of falls in adults with ID (25 – 45%) and with the rate of falls in the past year among community-dwelling older adults in Wave 4 of the TILDA study (n = 5,200) and a report on falls and fall injuries in adults 65 years or older in the United States (20% - 30%) (279, 280, 364-366). A systematic review of risk factors for falls in people with ID suggested that the cause of falls is multifactorial (367).

Similar to the findings in *Chapter 3* of this thesis, some studies have found univariate association between medicine use (especially central nervous system active agents) and falls, which, after adjusting for multivariate analysis, is no longer a significant association (278-280). The types of medications which were found to be significant at univariate but not multivariate level were typically antiepileptics, antipsychotics, anxiolytics, antidepressants and hypnotics/sedatives (278-280).

Several studies have been performed in order to identify some of the risk factors for falls in people with ID. For example, a Japanese study of individuals with primarily severe/profound ID living in a residential care facility found three multivariate predictors of falls – increasing age,

epilepsy and paretic conditions (278). A Dutch study examined falls in a similar group, a campus-based residential setting for adults with ID of all ages, though its analysis was limited to unadjusted Chi-squared tests, leaving confounding factors unaddressed. This study identified a number of risk factors, including age, functional state (mobility), past fracture, epilepsy, hemiplegia, impaired vision and use of antiepileptics (368). Both the Japanese and Dutch studies focused on individuals living in residential care settings, thus the results may only be representative of this group and might not necessarily be extrapolated to those living independently or in the community in group homes. In the United States, a longitudinal study of adults with primarily mild/moderate level of ID over 18 in various living arrangements used multivariate regression and found female gender, arthritis, seizure disorder, polypharmacy, using walking aids or difficulty lifting weights over 10lb were risk factors for falls in the total sample (n = 1,515). However, polypharmacy was not a significant factor in multivariate regression for those without a seizure disorder (81% of the population, n = 1,225) (279), suggesting multiple medicine use in epilepsy may be leading to polypharmacy and thus acting as a proxy measure for seizure disorders. In Australia, a study of participants over 18 living in both formal and non-formal care settings found seizures, past fracture and age to be independent risk factors for falls (280). The retrospective design of this study may have led to underestimation of the falls rates due to recall bias, a limitation shared by IDS-TILDA. Its focus on fracture history as a predictor for falls may also influence recall, as those experiencing a fracture are more likely to remember the fall that caused it. Existing literature, however, does not tend to focus on older adults with ID in relation to falls and medication use. These studies include individuals across the spectrum of age, from under 20 years to over 80 years, and a confounding factor surrounding the association between medication exposure and falls is that use of antiepileptic medications may act as proxy measures for epilepsy and seizure disorders – independent risk factors in themselves. Once this confounding factor has been addressed, either by exclusion of use of antiepileptic medication from analysis (280) or adjusting antiepileptic use for presence of a seizure disorder (278), there is no significant association between this type of medicine and falls. The IDS-TILDA study group, along with its exclusive focus on adults aged 40 and over, samples individuals from a range of living situations and with varying levels of ID. The findings with regard to medication burden measured by DBI and falls in IDS-TILDA are consistent with existing research.

It may be that while medication use may not be an independent risk factor for falls, it combines with other factors to reach a “tipping point”, after which falls may be more likely. A recent Swedish register study of people 55 years or older both with and without ID (n = 7,936 in each

group) found that although older people with ID were more likely to be prescribed fall-risk-increasing drugs, such as antidepressants, anxiolytics, hypnotics, sedative and antipsychotics, these medications implied a higher fall-risk among those without ID than with ID. This study concludes that this does not mean the prescribing practices for people with ID are less inappropriate, but that there are a higher number of risk factors for falls among people with ID compared to those without (369). While some of the risk factors for falls are applicable to both older adults with and without ID, a number of them are more prominent in the ID population due to the higher rates of these risk factors – cerebral palsy and epilepsy in particular. The seizure control provided by antiepileptics may also confer a protective rather than detrimental effect with regard to falls, considering the significant role epilepsy plays in falls in people with ID. Polypharmacy and medication use may not appear to be as dramatically associated with falls as seen in older adults without ID due to the lifelong exposure to psychotropic medications and polypharmacy experienced by people with ID (278).

This study found that higher level of DBI exposure (score  $\geq 1$ ) was significantly associated with poorer performance in Barthel Index ADLs after adjusting for confounding factors (*Chapter 3, Figure 3.3*). Barthel Index ADLs are of great importance to older people both with and without ID as they age. It provides a measure of dependency in basic measures including grooming, toileting and dressing. The toileting aspect of the Barthel Index includes details on difficulty using the toilet as well as measuring urinary and bowel incontinence, adding on to the findings around constipation as an adverse effect.

A few studies have reported the factors associated with poorer performance in Barthel Index activities in people with ID. Physical fitness, age and level of ID are factors identified which are associated with Barthel Index score in older adults with ID (172, 370). However, to our knowledge, no investigation of the influence of medication use on Barthel Index in older adults with ID had been performed prior to that which is outlined in this thesis. The findings indicate that there is a significant association between high medication burden as measured by DBI and dependence. This adds substantially to the existing evidence base with relation to studies of Barthel Index in older adults with ID, as previously two demographic factors (age, level of ID) and physical fitness were recognised to impact on daily activities as measured by Barthel Index (172, 370).

## 6.3 Aim 2

*To examine the association between Drug Burden Index and performance in two physical function measures, grip strength and timed up and go, and a measure of dependency, Barthel Index Activities of daily living, in a cohort of older adults with ID at a cross-sectional level to establish if exposure in people with ID leads to the same functional effects as has been reported in the general population.*

No statistically significant association was identified between DBI, anticholinergic only DBI (DBA) or sedative only DBI (DBS) and mean grip strength after adjusting for confounding factors in either females or males in this study. The length of exposure to medications with anticholinergic or sedative effects may play an important role in weak grip strength. Typically, adults with ID begin medications with these effects earlier in life than older adults without ID. Neurological impairment may also be a cause of poorer physical function in older adults with ID. Among community-dwelling older adults without ID, subtle neurological abnormalities have been found to be associated with poorer physical performance (371). The prevalence and onset of neurological conditions including epilepsy and dementia in adults with ID as they age (57, 82, 289) could be having a much greater effect on performance in physical function measures than drug effects alone.

There may be other factors influencing our findings. The measurement of grip strength may be influenced by a floor effect, whereby a score lower than that measured can no longer be obtained, and as a result it is no longer able to distinguish between individuals after a certain point (372). Although there is large variation between scores in this population, the floor effect still limits variation beyond a certain point. This issue has been suggested elsewhere – that grip strength may be too low at baseline in this population to be able to find predictive relationships (289, 298).

Interestingly, our findings indicated that poorer female grip strength was not significantly associated with increased age, while male grip strength was statistically significantly poorer in older age groups. Female grip strength was poorer across the age groups, but did not appear to decline with age. It has been found that women tolerate the deficits of frailty better than men in the general population, because they tend to have more deficits on average but a lower correlation with mortality (373). Since grip weakness is a frequent contributor in frailty models, these results complement each other, and suggest that women with ID may be more resistant to the effects of ageing and frailty. Among older adults without ID, similar trends have been observed, and it has been acknowledged that grip strength decline with age differs according to

gender, with men experiencing greater decline. This is thought to be because men exhibit larger age-related decreases in muscle mass than women (374).

Even though those with mild/moderate level of ID and those with lower DBI score were over-represented in the study sample, grip strength scores were still much lower than those which have been reported in a similar, albeit larger study of ageing in people with ID – the “Healthy Ageing and Intellectual Disability” (HA-ID) study (289, 297). HA-ID included 1,050 (of which 725 provided grip strength data) adults with ID aged 50 and over, mainly living in residential care settings. Participants with borderline to profound levels of ID were represented (289, 297). This is interesting, as the development of ID services in the Netherlands is similar to that of Ireland and elsewhere, although they did come about earlier in history than Ireland. Special education services for people with ID were established as far back as the 1850s in the Netherlands, and sheltered employment became available in the 1920s to 1930s (375), in comparison to the 1950s and 1960s in Ireland (376). A large percentage of ID care in the Netherlands is provided in a residential setting: 49% in 2011 (377). In the Netherlands, like Ireland, the process of deinstitutionalisation is still ongoing (377). The HA-ID sampled individuals primarily living in residential centres, which does represent a departure from the method in IDS-TILDA, whereby a nationally representative sample of individual with ID from all care settings, including those living independently, was selected. The population living in residential care in the Netherlands was over-represented in the HA-ID study, as they noted difficulties in recruiting those with ID in supported living and those receiving ambulant care only (297). These methodological differences could account for some of the variation observed in grip strength scores between the two studies.

TUG scores were not significantly associated with DBI, DBA or DBS exposure, similar to the findings from grip strength. Among older adults without ID, an association has been found between higher DBI scores and slower TUG (164). Similar explanations to those presented for grip strength for this result may be hypothesised for the lack of association of medication exposure with TUG.

Looking outside the DBI-specific literature, Gray et al (2003) (378) examined benzodiazepine use in 885 women without ID aged 70 years and older and found a prevalence of 10-12% benzodiazepine use among this group. Interesting, their findings revealed that physical performance (as measured by standing balance, walking speed and chair stands) of long-term benzodiazepine users declined significantly more than that of recent and past users. While these findings cannot be extrapolated to a population of mixed-gender older adults with ID, it does

present an interesting discovery with regard to length of use. Considering older adults with ID have typically been using these types of medications long-term, it is possible that their physical function has indeed declined, but we do not have pre-exposure data to investigate function prior to initiation of these medicines, so at present we cannot describe functional decline.

TUG in particular measures not only physical function, but also balance and executive function. For this reason, some participants were unable to complete this assessment. In particular, those who were wheelchair users or required support or a walking aid to walk across a room were excluded from this measure. As a result, individuals who reported low levels of physical activity were under-represented in the sample, and those with moderate levels of physical activity were over-represented. In spite of the fact that the sample consisted of some of the fitter, more active members of the cohort, the average TUG score was still higher than those in the 80-year group in TILDA (n = 5,791 completed TUG assessment at Wave 1 of the study). However, since TILDA is based on community-dwelling older adults and does not include people in nursing homes, this group is also potentially a fitter, more active sample of older adults. A small Dutch study (n = 76) of adults over 50 years found the same average TUG for adults with mild/moderate level of ID (299). TUG scores were found to increase with age, a trend which was statistically significant when the youngest age group was compared to the oldest age group. This reflects the trend observed in older adults without ID, where it has been found that TUG scores increase with age, though most evidence examines older age profiles. Average TUG scores in a meta-analysis by Bohannon in 2006 were found to be 9.0 seconds for 60-69-year olds, 10.2 seconds for 70-79-year olds and 12.7 seconds for 80-99-year olds (379). The trend of increasing TUG score with age appears to be similar among those both with and without ID.

The use of the separated DBI scores has not been validated, a limitation shared by Lowry et al, 2012 (169) and described in *Chapter 4* of this thesis. There is the possibility of confounding because anticholinergic medications according to the DBI may also have sedative effects but are categorised as primarily anticholinergic. Interestingly, this study found that in older adults with ID, there was no statistically significant association of Barthel Index with anticholinergic only DBI score, but there was a significant association between higher dependency in Barthel Index and high sedative only DBI score. This is in contrast to the findings of studies in older hospitalised patients in the general population, where anticholinergic only exposure seemed to be an important factor with regard to Barthel Index performance (169, 380).

Much of the literature around Barthel Index in relation to medication use focuses on older hospitalised patients rather than those with ID or those living in community settings. This is

because Barthel Index is often used to assess function after a medical intervention or rehabilitation (172). For example, a UK study of the anticholinergic component of the DBI demonstrated some independent association between higher DBI score and poorer performance in Barthel Index measures in older patients admitted to acute care. This study also highlighted the heterogeneity of the numerous scales of anticholinergic medication exposure, by finding associations between some but not all measures of anticholinergic activity. The Drug Burden Index anticholinergic component was significantly associated with Barthel Index in this population after adjusting for confounders (380). However, unlike the IDS-TILDA study, this study examined the Barthel Index in quartiles, which departs from the traditional classification into level of dependency as per Wade and Collin (233). They did not assess Barthel Index as a continuous variable. There is a possibility that if examined as a continuous variable, as performed in IDS-TILDA, or by using the Wade and Collin classification, different results may have been obtained. Another study of DBI in acutely ill hospitalised older people in Scotland found a unit increase in the total DBI, anticholinergic only DBI, and sedative only DBI scores was associated with a 29%, 51%, and 37% respective reduction in the odds of having a higher Barthel Index score (169). This population differs from IDS-TILDA, not only due to the hospital setting of the study but also the higher Barthel Index score and relatively small proportion of individuals with total or some degree of independence. This limits the comparability of the results found in that study with those of this thesis.

## **6.4 Aim 3**

*To describe frailty and examine the cross-sectional association between anticholinergic and sedative medication exposure using four tools (polypharmacy, Drug Burden Index, Anticholinergic Cognitive Burden and Sedative Load) with frailty in a cohort of older adults with intellectual disabilities.*

Chapter 5 described a study of frailty in older adults with ID. Frailty among this population of older adults with ID was higher than observed in older adults in the general population, with 64% categorised as pre-frail and 18.1% categorised as frail using the modified version of Fried's frailty phenotype. In comparison, a systematic review of 15 studies including 44,894 participants found a physical frailty measure identified frailty in 9.9% and pre-frailty in 44.2% of the community-dwelling population (184, 315).



Frailty is a state which includes a decline in functioning and increased dependency and vulnerability (310). Lower scores in Barthel Index ADLs were found to be significantly associated with pre-frailty and frailty after adjusting for confounders in ANCOVA analysis, and there was significant multicollinearity between both of these measures. Since it has been suggested that both Barthel Index ADLs and frailty as measured by Fried's frailty phenotype are influenced by mobility (172, 192, 311), this association is not unexpected. The findings from this study reinforce the concept of frailty as a state which is characterised by increased dependence.

Barthel Index ADLs have repeatedly been found to be associated with medication burden throughout the studies in this thesis. The association with frailty status also gives an important insight into function in this group. It is possible that Barthel Index ADLs are providing an understanding of function in this group which is more comprehensive than the measures typically examined in ID research, such as level of ID or type of residence. Its focus on the basic daily activities a person performs allows formation of a picture of the level of dependence in this population, where functional independence is an important marker of health ageing. It is a simple measure which is easy to perform, and should not be underestimated in studies of medication effects on ageing in people with ID.

Number of comorbidities as measured by the FCI was also significantly associated with frailty status, suggesting that pre-frail and frail older adults with ID have more comorbidities than their robust counterparts.

With regard to medication exposure, there was a statistically significant association between excessive polypharmacy and frailty. Although the study design means we cannot establish causality (i.e. does exposure to multiple medicines cause frailty or occur as a result of frailty?), it still highlights an important practical implication for medication use in older adults with ID. There was no significant association between DBI, ACB or Sedative Load with frailty status after adjusting for confounders in this cohort of older adults with ID.

During ageing, many changes to the pharmacokinetic and pharmacodynamic aspects of medications occur. In addition to the changes which occur with ageing, people with ID also have important differences in their response to medications from early in life. Brain damage underpins all of the conditions included in ID (111). People with ID have abnormalities in brain structure and function, and this can have implications on their response to medications. Impairments of the process of neurodevelopment – whereby the brain removes half of all synaptic connections from the age of six into adolescence – lead to many developmental disorders. Epilepsy and ID may result from neurones migrating incorrectly during foetal

development, which may also be a cause of schizophrenia, attention deficit hyperactivity disorder and dyslexia. Subtle abnormalities in the cell architecture of the brain have been observed in schizophrenia. In normal ageing, there is cell loss and reduction in dendritic processes, with a relative decrease in cortical grey matter compared to white matter (111).

Pharmacokinetics are not only different for older people versus younger people, and for frail people versus the “robust” older person, but also there is a difference between pharmacokinetics for people with ID compared to those without (110). Congenital conditions may occur along with genetic syndromes that lead to ID, including duodenal atresia, impacting on drug absorption, and renal abnormalities, influencing drug elimination (111).

People with ID also tend to be more sensitive to psychotropic medications than those without ID (110). Fewer receptors in the brain as a consequence of reduced quantity of brain substrate may necessitate lower doses of medication to achieve the same therapeutic effect as observed in adults without ID (111). Differences in the anatomy and histology of the brain may also affect medication effects (111). This is thought to be due to reduced amount of nerve tissue, leading to reduced number of receptors for a medication to interact with. As a result, in some cases lower doses of psychotropics can bring about the same therapeutic response as higher doses in another person. Paradoxically, higher doses may sometimes be required for the same reason – too few receptors, or decreased sensitivity of the existing receptors (111).

The potential pharmacokinetic and pharmacodynamic differences in older people with ID may be having a significant impact on all the measures presented in the studies of this thesis. The possible heterogeneity across the cohort of people with ID in terms of medication effects could be having a large influence on the findings. Considering so little is known about the actual differences in pharmacokinetics and pharmacodynamics, this could be an even more diverse population than we are already aware of. There is a variety of causes of ID, many of which are not known, that the umbrella term “ID” could be misleading when we study medication exposure and effects.

In the main regression analyses, it was not possible to adjust for a number of confounding factors which could impact on frailty in this population. Presence of Alzheimer’s disease or dementia in particular could not be investigated due to small group numbers in the frailty categories, potentially arising due to the difficulties in diagnosis of these conditions in people with ID. Dementia has been found to be associated with frailty (184, 322, 323), and considering that levels of dementia are much higher among adults with Down syndrome and that this condition develops earlier in their lives, this could be highlighting older adults with Down syndrome as

particularly at risk of frailty, though longitudinal analysis is required to determine this conclusively.

## 6.5 Other studies

A variety of outcome measures have been investigated with regard to DBI exposure across a number of different study settings. *Table 6.1* presents the findings of these studies. Five studies were identified to have investigated grip strength. Only two of these five studies found that DBI exposure was associated with grip weakness. These were studies of functional decline (longitudinal) (Hilmer et al, 2009 (150)) and of community-dwelling older men (Gnjidic et al, 2009 (151)). The studies which found no association were one cross-sectional study of men and women in low-level care facilities (Gnjidic et al, 2012 (166)), one cross-sectional study of community dwelling older adults (Gnjidic et al, 2012 (164)), and one longitudinal analysis which included older adults in residential aged care facilities (RACF) (Wilson et al, 2010 (178)). The longitudinal analysis performed by Hilmer et al, 2009 (150) covered six years, while the analysis performed by Wilson et al, 2010 (178) followed participants 12 months later. This could be a reason for the different findings, as perhaps the higher exposure at year one and long-term exposure (6 years) to DBI medications was the dominant factor in functional decline, and 12 months did not adequately capture this decline as it was a shorter period. In addition, the finding that DBI was associated with grip weakness among older men while it was not in mixed gender populations may indicate the greater susceptibility to this adverse outcome in men. However, more studies must be performed before this conclusion can be drawn. The inconclusive evidence around the association between DBI and grip strength is also shown in this thesis, since medication exposure also had no significant association with grip strength in IDS-TILDA.

A number of other outcomes were investigated in different patient groups. Hospitalised patients with high DBI were three times more likely to be admitted for delirium than those with no DBI exposure (210), higher DBI was associated with poor clinical outcomes and longer hospital stays (215), and increase in DBI during hospital stay was associated with a three-fold higher risk of falls (213). Exposure to DBI tripled the odds of reporting lower quality of life in people with dementia living in RACFs (211), and DBI was associated with hospitalisation and mortality among people both with and without Alzheimer's disease (155). *Table 6.1* provides an overview of the breadth of research which has been performed in relation to DBI, but it is important to expand this research to different patient groups, such as those with ID, in order to gain a complete picture of the applicability of this measure for measuring outcomes.

Prior to the commencement of this thesis in 2016, no study of Drug Burden Index had been performed in a cohort of older adults with ID. This is despite the evidence that higher DBI is associated with a number of negative outcomes in older adults – poorer physical function, poorer balance, falls, frailty, hospitalisation and increased GP visits (149) – and the prevalent use of medications with anticholinergic and sedative effects among older people with ID (101, 103).

Since 2016, several studies have been published in relation to DBI. A national database study of DBI in older adults in Ireland was published in 2018 (381). This study, which captured data from a large sample of adults 65 years or older (n = 428, 516) identified exposure to DBI medications in two-thirds of the study sample, with a median DBI score of 0.52. While this proportion is lower than that observed in IDS-TILDA (78.6%), it is still higher than some previous studies of DBI in similar populations. A caution noted by the authors is that the study population came from General Medical Services (GMS) patients and as a result may over-represent a population from lower socio-economic classes, and also the study design cannot determine treatment duration or actual consumption of medication as it is based only on dispensing data. It may also exclude some medications, as medications which are unlicensed in Ireland are typically not reimbursed by the GMS and may constitute a proportion of anticholinergic and sedative exposure.

Anticholinergic Cognitive Burden analysis has been performed previously in the IDS-TILDA cohort. Since this publication in 2016, one other study of the ACB scale has been performed in a population of older adults with ID. An Italian multicentre cross-sectional study of 276 people with ID aged 40 and over was carried out recently (120). Participants lived in a range of settings (independent, community housing and nursing homes) and had mild to profound level of ID. This study found that high anticholinergic burden was significantly associated with living in community housing and nursing home facilities. It was also significantly associated with mental health conditions, neurological disease and laxative use. However, this study used different categorisation of high anticholinergic burden, as it classified a score of 3+ as high, in contrast to the existing publication which used a categorisation of 5+ as high ACB. Interestingly, medication use appeared to be lower in this study compared to IDS-TILDA in most areas – antipsychotic use was lower (28.6% in the Italian study vs 43.2% in IDS-TILDA), laxative use was lower (10.5% vs 37.8%) and excessive polypharmacy was reported at 2.2% in contrast to 20.1% in IDS-TILDA. There were also some differences in medication inventory and scoring and almost half of this cohort lived independently or with family in contrast to IDS-TILDA.

Table 6.1 Findings of Drug Burden Index Studies

| Study                              | Population                                                                                                                              | Outcome Measures                                                                                                      | Findings                                                                                                                                                                                                                   |
|------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Best et al, 2013 (210)</b>      | (n = 329)<br>People (aged ≥ 65 years) with and without dementia in geriatric medical or rehabilitation team                             | The main outcome measures were admission for falls, admission for delirium and length of stay > 10 days.              | Patients with a high DBI (≥1) were approximately three times more likely to be admitted for delirium than those with no DBI exposure.                                                                                      |
| <b>Bosboom et al, 2012 (211)</b>   | (n = 351)<br>People aged > 65 years diagnosed with dementia residing in Residential Aged Care Facilities and with MMSE ≤ 24.            | The primary outcome measure was the self-rated Quality of Life – Alzheimer’s disease questionnaire (QoL-AD).          | DBI > 0 and polypharmacy were associated with QoL-AD ratings. Exposure to DBI > 0 tripled the odds of lower QoL-AD ratings.                                                                                                |
| <b>Castelino et al, 2010 (212)</b> | (n = 372)<br>Community-dwelling older people (aged ≥ 65 years) who received an Home Medicines Review (HMR) service from the pharmacist. | The main outcome measure was the total DBI score at baseline and post-HMR.                                            | There was a significant reduction in the sum total of DBI scores for all patients following pharmacists’ recommendations during the HMR service.                                                                           |
| <b>Dauphinot et al, 2014 (213)</b> | (n = 337)<br>Inpatients aged ≥ 65 years in a multicentre cohort                                                                         | The main outcome measures were falls and mortality.                                                                   | The risk of fall was nearly 3-fold in patients whose DBI increased during hospital stay compared to those with stable or decreased DBI. The increase of DBI during hospital stay was not related to the risk of mortality. |
| <b>Dauphinot et al, 2016 (214)</b> | (n = 337)<br>Hospitalized patients aged ≥65 years using at least one drug at admission.                                                 | The primary outcome was change of exposure to anticholinergic and sedative drugs between admission and discharge.     | Drug burden index increased among patients hospitalized for stroke, inability to stay in their own home or post-surgery, and for patients with diabetes mellitus or hypertension.                                          |
| <b>Floroff et al, 2014 (215)</b>   | (n = 112)<br>Critically ill elderly patients (≥65 years) admitted to the neuroscience intensive care unit (NSICU).                      | Clinical outcomes (discharge Glasgow Coma Scale, NSICU length of stay, hospital length of stay in-hospital mortality) | Higher DBI scores were associated with poor clinical outcomes and longer lengths of stay.                                                                                                                                  |

Table 6.1 Findings of Drug Burden Index Studies (continued)

| Study                     | Population                                                                                       | Outcome Measures                                                                                                                                                                                              | Findings                                                                                                                                                                                                                                                                                                                      |
|---------------------------|--------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Gnjidic et al, 2009 (151) | (n = 1705)<br>Community-dwelling older men with and without cognitive impairment; ≥70 years.     | Outcomes included chair stands, walking speed over 6m, 20-cm narrow walk speed, balance, grip strength and Instrumental Activities of Daily Living score (IADLs).                                             | Drug Burden Index was associated with slower walking speed, slower narrow walk speed, balance difficulty, grip weakness and poorer performance on IADLs. Associations with physical performance and function were stronger for the sedative than for the anticholinergic component of the Drug Burden Index.                  |
| Gnjidic et al, 2010 (216) | (n = 115)<br>Participants were volunteers aged >70 years living in self-care retirement villages | The main outcome measure was change in DBI score.                                                                                                                                                             | The intervention targeting GPs' prescribing practices was less effective than anticipated in reducing anticholinergic and sedative drug exposure, and barriers were identified.                                                                                                                                               |
| Gnjidic et al, 2012 (166) | (n = 115)<br>Residents living in low-level care facilities (aged ≥ 70 years).                    | The main outcome measures were objective measures of physical function: Short Performance Physical Battery (SPPB) and grip strength.                                                                          | For every unit increase in DBI, the SPPB score decreased by 1.3<br>DBI was not associated with weaker grip strength.                                                                                                                                                                                                          |
| Gnjidic et al, 2012 (164) | (n = 700)<br>Community-dwelling older people (aged ≥ 75 years)                                   | The main outcome measures included walking speed, chair stands test, grip strength, timed up and go (TUG) test, instrumental activities of daily living (IADL), and Barthel Index activities of daily living. | Exposure to DBI drugs was associated with slower walking speed, poorer performance on chair stands and TUG, difficulties in IADLs and Barthel Index.<br>The mean adjusted walking speed, time to complete chair stands and TUG, IADL, and Barthel scores were significantly poorer among participants with higher DBI ranges. |

Table 6.1 Findings of Drug Burden Index Studies (continued)

| Study                            | Population                                                                                                                                                                               | Outcome Measures                                                                                                                                                                                                                                                      | Findings                                                                                                                                                      |
|----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Gnjidic et al, 2012 (153)</b> | (n = 987)<br>Community-dwelling older men, ≥ 70 years.                                                                                                                                   | The main outcome measures were the Addenbrooke's Cognitive Examination (ACE) and the Trail Making Task (TMT) cognitive tests.<br>Participants were categorised as having intact cognition, mild cognitive impairment, or dementia using clinical diagnostic criteria. | DBI exposure was not associated with poorer performance on the ACE or the TMT tests.<br>Similarly, DBI exposure was not associated with cognitive impairment. |
| <b>Gnjidic et al, 2014 (155)</b> | Community-dwelling people aged ≥ 65 years and over, with Alzheimer's disease (AD) (n = 16,603) and individually matched (n = 16,603) comparison persons (age, sex, region of residence). | The main outcome measures were hospitalisation and mortality data.                                                                                                                                                                                                    | There was an association between DBI exposure and hospitalisation and mortality in people with and without AD.                                                |
| <b>Hilmer et al, 2007 (146)</b>  | (n = 3,075)<br>Community dwelling persons aged 70 to 79 years.                                                                                                                           | The outcome measures were validated composite continuous measures for physical function and the Digit Symbol Substitution Test for cognitive performance.                                                                                                             | Use of anticholinergic and sedative medications was associated with poorer physical performance score and cognitive performance.                              |
| <b>Hilmer et al, 2009 (150)</b>  | Longitudinal study<br>(n = 3,075 at baseline; n = 2,172 for longitudinal analysis)<br>Community dwelling older persons (aged 70 – 79 years at baseline)                                  | The main outcome measures were physical performance as measured using the short physical performance battery (SPPB), usual gait speed, and grip strength.                                                                                                             | Higher DBI at years 1, 3 and 5 was consistently associated with poorer function at year 6.                                                                    |

Table 6.1 Findings of Drug Burden Index Studies (continued)

| Study                             | Population                                                                          | Outcome Measures                                                                                                                                                          | Findings                                                                                                                                                                                                                                                                                                                                                               |
|-----------------------------------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Jansen et al, 2016 (196)</b>   | (n = 1,705)<br>Community-dwelling men aged ≥70.                                     | The main outcome measures were frailty as measured by the modified Fried frailty phenotype and data on mortality.                                                         | Each additional medication was associated with a 22% greater risk of transitioning from the robust state to death.<br>Every unit increase in DBI was associated with a 73% greater risk of transitioning from the robust state to the prefrail state and a 2.75 times greater risk of transitioning from the robust state to death.                                    |
| <b>Lonnroos et al, 2012 (220)</b> | (n = 339)<br>Community dwelling older adults ≥ 75 years old                         | The main outcome measure was data on hospitalizations, including the proportion of hospitalized participants and the number of hospital days per person-year.             | Exposure to DBI medications was associated with a greater use of hospital days, but a cumulative dose-response relationship between DBI and hospitalization was not observed.                                                                                                                                                                                          |
| <b>Lowry et al, 2012 (169)</b>    | (n = 362)<br>Consecutive patients (> 60 years) admitted to 2 acute geriatric units. | The primary outcome was reduced physical function (as measured by Barthel Index)<br>The secondary outcomes were adverse outcomes (length of stay, in-hospital mortality). | Each unit increase in DBI was associated with a 29% reduction in the odds of being in a higher Barthel Index quartile than a lower quartile.<br>The Barthel Index components mostly affected were bathing, grooming, dressing, bladder function, transfers, mobility and stairs.<br>A higher DBI independently predicted length of stay but not in-hospital mortality. |
| <b>Nishtala et al, 2009 (222)</b> | (n = 500)<br>Residents in aged care facilities (aged ≥ 65 years)                    | The main outcome measure was decrease in DBI score.                                                                                                                       | A statistically significant decrease in median DBI score was observed as a result of uptake of pharmacist recommendations by the GP.                                                                                                                                                                                                                                   |



Table 6.1 Findings of Drug Burden Index Studies (continued)

| Study                             | Population                                                                                               | Outcome Measures                                                                                           | Findings                                                                                                                                                                                                                         |
|-----------------------------------|----------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Nishtala et al, 2014 (223)</b> | (n = 537,387)<br>Data obtained from Pharmacy Claims<br>Data on adults aged ≥65 years                     | The main outcome measures were falls, healthcare utilisation and mortality.                                | DBI drugs were associated with fall-related hospitalisations and greater number of GP visits.<br>Individuals with DBI>0 had a 1.29 times higher mortality risk.<br>Polypharmacy is also associated with a higher mortality risk. |
| <b>Wilson et al, 2010 (178)</b>   | (n = 602 at baseline; n = 526 for longitudinal analysis)<br>Older adults living in RACFs aged >70 years. | The main outcome measures were physical function (grip strength, reaction time, walking speed and balance) | Increasing DBI was not independently associated with impairments in measures of physical function.                                                                                                                               |
| <b>Wilson et al, 2011 (154)</b>   | (n = 602)<br>Older adults living in RACFs (aged ≥ 70 years)                                              | The main outcome measure was falls.                                                                        | DBI was significantly and independently associated with falls.                                                                                                                                                                   |
| <b>Wilson et al, 2012 (226)</b>   | (n = 602)<br>Older adults living in RACFs (aged ≥ 70 years)                                              | The main outcome measure was mortality.                                                                    | One-year mortality multivariate models showed that the DBI categories low and high were not associated with mortality.                                                                                                           |

## 6.6 Limitations

The primary limitation of this study is that the observational study design means we can only examine association and not causality. While multivariate analysis was adjusted for identifiable confounding factors, residual confounding bias may remain.

It is necessary to consider that IDS-TILDA only sampled people registered with NIDD, and as a result it may not have captured those individuals with borderline ID who do not receive ID services.

A validated measure of the three adverse effects of interest (chronic constipation, daytime dozing and falls) was not available for use from the IDS-TILDA population at Wave 2. Chronic constipation was recorded as reported doctor's diagnosis, which may be prone to recall bias or may have been a diagnosis relevant in the past but no longer an existing condition. At Wave 3, the Pittsburgh Sleep Quality Index was introduced as a measure of sleep quality, latency, duration, efficiency, disturbances, medication and daytime dysfunction. This has clear advantages over the existing sleep measure used in IDS-TILDA as it is a validated instrument designed for use in psychiatric practice and research (382). History of falls in the previous 12 months may also be affected by recall bias, and a prospective study using monthly fall calendars found higher rates of falls among older adults with ID (45%) than other retrospective studies (364).

It is important to highlight the heterogenous nature of the study population. While there appear to be trends in the characteristics of participants living independently, in community group homes and in residential care settings, it is still a largely heterogenous group, with a mixture of younger individuals with mild ID living in the same settings as older individuals with severe/profound ID. The wide confidence intervals obtained in the multinomial regression are a result of the relatively small sample size of the study and also reflects the greater dispersion of values among this highly heterogenous population. As a result, findings of no statistical significance do not necessarily have no clinical relevance (383, 384).

The use of cross-sectional studies to examine associations of risk, particularly in the study of ageing, has certain limitations. While average population changes may emulate the more frequently observed associations with age-related processes, examining mean trends is not ideally suited to understand the processes associated with individual variations in ageing. The study of individual differences in ageing is of pivotal importance to gather a comprehensive understanding, as genetic influences, environmental factors and the variations in the pattern of

the ageing process differs among individuals (385), particularly those with ID. In the current context, a variety of factors may be influencing the outcomes of interest, such as functional limitations, physical function and frailty, at a much earlier point in time than a cross-sectional study may capture. The temporal relationship between exposure to medications and the development or presentation of deficits in function cannot be captured by the current study design. In addition, cross-sectional studies are valuable for describing the prevalence of a risk factor at a certain point in time and its association with other factors at that point in time, but this association may not be extrapolated to describe causality as it is not possible to capture information in the period leading up to the appearance of the risk. Cross-sectional study design cannot give indication of the sequence of events, such as if exposure to a risk preceded an identified outcome (386). Cross-sectional studies also introduce prevalence-incidence bias (or Neyman bias), as certain risk factors may be under-represented by the selected population(386).

The method of literature review employed in this thesis was a “targeted” or “focused” literature review, rather than a systematic review. Systematic literature reviews offer a number of potential advantages over targeted literature reviews, because they follow established guidelines, such as those set out by the Preferred Reporting Items for Systematic Reviews and Meta- Analyses (PRISMA) Statement(387) and employ a defined protocol with pre-defined search terms. Multiple databases are employed, and grey literature may also be included(388). The conclusions of a systematic review can be considered more reliable than those obtained from a single study. The methods employed during systematic review can help to reduce bias in selection of studies and can produce more reliable and accurate conclusions. It also presents a summary of multiple reviews for the reader to examine. Systematic reviews are useful in identifying the gaps in current knowledge (388). Non-systematic review may include bias towards known literature, literature which is easy to access and studies with significant findings (389). The current studies may have benefitted from systematic literature review and structured critical appraisal of literature, rather than employing a targeted literature review.

Missing data is an issue which persisted throughout all studies of the medication burden at Wave 2. In *Chapter 3*, 70% of the population had available data for the study, therefore conservative interpretation of results is advised. In *Chapter 4*, missing data from the objective measures of physical function resulted in over-representation of people with mild to moderate level of ID and those living independently or in community group homes. As a result, extrapolation of the results to all levels of ID is not possible. Missing data also impacted on the power of the studies carried out in *Chapter 4*. In particular, three level analysis with 6 covariates for male grip strength achieved a power of 0.72 – a 72% chance of detecting an effect when there is an effect there to

be detected. This means the probability of making a Type II error, or concluding there is no effect when, in fact, there is one, is 28%.

The nature of the IDS-TILDA study and the variation in level of engagement of the population may be responsible for much of the missing data. Data in IDS-TILDA is most likely missing at random (as opposed to missing completely at random or missing not at random), due to variations in participant engagement and frequent employment of proxies to complete interviews either entirely or in parts. Study design of future waves of IDS-TILDA may help to minimise missing data going forward – reducing the need for follow-up visits is encouraged in field researcher training, and for Wave 4 the length of interview has been reduced. Specific training has been provided to field researchers on avoidance of missing data wherever possible.

However, in the current context, a number of approaches may have been employed in the handling of missing data. The approach taken in this study – complete case analysis – is one of the most frequently employed methods of managing missing data. It is possible that this method introduced bias, and this caveat was emphasised in *Chapters 3, 4 and 5*. Other methods of handling missing data include mean substitution, regression imputation, maximum likelihood, expectation-maximisation, multiple imputation and sensitivity analysis(390). Mean substitution is not generally accepted, as it provides no new information and underestimates errors, though it does increase sample size(390). Regression imputation, which replaces missing values with estimated values derived from other available information, may be used, although, similarly to mean substitution, it provides no new information(390). Maximum likelihood uses the assumption that the observed data are drawn from a normal distribution, but this method is most useful in a relatively complete dataset(390). Expectation-maximisation creates a new dataset using the maximum likelihood method which incorporates a random disturbance term to accommodate for the uncertainty associated with the imputation. However, this approach may take a long time to converge to produce a dataset with no missing data and may be too complex(390). Multiple imputation replaces missing values with a set of credible values, rather than one single value. This offers the advantage of incorporating natural variability and uncertainty into the imputed values(390). Multiple imputation may be a beneficial approach to handling of missing data in IDS-TILDA. Sensitivity analysis provides an evaluation of the robustness of results to the deviations from the missing at random assumption, and may be helpful in IDS-TILDA(390).

In order to determine if the study sample remains “nationally representative”, a weighted cases approach may be used to conduct a one-sample chi-square test which helps to determine how

well the sample represents the population(391). A one-sample chi-square test can determine how well a subgroup of participants generalises to all participants in the sample(391). This method was employed in *Chapter 4*, but could have been used more generally throughout the studies in the thesis.

There is a lack of baseline data in the study. People with ID have typically been taking medications with anticholinergic and/or sedative effects long-term, so it is not possible to examine pre-exposure data in this group.

The investigation of frailty using a modified Fried's frailty phenotype, while interesting as an exploratory analysis, may have limitations for older adults with ID. An accumulation of deficits frailty index or ID-specific frailty model may be more useful for investigation and for comparison of the association between anticholinergic and sedative exposure and frailty in this population. The analyses did not adjust for a number of factors which could potentially impact on frailty in this group due to small sample size, such as Alzheimer's disease and dementia, comorbidities and cognitive impairment.

## **6.7 Recommendations/Implications for Practice**

### *1. Multidisciplinary team involvement*

One of the prominent discussion points of this thesis is the multifactorial nature of the adverse effects and physical function outcomes among older adults with ID. Repeatedly, it was found that anticholinergic and sedative medication burden were not the predominant factors associated with adverse effects including daytime dozing, chronic constipation and falls. Analysis also revealed no significant association with poorer performance in grip strength and TUG assessments and frailty. From these findings, it may be suggested that the causes of the adverse effects and outcomes investigated are multifactorial. Low levels of physical activity and neurological impairment may be contributing to these effects in addition to medication exposure. As a result, it is necessary for multidisciplinary involvement to address these factors. Physician and pharmacist input alone is unlikely to resolve the high levels of functional limitations in this group. By collaboration with different medical and allied health professionals, firstly we may understand more about the factors associated with and contributing to poorer physical performance and frailty among this population, but we may also provide better care for these individuals by coordination of care plans across all disciplines. Physiotherapists, occupational therapists, specialist nurses in ID, psychiatrists, neurologists and pharmacists all

have the potential to positively influence the quality of life for people with ID as they age by understanding more about the ageing process and developing interventions which do not solely address one area, like medicine use or physical activity, but combine care plans with cooperation from all individuals involved. Social workers and care staff also have a role to play, and could strongly influence the success of interventions, as evidenced by de Kuijper et al, 2019 (392). de Kuijper et al, 2019 describe how a discontinuation trial for long-term antipsychotics in the Netherlands recently found that there was a substantial impact from staff attitudes on the success of de-prescribing, and found that negative attitudes had a detrimental effect on the success of deprescribing (392).

This multidisciplinary team involvement is certainly easier said than done, but research in other areas into similar outcomes from a different angle may reveal more about the factors influencing physical function in this group. This is a good place to start, and development of interventional studies as a result will further guide the knowledge and experience of those involved in the care of people with ID.

## *2. Development and dissemination of national policy around medication use in older people with ID who live in all settings*

There is currently a lack of national policy around medication use in older adults with ID. The Health Information and Quality Authority (HIQA) is the independent authority responsible for setting standards for care of people with ID. However, little guidance is provided around use of medications in people with ID. The only reference to psychotropics which appears in its standards for services for people with disabilities (44) states:

*“Special consideration is given to the use of: antipsychotic medication, sedative medication, antiepileptic medication, medication for the management of depression, analgesic medications, and different medications and their potential interactions.”*

The absence of specific policy surrounding psychotropic use in Irish people with ID potentially reflects the fact that evidence in this area within an Irish context has only emerged in recent years. Building this evidence base in IDS-TILDA, however, offers the opportunity to inform policy going forward, and specifically target psychotropic use in this population.

A considerable amount of literature has been published in the UK with regard to medical care and prescribing for people with ID. The Royal Pharmaceutical Society has published a medicines optimisation briefing with a focus on people with ID for use by pharmacy professionals (393).

More generally, in 2016, Health Education England launched a new learning disabilities core skills education and training framework which was followed in 2017 by a learning disabilities programme from the Centre for Pharmacy Postgraduate Education (394). Pharmacy professionals can avail of the training in this programme in order to improve their knowledge and quality of interaction with people with ID.

In 2016, the UK launched the STOMP project (stopping over medication of people with a learning disability, autism or both with psychotropic medicines), a three-year programme ending in March 2019 supported by the National Health Service (NHS) (339). This came in response to a cascade of events and reports dating back to the 1970s, when initial concern around psychotropic prescribing in people with ID and autism began to gain traction (339). The 2012 publication of the Winterbourne View serious case review, an investigation into mistreatment in a hospital facility for patients detained under the UK Mental Health Act 1983, highlighted concerns regarding the overuse of antidepressants and antipsychotic medications (339, 395). In response, the Chief Pharmaceutical Officer for England commissioned three pieces of work – the clinical practice research datalink study, second opinion authorised doctor data and a collaborative improvement programme (339). In 2013, the ID hospital census further emphasised concerns around high levels of psychotropic use. Independent research also carried out by the Department of Psychiatry in University College London expressed similar conclusions (339). The National Institute for Clinical Excellence (NICE) in 2015 issued “Challenging behaviour and learning disabilities: prevention and interventions for people with learning disabilities whose behaviour challenges” (NG11) (339). Subsequently, the NHS England issued a “Call to Action” which took the form of STOMP (339).

With STOMP reaching the end of its term, much analysis still remains to be performed in order to measure its success. Depending on the level of success of this programme in the UK, elements could be adopted in Ireland in order to address overmedication of people with ID.

Findings from STOMP could tie in with an Irish effort towards the WHO’s third Global Patient Safety Challenge: “Medication without Harm” (396). Its goal is to reduce severe, avoidable medication-related harm by 50% over the next five years. It has identified three key action areas: high-risk situations; polypharmacy; and transitions of care. Of particular interest in the area of ageing in intellectual disability is polypharmacy and transitions of care (397). Standardised policies and protocols are critically important to manage polypharmacy, both at initial prescribing and regular review (397). Transitions of care take place when a patient moves between facilities and staff members (397). While movement between the hospital and

community setting is recognised broadly as a major transition of care among the general population, in older adults with ID, the policy of deinstitutionalisation in recent years adds the element of movement of living circumstances. While better quality of life outcomes have been identified in the post-deinstitutionalisation era (398), the WHO recognises that transitions of care can increase the possibility of errors in communication, resulting in serious medication errors (397).

Development of national policy around prescribing practices and medication monitoring, similar to the UK, could greatly enhance care for people with ID in Ireland. Monitoring of adverse effects and functional decline are particularly important, because often the person with ID may not be able to communicate these easily. The HSE is the body with responsibility for the development of these policies. It is necessary for the HSE to engage with key stakeholders and review the existing evidence on medication use in older adults with ID in order to produce a “Call to Action” similar to that of the UK’s STOMP. Key stakeholders should include people with ID themselves, carers, family members, healthcare professionals such as pharmacists, GPs, psychiatrists, neurologists and nurses, care staff, social workers, HIQA, regulatory bodies such as the Irish Medical Council, Pharmaceutical Society of Ireland, the Irish College of General Practitioners, the Irish Institute of Pharmacy, the College of Psychiatrists of Ireland, and advocacy organisations (Enable Ireland, Down syndrome Ireland etc), among many others. A series of national consultations, round table discussions and public meetings with these key stakeholders could then lead to drafting of a policy document, which could be revised as necessary until stakeholders are in agreement. The findings of the studies included in this thesis could inform translation into policy around anticholinergic and sedative medication prescribing. It can highlight the high levels of anticholinergic and sedative medications exposure and the association of these with higher dependence in ADLs.

### *3. Computer-based calculation of drug burden measures*

Bedside calculation of drug burden measures, such as the DBI, and to a lesser extent ACB and Sedative Load, is not practical. A recent study of education of pharmacists in use of the Drug Burden Index calculation found that while pharmacists understood the DBI tool well, they struggled with the calculation of the score, and 18.1% failed to correctly complete a case study sample calculation (399). By incorporating these calculations into computer based prescribing and dispensing software, scores could be generated automatically, instantly highlighting to the prescriber or dispenser that a patient is exposed to a high drug burden. This could act as a



catalyst to examine the individual involved for potential adverse effects and trigger medication review. By producing a report on the medication burden, general areas to reduce burden could be automatically generated for the pharmacist and prescriber to examine.

#### *4. Targeted de-prescribing*

De-prescribing of medications comes with a number of challenges. De-prescribing, particularly of central nervous system agents, may be associated with Adverse Drug Withdrawal Events, many of which are physiological (400, 401). Withdrawal of antipsychotics can lead to dyskinesias, insomnia, nausea and restlessness. Discontinuing antiepileptics can cause anxiety, depression and seizures. Antidepressant withdrawal can lead to akathisia, anxiety, chills, coryza, gastrointestinal distress, headache, insomnia, irritability, malaise and myalgia in addition to the recurrence of depression. Benzodiazepine withdrawal may cause agitation, anxiety, confusion, delirium, insomnia and seizures. Sedative/hypnotic discontinuation may cause anxiety, dizziness, muscle twitches and tremor (401). Considering that medication exposure according to the DBI, ACB and Sedative Load in this thesis measured only exposure to regular medications, the high rate of regular use of central nervous system agents could foreshadow greater difficulty in their withdrawal. It has been suggested that clinicians proactively look for reasons to discontinue medications as part of routine practice consultation (401). The feasibility of this activity, however, is questionable, considering the movement of healthcare management for people with ID to primary care settings, which are already under significant time and resource constraints. Some physicians may not feel comfortable discontinuing a medication which was initiated by another prescriber (400). In addition, de-prescribing of medications initiated as a result of the prescribing cascade may cause previously hidden adverse effects to re-emerge (401). The unrecognised withdrawal effects of discontinuing antipsychotic medications could be misattributed to a re-emergence of behavioural disturbances, prompting the re-introduction of the medication (392).

Four steps have been suggested for successful de-prescribing in the general population (401, 402):

- 1) recognizing an indication for discontinuing a medication, such as reduced benefit or adverse drug effects;
- 2) identifying and prioritising the medication(s) to be targeted for discontinuation;
- 3) planning a de-prescribing regimen for discontinuing the medication which includes communicating and coordinating with the patient, their carer and other clinicians;
- 4) monitoring the patient for positive or detrimental effects.

However, de-prescribing for people with ID requires additional considerations. Ten principles of good de-prescribing during medication review for people with ID have been proposed by Flood, 2018 (403) based on the British Pharmacological Society's Principles for Good Prescribing 2010 (404). Clarity around the motivations and reasons for de-prescribing psychotropic medications and unambiguous documentation of these reasons are essential, especially considering the multiple healthcare providers involved in the management of the health of people with ID. Acknowledgement of the limitations of knowledge, skills and experience when de-prescribing in this group is also highlighted (403).

It was recommended that education of support workers on the effects of antipsychotics, including side effects and withdrawal effects, could positively influence the success of efforts to de-prescribe.

Producing specific policy in Ireland would help to address issues around targeted de-prescribing. Algorithms and guidelines around specific steps for discontinuation, such as those available in the UK (405), would greatly benefit the medication review, and allow GPs, psychiatrists, pharmacists, patients and carers to collaborate in order to manage de-prescribing of the more difficult-to-discontinue therapeutic classes, which may often takes months of careful tapering and monitoring before it is finally achieved.

#### *5. Recognition of the impact of medicines on quality of life*

The consequences of some adverse effects are not easy to measure, but can have a significant impact on overall quality of life through a cascade of events. Highlighting the prevalence of anticholinergic and sedative burden is the first step towards addressing it. This is particularly important for individuals with ID, as communication can be difficult for them. A person with ID with high anticholinergic burden may suffer from dry mouth, causing tooth decay, loss of appetite and subsequent weight loss. Reducing that burden may allow this individual to once again be able to enjoy food due to increased salivary flow and taste sensation. They may also suffer less from dental caries and tooth loss, reducing the pain and discomfort associated with dental work. Existing difficulties with speech may be compounded by the dysphonia associated with anticholinergic use, leading to an increase in behaviours that challenge arising from the inability to effectively communicate. A patient with constipation caused by anticholinergic load may benefit from de-prescribing which then allows them to leave home more often and get greater opportunities to socialise, as they are no longer restricted by this side effect. A patient experiencing urinary retention may have this resolved, and subsequently may be less prone to

urinary tract infections and the adverse effects associated with the antibiotics used to treat these. Pain associated with constipation and urinary tract infections may also be reduced, further reducing behaviours that challenge as the person with ID no longer needs to try and communicate their discomfort. Drowsiness and daytime sedation caused by regular sedative medication use may be lessened by de-prescribing, allowing an individual to go out and socialise more, and be less inclined to boredom and frustration. These outcomes are difficult to measure, especially since the adverse effects experienced by people with ID tend to be multifactorial. However, they represent potential to significantly improve the quality of life of a person with ID.

## **6.8 Future Research**

A further health assessment is planned for Wave 4 (2019/2020) of IDS-TILDA. This health assessment will repeat measures carried out at Wave 2 (including grip strength and TUG) and will enable analysis of functional decline and its association with medication exposure. It may be possible to examine the association of DBI, ACB and Sedative Load exposure at Wave 2 with physical performance at Wave 4 and the cumulative effect of medication exposure using an area under the curve model, similar to the method that which was used in a longitudinal analysis of DBI and functional decline in older adults without ID (150).

An accumulation of deficits frailty index is currently under construction from the Wave 2 IDS-TILDA data. This frailty measure may present another insight into frailty in this population, as accumulation of deficits frailty indices are typically less prone to the influence of low mobility and could prove more useful for assessing the association of drug exposure with frailty. It has been argued by authors reporting data from HA-ID that an accumulation of deficits frailty index is a more suitable measure for frailty among older adults with ID (192), so investigation of this index in IDS-TILDA may reveal more information about the association between frailty and other factors, including medication use, in this population.

More specific research into the adverse effects of particular classes of medications may produce further insight into the effect of medication exposure. The Matson Evaluation of Drug Side Effects (MEDS) was developed to measure medication adverse effects in people with ID. At present, it is the most comprehensive specific measure available for use in this population (406). However, the MEDS scale is a 90-item measure of medication side effects, which rates occurrence, severity and duration of symptoms across nine domains – gastrointestinal, endocrine/genitourinary, eye/ear/nose/throat, skin/allergies/temperature, CNS-general, CNS-

dystonia, CNS-parkinsonism/dyskinesia and CNS-akathisia (407). The level of detail captured by the MEDS would provide very specific insight into the adverse effects potentially occurring as a direct effect of psychotropic medications. However, the complex nature of the data required may be difficult for non-clinical field researchers to capture and for participants to answer questions on, especially considering that the IDS-TILDA interview is already relatively lengthy. As a compromise, a pilot project to determine feasibility in a small sample of older adults with ID could be completed, and based on these findings the utility of this scale could be considered further.

Little is known yet about the effects of long-term exposure to anticholinergic and sedative medications on a person with ID's physical function and independence. A key recommendation for future research is longitudinal analysis in IDS TILDA to examine the impact of long-term use of medications, particularly those with anticholinergic and sedative activity on frailty, functional decline and mortality in older adults with ID.

IDS-TILDA is a longitudinal study, while the data presented in this thesis are cross-sectional, from Wave 2. The IDS-TILDA design will allow for longitudinal analysis, and this will form an important part of future research in this area. Longitudinal studies will allow analysis of changes in the characteristics of people ageing with an ID, both at group level and individual level. This offers an advantage over cross-sectional analysis, as it will allow examination of the sequence of events leading up to an outcome. Longitudinal analysis can alleviate recall bias and allow separation of time effects, something of great importance in ageing research (408, 409). Future research will include longitudinal analysis of medication exposure and functional limitations, physical function and frailty.

Future research could also include conducting a systematic literature review around anticholinergic and sedative drug burden exposure and functional outcomes in adults with ID. This would add significantly to the existing knowledge-base and eliminate any potential bias which was introduced through the completion of a targeted literature review.

Further analysis of missing data could be conducted, and different methods of handling missing data could be employed in future research. Multiple imputation may be considered to handle missing data, particularly with respect to physical function measures. Sensitivity analysis may also be performed to evaluate deviation of data from the missing at random assumption. Chi-squared automatic interaction detection (CHAID) may be used as a data-mining tool to population missing data values. CHAID offers the advantage of creating optimal homogenous groups which ensure reliable imputation estimates (410).

In addition, more extensive use of chi-squared analysis could be made in order to assess representativeness of the sample in IDS-TILDA going forward.

Future research could also involve an examination of the current status of medication management services for people with ID in Ireland. There is great heterogeneity in how medication services are provided to people with ID, due to the variety of services and care models in practice in Ireland. It would be helpful to investigate the approaches taken to medication management services across the ID service providers in Ireland, potentially through surveys, questionnaires and focus groups. This qualitative data could inform current practice, and identify areas where medication management services for this populations may be standardised and improved upon.

A valuable tool for future analysis would be linking the medicines dispensed under the Primary Care Reimbursement Service in Ireland (in particular General Medical Services and Long-Term Illness schemes) to the data in IDS-TILDA. This would give a fuller picture, not just of regularly used medications, but also of medications dispensed for short-term illness. Considering the historical impact of respiratory infections on mortality in people with ID, examining the data for antibiotic use patterns would be of interest. This method of analysis may also allow matching to older adults without ID based on age and gender in order to examine the differences in medication use in a comparable group more closely, similar to studies performed in Sweden using their Prescribed Drug Register (58, 102, 369).

## **6.9 Conclusion**

Older adults with ID are living longer than ever before and now experience greater community participation and social engagement with the advent of deinstitutionalisation. However, they are experience high medication exposure when measured by a number of burden scales, in particular scales measuring anticholinergic and sedative effects. The medication exposure experienced by this population is associated with greater dependency in routine daily activities. Performance in measures of physical function is poorer than that observed in the general population, and the cause of this poor physical function is thought to be multifactorial. While medication exposure was not found to be independently associated with reduced physical function, it could be a contributing factor when taking into account the other health effects experienced by older adults with ID, such as neurological impairment, lifelong physical inactivity

and premature ageing. Frailty as measured by a traditional method, a modified version of Fried's frailty phenotype, was higher in older adults with ID than their counterparts without ID, and excessive polypharmacy was associated with both pre-frailty and frailty.

National policy around the use of medications and appropriate prescribing in this population is lacking, and there is a need to develop specific tools for measuring appropriate prescribing specific to older adults with ID rather than extrapolating practices from other populations.

The association between medication exposure and functional decline has not yet been investigated in older adults with ID, but would produce an important insight into the long-term effects of anticholinergic and sedative medications in this population, especially considering these adults are typically exposed to these medications from a young age.

Functional independence is an important marker of healthy ageing in older adults without ID, and there is no reason why it should not be applied to older adults with ID. Preserving the independence and dignity of an older adult with ID as they age is critical to ensure their quality of life as they move into their 70s, 80s and beyond.

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# Appendices

Appendix 1 IDS-TILDA Study Ethical Approval



THE UNIVERSITY OF DUBLIN

TRINITY COLLEGE

SCHOOL OF MEDICINE

FACULTY OF HEALTH SCIENCES

Professor Dermot Kelleher, MD, FRCPI, FRCP, F Med Sci  
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Prof. Mary McCarron  
School of Nursing and Midwifery,  
Trinity College Dublin,  
24 D'Olier Street, Dublin 2

10th July, 2008

**Study Title: An Intellectual Disability Supplement to the Irish Longitudinal Study  
on Ageing (TILDA)**

Dear Prof. McCarron,

Further to the meeting of the Faculty of Health Sciences Research Ethics Committee on 27<sup>th</sup> May 2008, I am pleased to inform you that the above project has been approved without further audit.

Yours sincerely,

  
Dr. Orla Sheils  
Chairperson  
Faculty of Health Sciences Ethics Committee

Appendix 2 Correspondence from the Health Research Consent Declaration Committee

|                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|--------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Application Ref</b>                                       | <b>19-015-AF2</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <b>Application Title</b>                                     | IDS - TILDA                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <b>Applicant Organisation (Data Controller)</b>              | Trinity College Dublin                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| <b>Lead Applicant</b>                                        | Mary McCarron                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| <b>Research commenced prior to submission of application</b> | Yes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| <b>Research Objective</b>                                    | <p>Intellectual Disability Study-The Irish Longitudinal Study on Ageing (IDS-TILDA) is a longitudinal study researching ageing in Ireland of a representative sample of people with an intellectual disability aged 40 and over at all levels of functioning and in all living situations. IDS-TILDA aims to identify the principle influences on successful ageing in persons with an intellectual disability, and to then determine if they are the same or different influences for the general population.</p> <p>Data will be examined to determine similarities to and differences from the influences on the ageing lives of the general population and if there are changes in influences over time for people with an intellectual disability, and to analyse the data to inform and guide the planning, implementation and evaluation of future national policies, programmes and services.</p> |
| <b>Reason for seeking a Declaration</b>                      | IDS-TILDA is seeking a consent declaration for the processing of data from individuals with an intellectual disability who are not able to give explicit consent or to designate a proxy to act on their behalf.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <b>HRCDC Meeting Date</b>                                    | 17th October, 2019                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |

|                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|-------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| HRCDC Decision Date                 | 17th October, 2019                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| HRCDC Decision                      | Conditional Declaration                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Specific Conditions attached        | <p><b>Condition 1:</b> The Applicant is requested to review and consider amendments to the PIL and consent forms with regards to the inclusion of both 'yes' and 'no' options and information on the use of the Primary Care Reimbursement Scheme numbers.</p> <p><b>Condition 2:</b> The Applicant is requested to provide more information on the process that will be implemented to inform and support participants where the analysis of their bio-samples identifies any health issues. The HRCDC wish to seek assurances that participants with intellectual disabilities are appropriately supported in such circumstances where they may need to seek further medical advice.</p> |
| Deadline for meeting any conditions | N/A                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Duration of Declaration             | The Declaration is made commencing August 8th, 2018 and shall be valid until October 31st, 2021 and 5 years thereafter (until October 31st, 2026), or upon confirmation that the data has been rendered anonymised or destroyed, or whichever occurs sooner.                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Status of Declaration               | Declaration Live                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

|                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                      |
|-------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Additional Comments/Recommendations from HRCDC</b> | <p><b>Recommendation 1:</b> The Applicant is requested to review and consider the adequacy of the GDPR training that is completed by individuals involved in the study, specifically the 35-minute session.</p> <p><b>Recommendation 2:</b> The Applicant is requested to consider the timeframe and safeguards for the retention of personal data, in soft or hard copy format, held by the study fieldworkers.</p> |
|-------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

## Appendix 3 Medication Data Collection Form

### 144. MEDICATIONS



We would like to record all medications that you take on a regular basis, take every day or every week. This will include prescription and non-prescription medications, over-the-counter medicines, vitamins and herbal and alternative medicines.

PLEASE WRITE DOWN ALL MEDICATIONS/TABLETS YOU TAKE AND HOW OFTEN YOU TAKE THEM, PLEASE USE ONE LINE PER MEDICATION

Don't know what medication I take, record by proxy

☐

PLEASE COMPLETE MEDICATION FORM

Don't take any medication

<sup>1</sup> GO TO QUESTION 145

| Name of Medication                              | Dosage Strength    | Frequency        | Route      | Date First Prescribed |
|-------------------------------------------------|--------------------|------------------|------------|-----------------------|
| <b>Examples of medication completion form :</b> |                    |                  |            |                       |
| Epilim Chrono                                   | 200mgs             | Twice a day (BD) | Orally(PO) | Sept 2009             |
| One touch ultra test strip(blood glucose)       | 1 strip            | Before meals     | -          | June 2010             |
| Neo-cytamen Injection(hydroxycobalamin)         | 1000micrograms     | Monthly          | IM         | Nov 2010              |
| Xalatan eye drops                               | 2 drops (left eye) | Nocte (At night) | Instill    | June 2010             |
| Emulsifying Ointment                            |                    | PRN              | Topically  | Jan 2009              |
| Vegepa (Omega fishoil)                          |                    | 2 daily          | PO         | June 2005             |
| Ensure Plus                                     |                    | 1 daily          | PO         | Oct 2007              |



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COLÁISTE NA TRÍONÓIDE

THE  
UNIVERSITY  
OF DUBLIN

| Name of Medication | Dosage Strength | Frequency | Route | Date Prescribed |
|--------------------|-----------------|-----------|-------|-----------------|
| 1                  |                 |           |       |                 |
| 2                  |                 |           |       |                 |
| 3                  |                 |           |       |                 |
| 4                  |                 |           |       |                 |
| 5                  |                 |           |       |                 |
| 6                  |                 |           |       |                 |
| 7                  |                 |           |       |                 |
| 8                  |                 |           |       |                 |
| 9                  |                 |           |       |                 |
| 10                 |                 |           |       |                 |
| 11                 |                 |           |       |                 |
| 12                 |                 |           |       |                 |
| 13                 |                 |           |       |                 |
| 14                 |                 |           |       |                 |
| 15                 |                 |           |       |                 |
| 16                 |                 |           |       |                 |
| 17                 |                 |           |       |                 |
| 18                 |                 |           |       |                 |



#### Appendix 4 Drug Burden Index Anticholinergic Medications Inventory

| International Non-Proprietary Name | ATC Code                                                   | Source for Consideration | Reason for Inclusion | Minimum Effective Daily Dose                                                                                                                                      |
|------------------------------------|------------------------------------------------------------|--------------------------|----------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Alimemazine                        | R06AD01                                                    | (103)                    | ACB 1                | 10mg                                                                                                                                                              |
| Alprazolam                         | N05BA12                                                    | (103, 150)               | ACB 1                | 0.5mg                                                                                                                                                             |
| Alverine                           | A03AX08<br>A03AX58                                         | (103)                    | ACB 1                | 60mg                                                                                                                                                              |
| Amantadine                         | N04BB01                                                    | (103)                    | ACB 2                | 200mg                                                                                                                                                             |
| Amisulpride                        | N05AL05                                                    | (103, 161)               | ACB 1                | 50mg                                                                                                                                                              |
| Amitriptyline                      | N06AA09<br>N06CA01                                         | (103, 143, 150, 164)     | ACB 3                | 50mg                                                                                                                                                              |
| Amoxapine                          | N06AA17                                                    | (103)                    | ACB 3                | No SmPC available in Ireland or UK                                                                                                                                |
| Aripiprazole                       | N05AX12                                                    | (103, 161)               | ACB 1                | 15mg                                                                                                                                                              |
| Asenapine                          | N05AH05                                                    | (103)                    | ACB 1                | 10mg                                                                                                                                                              |
| Atenolol                           | C07AB03<br>C07BB03<br>C07CB(03)/(53)<br>C07DB01<br>C07FB03 | (103, 143)               | ACB 1                | 50mg                                                                                                                                                              |
| Atropine                           | A03BA01<br>A03CB03<br>S01FA01                              | (103)                    | ACB 3                | 2 drops (0.001mg)                                                                                                                                                 |
| Baclofen                           | M03BX01                                                    | (103, 143)               | ACB 1                | 30mg                                                                                                                                                              |
| Belladonna                         | A03BA04<br>A03CB02<br>A06AB30                              | (103, 150)               | ACB 2                | No SmPC available in Ireland or UK                                                                                                                                |
| Bendroflumethiazide                | C03AA01<br>C03AB01<br>C03EA13                              | (103)                    | ACB 1                | 2.5mg                                                                                                                                                             |
| Benperidol                         | N05AD07                                                    | (103, 161)               | ACB 1                | 0.125mg                                                                                                                                                           |
| Benzatropine                       | N04AC01                                                    | (103, 150, 161)          | ACB 3                | 1mg                                                                                                                                                               |
| Biperiden                          | N04AA02                                                    | (103, 143)               | ACB 3                | 2mg                                                                                                                                                               |
| Brompheniramine                    | R06AB01<br>R06AB51                                         | (103, 150)               | ACB 3                | 3mg                                                                                                                                                               |
| Captopril                          | C09AA01<br>C09BA01                                         | (103, 143)               | ACB 1                | Hypertension: 100mg<br>Active Renin-Angiotensin-Aldosterone-System: 50mg<br>Heart Failure: 75mg<br>Diabetic Nephropathy: 75mg<br>Post-Myocardial Infarction: 75mg |
| Carbamazepine                      | N03AF01                                                    | (103, 143, 150)          | ACB 2                | 800mg                                                                                                                                                             |
| Carbinoxamine                      | R06AA08                                                    | (103)                    | ACB 3                | No SmPC available in Ireland or UK                                                                                                                                |
| Cetirizine                         | R06AE07                                                    | (103, 143, 150)          | ACB 1                | 10mg                                                                                                                                                              |
| Chlorphenamine                     | R06AB04<br>R06AB54                                         | (103, 150)               | ACB 3                | 4mg                                                                                                                                                               |

| International Non-Proprietary Name | ATC Code                                                         | Source for Consideration | Reason for Inclusion       | Minimum Effective Daily Dose                      |
|------------------------------------|------------------------------------------------------------------|--------------------------|----------------------------|---------------------------------------------------|
| Chlorpromazine                     | N05AA01                                                          | (103, 150)               | ACB 3                      | 10mg                                              |
| Chlortalidone                      | C03BA04<br>C03BB04<br>C03EA06                                    | (103)                    | ACB 1                      | 12.5mg                                            |
| Cimetidine                         | A02BA01<br>A02BA51                                               | (103, 143)               | ACB 1                      | 400mg                                             |
| Cinnarizine                        | N07CA02<br>N07CA52                                               | (103, 143)               | ACB 1                      | 100mg                                             |
| Citalopram                         | N06AB04                                                          | (103, 143, 150, 164)     | ACB 1                      | 10mg                                              |
| Clemastine                         | R06AA04<br>R06AA54                                               | (103, 150)               | ACB 3                      | 2mg                                               |
| Clidinium                          | A03CA02                                                          | (103, 150)               | ACB 1                      | No SmPC available in Ireland or UK                |
| Clomipramine                       | N06AA04                                                          | (103, 143, 150)          | ACB 3                      | 30mg                                              |
| Clorazepate                        | N05BA05                                                          | (103, 150)               | ACB 1                      | No SmPC available in Ireland or UK                |
| Clozapine                          | N05AH02                                                          | (103, 161)               | ACB 3                      | Schizophrenia: 200mg<br>Parkinson's Disease: 25mg |
| Codeine                            | R05DA04<br>N02AA59<br>N02AJ(06)/(07)/(08)/(09)<br>N02AA(59)/(79) | (103, 143, 150, 164)     | ACB 1                      | 15mg                                              |
| Colchicine                         | M04AC01                                                          | (103)                    | ACB 1                      | 1mg                                               |
| Cyclobenzaprine                    | M03BX08                                                          | (103, 150)               | ACB 2                      | No SmPC available in Ireland or UK                |
| Cyproheptadine                     | R06AX02                                                          | (103, 150)               | ACB 2                      | 4mg                                               |
| Darifenacin                        | G04BD10                                                          | (103)                    | ACB 3                      | 7.5mg                                             |
| Desipramine                        | N06AA01                                                          | (103, 150)               | ACB 3                      | No SmPC available in Ireland or UK                |
| Desloratadine                      | R06AX27                                                          | (103)                    | ACB 1                      | 5mg                                               |
| Diazepam                           | N05BA01                                                          | (103, 143, 150)          | ACB 1                      | 3mg                                               |
| Dicycloverine (Dicyclomine)        | A03AA07                                                          | (103, 150)               | ACB 3                      | 30mg                                              |
| Digoxin                            | C01AA05                                                          | (103)                    | ACB 1                      | 0.0625mg                                          |
| Dimenhydrinate                     | N07CA52                                                          | (103, 150)               | ACB 3                      | 120mg                                             |
| Diphenhydramine                    | R06AA02<br>R06AA52                                               | (103, 150)               | ACB 3                      | 25mg                                              |
| Dipyridamole                       | B01AC07                                                          | (103)                    | ACB 1                      | 400mg                                             |
| Disopyramide                       | C01BA03                                                          | (103, 150)               | ACB 1                      | 500mg                                             |
| Dosulepin                          | N06AA16                                                          |                          | Anticholinergic properties | 50mg                                              |
| Doxazosin                          | C02CA04                                                          | (103, 150)               | ACB 1                      | 1mg                                               |
| Doxepin                            | N06AA12                                                          | (103, 143, 150, 161)     | ACB 3                      | 75mg                                              |
| Escitalopram                       | N06AB10                                                          | (103, 150)               | ACB 1                      | 5mg                                               |

| International Non-Proprietary Name  | ATC Code                                                                                     | Source for Consideration | Reason for Inclusion       | Minimum Effective Daily Dose            |
|-------------------------------------|----------------------------------------------------------------------------------------------|--------------------------|----------------------------|-----------------------------------------|
| Fentanyl                            | N02AB03                                                                                      | (103, 143, 150)          | ACB 1                      | 0.288 (transdermal)<br>0.1 (sublingual) |
| Fesoterodine                        | G04BD11                                                                                      | (103)                    | ACB 3                      | 4mg                                     |
| Flavoxate                           | G04BD02                                                                                      | (103, 150)               | ACB 3                      | 600mg                                   |
| Flupentixol                         | N05AF01                                                                                      | (103, 161)               | ACB 1                      | 20mg every 2 weeks (depot)              |
| Fluphenazine                        | N05AB02                                                                                      | (103, 150, 161)          | ACB 1                      | 0.45mg                                  |
| Fluvoxamine                         | N06AB08                                                                                      | (103, 143)               | ACB 1                      | 100mg                                   |
| Furosemide                          | C03CA01<br>C03CB01<br>C03EB01                                                                | (103)                    | ACB 1                      | 40mg                                    |
| Haloperidol                         | N05AD01                                                                                      | (103, 150, 161)          | ACB 1                      | 1.5mg                                   |
| Hydralazine                         | C02DB02<br>C02LG02                                                                           | (103)                    | ACB 1                      | 50mg                                    |
| Hydrochlorothiazide                 | C03AA03<br>C03AB03<br>C03AX01<br>C03EA01<br>C09BX03<br>C09DX(01)/(03)/(06)<br>C09XA(52)/(54) | (103)                    | ACB 1                      | 12.5mg                                  |
| Hydroxyzine                         | N05BB01<br>N05BB51                                                                           | (103, 143, 150, 161)     | ACB 3                      | 25mg                                    |
| Hyoscine (Butylscopolamine)         | A03BB01                                                                                      | (103)                    | ACB 3                      | 80mg                                    |
| Iloperidone                         | N05AX14                                                                                      | (103)                    | ACB 1                      | No SmPC available in Ireland or UK      |
| Isosorbide mononitrate              | C01DA14                                                                                      | (103)                    | ACB 1                      | 20mg                                    |
| Levocetirizine                      | R06AE09                                                                                      | (103)                    | ACB 1                      | 5mg                                     |
| Levomepromazine (Methotrimeprazine) | N05AA02                                                                                      | (103)                    | ACB 2                      | 12.5mg                                  |
| Lofepramine                         | N06AA07                                                                                      |                          | Anticholinergic properties | 140mg                                   |
| Loperamide                          | A07DA03<br>A07DA53                                                                           | (103, 150)               | ACB 1                      | 4mg                                     |
| Loratadine                          | R06AX13                                                                                      | (103, 143, 150)          | ACB 1                      | 10mg                                    |
| Loxapine                            | N05AH01                                                                                      | (103, 150)               | ACB 2                      | 9.1mg (by inhalation)                   |
| Mebeverine                          | A03AA04                                                                                      | (103)                    | ACB 1                      | 405mg                                   |
| Meclozine                           | R06AE05<br>R06AE55                                                                           | (103, 143, 150)          | ACB 3                      | 25mg                                    |
| Meperiden/Pethidine                 | N02AB02<br>N02AG03<br>N02AB(52)/(72)                                                         | (103)                    | ACB 2                      | 300mg                                   |
| Methocarbamol                       | M03BA03<br>M03BA(53)/(73)                                                                    | (103, 150)               | ACB 3                      | 2250mg                                  |

| International Non-Proprietary Name | ATC Code                                                                 | Source for Consideration | Reason for Inclusion | Minimum Effective Daily Dose                   |
|------------------------------------|--------------------------------------------------------------------------|--------------------------|----------------------|------------------------------------------------|
| Metoprolol                         | C07AB02<br>C07BB(02)/(52)<br>C07CB02<br>C07FB(02)/(13)<br>C07FX(03)/(05) | (103, 143)               | ACB 1                | 12.5mg                                         |
| Mirtazapine                        | N06AX11                                                                  | (103, 143, 150, 164)     | ACB 1                | 15mg                                           |
| Molindone                          | N05AE02                                                                  | (103)                    | ACB 2                | No SmPC available in Ireland or UK             |
| Nefopam                            | N02BG06                                                                  | (103)                    | ACB 2                | 90mg                                           |
| Nifedipine                         | C07FB03<br>C08CA05<br>C08CA55<br>C08GA01                                 | (103, 143)               | ACB 1                | 30mg                                           |
| Nortriptyline                      | N06AA10                                                                  | (103, 143, 150)          | ACB 3                | 30mg                                           |
| Olanzapine                         | N05AH03                                                                  | (103, 143, 150)          | ACB 3                | 5mg                                            |
| Orphenadrine                       | M03BC01<br>M03BC51<br>N04AB02                                            | (103, 143, 150)          | ACB 3                | 150mg                                          |
| Oxcarbazepine                      | N03AF02                                                                  | (103, 150)               | ACB 2                | 600mg                                          |
| Oxybutynin                         | G04BD04                                                                  | (103, 143, 150, 164)     | ACB 3                | 5mg (oral)<br>3.9mg (transdermal)              |
| Paliperidone                       | N05AX13                                                                  | (103)                    | ACB 1                | 3mg (oral)<br>25mg every month (depot)         |
| Paroxetine                         | N06AB05                                                                  | (103, 143, 150)          | ACB 3                | 20mg                                           |
| Periciazine                        | N05AC01                                                                  | (103, 161, 164)          | ACB 3                | Schizophrenia: 15mg<br>Short term anxiety: 5mg |
| Perphenazine                       | N05AB03                                                                  | (103, 150)               | ACB 3                | No SmPC available in Ireland or UK             |
| Pimozide                           | N05AG02                                                                  | (103)                    | ACB 2                | 2mg                                            |
| Prednisolone                       | A01AC54<br>A07EA01<br>C05AA04<br>H02AB06<br>R01AD(02)/(52)               | (103)                    | ACB 1                | 5mg                                            |
| Prochlorperazine                   | N05AB04<br>(recoded to A04A)                                             | (103, 150)               | ACB 1                | 10mg                                           |
| Procyclidine                       | N04AA04                                                                  | (103, 161)               | ACB 3                | 7.5mg                                          |
| Promazine                          | N05AA03                                                                  | (103)                    | ACB 3                | 50mg                                           |
| Promethazine                       | R06AD(02)/(52)                                                           | (103, 150)               | ACB 3                | 25mg                                           |
| Propantheline                      | A03AB05<br>A03CA34                                                       | (103, 150)               | ACB 3                | 75mg                                           |
| Propiverine                        | G04BD06                                                                  | (103)                    | ACB 3                | 15mg                                           |
| Quetiapine                         | N05AH04                                                                  | (103, 143, 150)          | ACB 3                | 150mg                                          |
| Quinidine                          | C01BA01<br>C01BA(51)/(71)                                                | (103)                    | ACB 1                | No SmPC available in Ireland or UK             |

| <b>International Non-Proprietary Name</b> | <b>ATC Code</b>           | <b>Source for Consideration</b> | <b>Reason for Inclusion</b> | <b>Minimum Effective Daily Dose</b>        |
|-------------------------------------------|---------------------------|---------------------------------|-----------------------------|--------------------------------------------|
| Ranitidine                                | A02BA02                   | (103, 143)                      | ACB 1                       | 300mg                                      |
| Risperidone                               | N05AX08                   | (103, 143, 150, 164)            | ACB 1                       | 2mg (oral)<br>25mg every two weeks (depot) |
| Scopolamine                               | A04AD(01)/(51)<br>N05CM05 | (103, 143, 161)                 | ACB 3                       | 0.3mg                                      |
| Solifenacin                               | G04BD08<br>G04CA53        | (103)                           | ACB 3                       | 5mg                                        |
| Sulpiride                                 | N05AL01                   | (103, 143)                      | ACB 1                       | 400mg                                      |
| Theophylline                              | R03DA04                   | (103, 143, 161)                 | ACB 1                       | Asthma: 400mg<br>Emphysema: 600mg          |
| Tizanidine                                | M03BX02                   | (103, 143)                      | ACB 2                       | 12mg                                       |
| Tolterodine                               | G04BD07                   | (103, 150, 164)                 | ACB 3                       | 4mg                                        |
| Trazodone                                 | N06AX05                   | (103, 143, 150)                 | ACB 1                       | 100mg                                      |
| Triamterene                               | C03DB02                   | (103)                           | ACB 1                       | 150mg                                      |
| Trifluoperazine                           | N05AB06                   | (103, 150, 161)                 | ACB 3                       | 2mg                                        |
| Trihexyphenidyl                           | N04AA01                   | (103, 150)                      | ACB 3                       | 6mg                                        |
| Trimipramine                              | N06AA06                   | (103, 143, 150)                 | ACB 3                       | 25mg                                       |
| Trospium                                  | A03DA06<br>G04BD09        | (103)                           | ACB 3                       | 40mg                                       |
| Venlafaxine                               | N06AX16                   | (103, 143, 150)                 | ACB 1                       | 75mg                                       |
| Warfarin                                  | B01AA03                   | (103)                           | ACB 1                       | 3mg                                        |
| Ziprasidone                               | N05AE04                   | (150, 161)                      | Anticholinergic properties  | 40mg                                       |
| Zuclopenthixol                            | N05AF05                   | (103, 161)                      | ACB 2                       | 20mg (oral)<br>7.1mg (depot)               |

Appendix 5 Drug Burden Index Sedative Medications Inventory

| International Non-Proprietary Name | ATC Code                      | Source for Consideration | Reason for Inclusion                                                                                                                                                          | Minimum Effective Daily Dose             |
|------------------------------------|-------------------------------|--------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------|
| Aciclovir                          | J05AB01                       | HPRA Search              | Fatigue is a “Very Common” adverse effect. (SmPC)                                                                                                                             | 800mg                                    |
| Agomelatine                        | N06AX22                       | (161)                    | Somnolence and fatigue are “Common” adverse effects. (SmPC)                                                                                                                   | 25mg                                     |
| Anastrozole                        | L02BG03                       | HPRA Search              | Asthenia is a “Very Common” adverse effect. Somnolence is a “Common” adverse effect. (SmPC)                                                                                   | 1mg                                      |
| Aprepitant                         | A04AD12                       | HPRA Search              | Fatigue is a “Common” adverse effect. (SmPC)                                                                                                                                  | 40mg                                     |
| Atomoxetine                        | N06BA09                       | HPRA Search              | Somnolence is a “Very Common” adverse effect. Fatigue and asthenia are “Common” adverse effects. (SmPC)                                                                       | 80mg                                     |
| Axitinib                           | L01XE17                       | HPRA Search              | Fatigue and asthenia are “Very Common” adverse effects. (SmPC)                                                                                                                | 10mg                                     |
| Azithromycin                       | J01FA10                       | HPRA Search              | Fatigue is a “Common” adverse effect. Somnolence is an “Uncommon” adverse effect (SmPC)                                                                                       | 250mg                                    |
| Bicalutamide                       | L02BB03<br>L02AE51            | HPRA Search              | Asthenia is a “Very Common” adverse effect. Somnolence is a “Common” adverse effect. (SmPC)                                                                                   | 50mg                                     |
| Bilastine                          | R06AX29                       | HPRA Search              | Somnolence is a “Common” adverse effect (SmPC)                                                                                                                                | 20mg                                     |
| Bosutinib                          | L01XE14                       | HPRA Search              | Fatigue is a “Very Common” adverse effect. Asthenia is a “Common” adverse effect. (SmPC)                                                                                      | 500mg                                    |
| Bromazepam                         | N05BA08                       | HPRA Search              | Somnolence and fatigue are reported adverse effects (SmPC)                                                                                                                    | 1.5mg                                    |
| Bromocriptine                      | G02CB01<br>N04BC01            | (143)                    | Drowsiness is a “Common” adverse effect. Somnolence is a “Rare” adverse effect. Excessive daytime somnolence and sudden onset of sleep are “Very Rare” adverse effects (SmPC) | 5mg                                      |
| Bucizine                           | R06AE(01)/(51)                | HPRA Search              | Somnolence is a “Very Common” adverse effect (SmPC)                                                                                                                           | 0.5mg                                    |
| Bumetanide                         | C03CA02<br>C03CB02<br>C03EB02 | HPRA Search              | Fatigue (including lethargy, somnolence, asthenia and malaise) is a “Common” adverse effect. (SmPC)                                                                           | 0.5mg                                    |
| Buprenorphine                      | N02AE01<br>N07BC(01)/(51)     | (143)                    | Somnolence is a “Very Common” adverse effect. Fatigue is an “Uncommon” adverse effect. (SmPC)                                                                                 | 0.4mg (sublingual)<br>0.12 (transdermal) |
| Buserelin                          | L02AE01                       | HPRA Search              | Fatigue is noted as an adverse effect. (SmPC)                                                                                                                                 | 0.6mg                                    |
| Cabergoline                        | G02CB03<br>N04BC06            | HPRA Search              | Somnolence is a “Common” adverse effect. (SmPC)                                                                                                                               | G02CB03: 0.04mg<br>N04BC06: 2mg          |

| International Non-Proprietary Name | ATC Code                              | Source for Consideration | Reason for Inclusion                                                                                     | Minimum Effective Daily Dose                                                       |
|------------------------------------|---------------------------------------|--------------------------|----------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|
| Calcitonin                         | H05BA01                               | (143)                    | Fatigue is a “Common” adverse effect (SmPC)                                                              | Paget’s Disease: 50 IU<br>Prevention of Bone Loss: 50 IU<br>Hypercalcaemia: 300 IU |
| Capecitabine                       | L01BC06                               | HPRA Search              | Fatigue is a “Very Common” adverse effect. (SmPC)                                                        | 1150mg (calculated per m <sup>2</sup> )                                            |
| Carmustine                         | L01AD01                               | HPRA Search              | Somnolence and asthenia are “Very Common” adverse effects. (SmPC)                                        | 7.7mg                                                                              |
| Chlordiazepoxide                   | N05BA02                               | (143, 150)               | Drowsiness, drowsiness during the day, reduced alertness and fatigue are noted as adverse effects (SmPC) | 15mg                                                                               |
| Clobazam                           | N05BA09                               | HPRA Search              | Drowsiness is noted as an adverse effect in the SmPC.                                                    | 10mg                                                                               |
| Clonazepam                         | N03AE01                               | (150)                    | Somnolence and fatigue are noted as adverse effects (SmPC)                                               | 4mg                                                                                |
| Clonidine                          | C02AC01<br>N02CX02                    | (150)                    | Sedation is a “Very Common” adverse effect. (SmPC)                                                       | C02AC01: 0.3mg<br>N02CX02: 0.1mg                                                   |
| Cyclizine                          | R06AE(03)/(53)                        | (143)                    | Somnolence and drowsiness are “Not Known Frequency” adverse effects (SmPC)                               | 50mg                                                                               |
| Cyproterone                        | G03HA01<br>G03HB01                    | HPRA Search              | Fatigue is a “Common” adverse effect. (SmPC)                                                             | 300mg                                                                              |
| Dabrafenib                         | L01XE23                               | HPRA Search              | Fatigue and asthenia are “Very Common” adverse effects. (SmPC)                                           | 30mg                                                                               |
| Dapoxetine                         | G04BX14                               | HPRA Search              | Somnolence is a “Common” adverse effect                                                                  | 250mg                                                                              |
| Didanosine                         | J05AF02                               | HPRA Search              | Fatigue and asthenia are “Common” adverse effects. (SmPC)                                                | 30mg                                                                               |
| Dihydrocodeine                     | N02AA(08)/(58)<br>N02AJ(01)/(02)/(03) | HPRA Search              | Drowsiness is noted as an adverse effect (SmPC)                                                          | 10mg                                                                               |
| Diphenoxylate                      | A07DA01                               | (150)                    | Malaise/lethargy/sedation/somnolence are reported adverse effects (SmPC)                                 | 10mg                                                                               |
| Disulfiram                         | N07BB01                               | (143)                    | Drowsiness, fatigue and somnolence are “Common” adverse effects (SmPC)                                   | 100mg twice weekly                                                                 |
| Donepezil                          | N06DA(02)/(52)/(53)                   | (143)                    | Fatigue is a “Common” adverse effect (SmPC)                                                              | 5mg                                                                                |
| Dronedarone                        | C01BD07                               | HPRA Search              | Fatigue is a “Common” adverse effect (SmPC)                                                              | 800mg                                                                              |
| Duloxetine                         | N06AX21                               | HPRA Search              | Somnolence is a “Very Common” adverse effect. Fatigue and lethargy are “Common” adverse effects (SmPC)   | 60mg                                                                               |

| International Non-Proprietary Name | ATC Code                                 | Source for Consideration | Reason for Inclusion                                                                          | Minimum Effective Daily Dose                                    |
|------------------------------------|------------------------------------------|--------------------------|-----------------------------------------------------------------------------------------------|-----------------------------------------------------------------|
| Dydrogesterone/<br>Estradiol       | G03FA14                                  | HPRA Search              | Asthenic conditions (asthenia, fatigue, malaise) are adverse effects. (SmPC)                  | Dydrogesterone:2.5mg<br>Estradiol: 0.5mg                        |
| Enalapril                          | C09AA02<br>C09BA02<br>C09BB02<br>C09BB06 | (143)                    | Asthenia is a “Very Common” adverse effect; fatigue is a “common” adverse effect (SmPC)       | Hypertension: 5mg<br>Heart failure: 2.5mg                       |
| Entacapone                         | N04BX02                                  | HPRA Search              | Fatigue is a “Common” adverse effect. (SmPC)                                                  | 200mg                                                           |
| Enzalutamide                       | L02BB04                                  | HPRA Search              | Fatigue and asthenia are “Very Common” adverse effects. (SmPC)                                | 160mg                                                           |
| Eslicarbazepine                    | N03AF04                                  | (161)                    | Somnolence is a “Very Common” adverse effect. Sedation is an “Uncommon” adverse effect (SmPC) | 400mg                                                           |
| Estradiol                          | G03CA03                                  | HPRA Search              | Asthenia is a “Common” adverse effect (SmPC)                                                  | 0.025mg                                                         |
| Ethosuximide                       | N03AD(01)/(51)                           | HPRA Search              | Somnolence is a “Common” adverse effect. Fatigue is an “Uncommon” adverse effect (SmPC)       | 500mg                                                           |
| Etonogestrel                       | G03AC08                                  | HPRA Search              | Fatigue is a “Common” adverse effect (SmPC)                                                   | 0.025mg                                                         |
| Exemestane                         | L02BG06                                  | HPRA Search              | Fatigue is a “Very Common” adverse effect. Asthenia is a “Common” adverse effect. (SmPC)      | 25mg                                                            |
| Exenatide                          | A10BX04                                  | HPRA Search              | Fatigue is a “Common” adverse effect (SmPC)                                                   | 0.01mg (daily)<br>0.288mg (daily dose when administered weekly) |
| Ezetimibe                          | C10AX09<br>C10BA(02)/(05)/(06)           | HPRA Search              | Fatigue is a “Common” adverse effect (SmPC)                                                   | 10mg                                                            |
| Famciclovir                        | J05AB09                                  | HPRA Search              | Somnolence is a “Common” adverse effect. (SmPC)                                               | 250mg                                                           |
| Fexofenadine                       | R06AX26                                  | HPRA Search              | Drowsiness is a “Common” adverse effect (SmPC)                                                | 120mg                                                           |
| Filgrastim                         | L03AA02                                  | HPRA Search              | Fatigue and asthenia are “Very Common” adverse effects. (SmPC)                                | Per kg                                                          |
| Flecainide                         | C01BC04                                  | HPRA Search              | Fatigue is a “Common” adverse effect (SmPC)                                                   | 100mg                                                           |
| Fluoxetine                         | N06AB03<br>N06CA03                       | (143, 150)               | Fatigue is a “Very Common” adverse effect. Somnolence is a “Common” adverse effect. (SmPC)    | 20mg                                                            |
| Flurazepam                         | N05CD01                                  | (150)                    | Somnolence and fatigue are “Common” adverse effects (SmPC)                                    | 15mg                                                            |



| International Non-Proprietary Name | ATC Code                             | Source for Consideration | Reason for Inclusion                                                                                              | Minimum Effective Daily Dose |
|------------------------------------|--------------------------------------|--------------------------|-------------------------------------------------------------------------------------------------------------------|------------------------------|
| Fosphenytoin                       | N03AB05                              | HPRA Search              | Somnolence is a “Common” adverse effect. Drowsiness is a “Not Known” adverse effect.                              | Per kg                       |
| Gabapentin                         | N03AX12                              | (143, 150, 164)          | Somnolence and fatigue are “Very Common” adverse effects. (SmPC)                                                  | 900mg                        |
| Galantamine                        | N06DA04                              | (143)                    | Somnolence and Fatigue are “Common” adverse effects (SmPC)                                                        | 16mg                         |
| Ganciclovir                        | J05AB06                              | HPRA Search              | Fatigue and asthenia are "Common" adverse effects (SmPC)                                                          | 900mg                        |
| Glatiramer acetate                 | L03AX13                              | HPRA Search              | Asthenia is a “Very Common” adverse effect. (SmPC)                                                                | 17mg                         |
| Hydroxycarbamide                   | L01XX05                              | HPRA Search              | Asthenia is a “Very Common” adverse effect. Somnolence is a “Common” adverse effect. (SmPC)                       | Per kg                       |
| Ibuprofen                          | M01AE(01)/(51)<br>M02AA13<br>N02AJ19 | (143)                    | Somnolence and fatigue are “Common” adverse effects (SmPC)                                                        | 600mg                        |
| Imatinib                           | L01XE01                              | HPRA Search              | Fatigue is a “Very Common” adverse effect. Weakness is a “Common” adverse effect. (SmPC)                          | 100mg                        |
| Interferon Alfa-2b                 | L03AB05                              | HPRA Search              | Fatigue and asthenia are “Very Common” adverse effects. (SmPC)                                                    | Per m <sup>2</sup>           |
| Interferon Beta-1a                 | L03AB07                              | HPRA Search              | Fatigue is a “Common” adverse effect (SmPC)                                                                       | 0.0094mg                     |
| Interferon Gamma                   | L03AB03                              | HPRA Search              | Fatigue is a “Very Common” adverse effect. (SmPC)                                                                 | Per m <sup>2</sup>           |
| Lacosamide                         | N03AX18                              | (161)                    | Somnolence and Fatigue are “Common” adverse effects (SmPC)                                                        | 200mg                        |
| Lamivudine                         | J05AF05                              | HPRA Search              | Fatigue is a “Common” adverse effect (SmPC)                                                                       | 150mg                        |
| Lamotrigine                        | N03AX09                              | (150)                    | Somnolence and tiredness are “Common” adverse effects (SmPC)                                                      | 100mg                        |
| Letrozole                          | L02BG04                              | HPRA Search              | Fatigue (including asthenia and malaise) is a “Very Common” adverse effect. (SmPC)                                | 2.5mg                        |
| Levetiracetam                      | N03AX14                              | (150)                    | Somnolence is a “Very Common” adverse effect. Lethargy, fatigue and asthenia are “Common” adverse effects. (SmPC) | 1000mg                       |
| Levodopa, combinations             | N04BA02                              | (143, 164)               | Fatigue, somnolence and excessive daytime somnolence are noted as adverse effects (SmPC)                          | 300mg                        |
| Liraglutide                        | A10BB07                              | HPRA Search              | Fatigue is a “Common” adverse effect (SmPC)                                                                       | 1.2mg                        |
| Lorazepam                          | N05BA06                              | (150)                    | Sedation, fatigue and drowsiness are “Very Common” adverse effects. (SmPC)                                        | 0.5mg                        |

| International Non-Proprietary Name | ATC Code                             | Source for Consideration | Reason for Inclusion                                                                                                                                                      | Minimum Effective Daily Dose       |
|------------------------------------|--------------------------------------|--------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------|
| Lormetazepam                       | N05CD06                              | HPRA Search              | Sedation and somnolence are “Common” adverse effects. Depressed level of consciousness is an adverse effect with “Not Known” frequency (SmPC)                             | 0.5mg                              |
| Medroxyprogesterone                | G03DA02<br>L02AB02<br>G03FA12        | HPRA Search              | Fatigue and somnolence are noted as adverse effects. (SmPC)                                                                                                               | 2.5mg (oral)<br>1.9mg (IM)         |
| Melatonin                          | N05CH01                              | (161)                    | Melatonin is indicated as monotherapy for the short-term treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 or over. (SmPC) | 2mg                                |
| Memantine                          | N06DX01<br>N06DA(52)/(53)            | HPRA Search              | Somnolence is a “Common” adverse effect (SmPC)                                                                                                                            | 20mg                               |
| Meptazinol                         | N02AX05                              | HPRA Search              | Somnolence and drowsiness are “Very Common” adverse effects (SmPC)                                                                                                        | 800mg                              |
| Methadone                          | N02AC52<br>N07BC02                   | (150)                    | Drowsiness is an adverse effect noted in the SmPC.                                                                                                                        | 40mg                               |
| Methotrexate                       | L04AX03                              | (143)                    | Fatigue and drowsiness are “Common” adverse effects (SmPC)                                                                                                                | 7.5mg once weekly                  |
| Methyldopa                         | C02AB01<br>C02LB01                   | (150)                    | Sedation is a “Not Known” adverse effect. (SmPC)                                                                                                                          | 500mg                              |
| Methylphenidate                    | N06BA04                              | HPRA Search              | Somnolence and fatigue are “Common” adverse effects. (SmPC)                                                                                                               | 5mg                                |
| Metoclopramide                     | A03FA01                              | (143, 150, 161)          | Somnolence is a “Very Common” adverse effect. (SmPC)                                                                                                                      | 10mg                               |
| Modafinil                          | N06BA07                              | HPRA Search              | Asthenia is a “Common” adverse effect. (SmPC)                                                                                                                             | 100mg                              |
| Morphine                           | A07DA52<br>N02AA(01)/(51)<br>N02AG01 | (143, 150)               | Somnolence is a “Common” adverse effect. (SmPC)                                                                                                                           | 60mg                               |
| Nalmefene                          | N07BB05                              | HPRA Search              | Somnolence, fatigue and asthenia are “Common” adverse effects. (SmPC)                                                                                                     | 18mg                               |
| Nitrazepam                         | N05CD02                              | HPRA Search              | Drowsiness and fatigue are “Common” adverse effects (SmPC)                                                                                                                | 2.5mg                              |
| Oseltamivir                        | J05AH02                              | HPRA Search              | Fatigue is a “Common” adverse effect (SmPC)                                                                                                                               | 75mg                               |
| Oxycodone                          | N02AA05                              | (143, 150)               | Somnolence is a “Very Common” adverse effect (SmPC)                                                                                                                       | 10mg                               |
| Paracetamol, combinations          | N02BE51                              | HPRA Search              | Check for individual ingredients in these preparations.                                                                                                                   | See individual product components. |

| International Non-Proprietary Name | ATC Code           | Source for Consideration | Reason for Inclusion                                                                                                                                                    | Minimum Effective Daily Dose   |
|------------------------------------|--------------------|--------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|
| Peginterferon Alfa-2b              | L03AB10            | HPRA Search              | Fatigue and asthenia are “Very Common” adverse effects. Somnolence is a “Common” adverse effect. (SmPC)                                                                 | Per m <sup>2</sup>             |
| Peginterferon Alfa-2a              | L03AB11            | HPRA Search              | Fatigue and asthenia are “Very Common” adverse effects. Somnolence is a “Common” adverse effect. (SmPC)                                                                 | 0.026mg                        |
| Peginterferon Beta-1a              | L03AB13            | HPRA Search              | Asthenia is a “Very Common” adverse effect. (SmPC)                                                                                                                      | 0.0089mg                       |
| Phenobarbital                      | N03AA02            | (150)                    | The most frequent adverse effect following administration of phenobarbital is sedation. (SmPC)                                                                          | 60mg                           |
| Phenytoin                          | N03AB(02)/(52)     | (150)                    | Somnolence and drowsiness are noted as adverse effects (SmPC)                                                                                                           | 200mg                          |
| Pholcodine                         | R05DA08            | HPRA Search              | Drowsiness is noted as an adverse effect (SmPC)                                                                                                                         | 10mg                           |
| Piroxicam                          | M01AC01<br>M02AA07 | (143)                    | Somnolence is a “Common” adverse effect (SmPC)                                                                                                                          | 20mg                           |
| Pizotifen                          | N02CX01            | HPRA Search              | Sedation (including somnolence) and fatigue are “Common” adverse effects (SmPC)                                                                                         | 1.5mg                          |
| Plerixafor                         | L03AX16            | HPRA Search              | Fatigue is a “Common” adverse effect (SmPC)                                                                                                                             | Per kg                         |
| Pramipexole                        | N04BC05            | (150)                    | Somnolence is a “Very Common”/“Common” adverse effect (SmPC). Fatigue is a “Common” adverse effect (SmPC). Sudden onset of sleep is an “Uncommon” adverse effect (SmPC) | 0.264mg (base)                 |
| Prazepam                           | N05BA11            | HPRA Search              | Drowsiness is an adverse effect stated in the SmPC                                                                                                                      | 5mg                            |
| Prazosin                           | C02CA01<br>C02LE01 | (150)                    | Drowsiness is a “Common” adverse effect in patients being treated for hypertension and “Rare” in those treated for congestive cardiac failure. (SmPC)                   | 0.5mg                          |
| Pregabalin                         | N03AX16            | HPRA Search              | Somnolence is a “Very Common” adverse effect (SmPC)                                                                                                                     | 150mg                          |
| Primidone                          | N03AA03            | (150)                    | Drowsiness is a “Common” adverse effect (SmPC)                                                                                                                          | 125mg                          |
| Progesterone                       | G03DA04            | HPRA Search              | Somnolence is noted as an adverse effect. (SmPC)                                                                                                                        | 200mg (oral)<br>90mg (vaginal) |
| Propafenone                        | C01BC03            | HPRA Search              | Fatigue is a “Common” adverse effect (SmPC)                                                                                                                             | 450mg                          |

| International Non-Proprietary Name | ATC Code                      | Source for Consideration | Reason for Inclusion                                                                                                                                | Minimum Effective Daily Dose                                                                                                                                                                                                                                                              |
|------------------------------------|-------------------------------|--------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Propranolol                        | C07AA05<br>C07BA05<br>C07FX01 | (143)                    | Fatigue is a “Common” adverse effect (SmPC)                                                                                                         | Hypertension: 160mg<br>Angina: 80mg<br>Arrhythmia: 30mg<br>Anxiety: 80mg<br>Migraine: 80mg<br>Tremor: 40mg<br>Anxiety Tachycardia: 30mg<br>Thyrototoxicosis 30mg<br>Portal hypertension: 80mg<br>Oesophageal varices: 80mg<br>Pheochromocytoma: 30mg<br>Post-Myocardial Infarction: 160mg |
| Prucalopride                       | A06AX05                       | HPRA Search              | Fatigue is a “Common” adverse effect (SmPC)                                                                                                         | 1mg                                                                                                                                                                                                                                                                                       |
| Retigabine                         | N03AX21                       | HPRA Search              | Somnolence and Fatigue are “Very Common” adverse effects (SmPC)                                                                                     | 600mg                                                                                                                                                                                                                                                                                     |
| Ribavirin                          | J05AB04                       | HPRA Search              | Fatigue and asthenia are “Common” adverse effects. (SmPC)                                                                                           | 800mg                                                                                                                                                                                                                                                                                     |
| Ritonavir                          | J05AE03                       | HPRA Search              | Fatigue including asthenia, is a “Very Common” adverse effect. (SmPC)                                                                               | 100mg                                                                                                                                                                                                                                                                                     |
| Rivaroxaban                        | B01AF01                       | HPRA Search              | Fatigue is a “Common” adverse effect (SmPC)                                                                                                         | 5mg                                                                                                                                                                                                                                                                                       |
| Rivastigmine                       | N06DA03                       | (143)                    | Somnolence and Fatigue are “Common” adverse effects (SmPC)                                                                                          | 6mg (oral)<br>9.5mg per 24hrs (transdermal)                                                                                                                                                                                                                                               |
| Ropinirole                         | N04BC04                       | (150)                    | Somnolence is a “Very Common”/“Common” adverse effect. Sudden onset of sleep and excessive daytime somnolence are “Uncommon” adverse effects (SmPC) | 3mg                                                                                                                                                                                                                                                                                       |
| Rotigotine                         | N04BC09                       | HPRA Search              | Fatigue and asthenia are “Very Common” adverse effects. Somnolence is a “Common” adverse effect. (SmPC)                                             | 1mg                                                                                                                                                                                                                                                                                       |
| Rufinamide                         | N03AF03                       | HPRA Search              | Somnolence and fatigue are “Very Common” adverse effects (medicines.org.uk SmPC)                                                                    | 400mg                                                                                                                                                                                                                                                                                     |

| International Non-Proprietary Name | ATC Code                       | Source for Consideration | Reason for Inclusion                                                                                   | Minimum Effective Daily Dose         |
|------------------------------------|--------------------------------|--------------------------|--------------------------------------------------------------------------------------------------------|--------------------------------------|
| Rupatadine                         | R06AX28                        | HPRA Search              | Somnolence, fatigue and asthenia are “Common” adverse effects (SmPC)                                   | 10mg                                 |
| Selegiline                         | N04BD01                        | (150, 164)               | No reported sedation in SmPC.                                                                          | 5mg                                  |
| Sertraline                         | N06AB06                        | (143, 150)               | Somnolence and fatigue are “Very Common” adverse effects. (SmPC)                                       | 50mg                                 |
| Sotalol                            | C07AA07<br>C07BA07<br>C07FX02  | (143)                    | Fatigue is a “Common” adverse effect (SmPC)                                                            | 80mg                                 |
| Spirolactone                       | C03DA01                        | (143)                    | Drowsiness is noted as an adverse effect. (SmPC)                                                       | 25mg                                 |
| Tamoxifen                          | L02BA01                        | (143)                    | Fatigue is a “Very Common” adverse effect (SmPC)                                                       | 20mg                                 |
| Tamsulosin                         | G04CA(02)/(52)/(53)            | (150, 164)               | No reported sedation as an adverse effect (SmPC)                                                       | 0.4mg                                |
| Tapentadol                         | N02AX06                        | HPRA Search              | Somnolence is a “Very Common adverse effect. Fatigue and asthenia are “Common” adverse effects. (SmPC) | 50mg                                 |
| Tasonermin                         | L03AX11                        | HPRA Search              | Fatigue is a "very Common" adverse effect                                                              | Upper limb: 3 mg<br>Lower limb: 4 mg |
| Temazepam                          | N05CD07                        | (150, 164)               | Drowsiness during the day, reduced alertness and fatigue are noted as adverse effects (SmPC)           | 10mg                                 |
| Temozolomide                       | L01AX03                        | HPRA Search              | Fatigue is a “Very Common” adverse effect. Somnolence is a “Common” adverse effect. (SmPC)             | Per m <sup>2</sup>                   |
| Tetrabenazine                      | N07XX06                        | HPRA Search              | Fatigue, sedation, somnolence and drowsiness are “Very Common” adverse effects. (SmPC)                 | 12.5mg                               |
| Tiagabine                          | N03AG06                        | (150)                    | Somnolence is a “Very Common” adverse effect) SmPC)                                                    | 30mg                                 |
| Topiramate                         | N03AX11                        | (161)                    | Somnolence and fatigue are “Very Common” adverse effects. Sedation is a “Common” adverse effect (SmPC) | 200mg                                |
| Tramadol                           | N02AX02<br>N02AJ(13)/(14)/(15) | (143, 150, 164)          | Somnolence and fatigue are “Common” adverse effect (SmPC)                                              | 50mg                                 |
| Tranylcypromine                    | N06AF04                        | (150)                    | Drowsiness is a “Common” adverse effect (SmPC)                                                         | 10mg                                 |
| Triazolam                          | N05CD05                        | (150, 161)               | Somnolence is a “Common” adverse effect. (SmPC)                                                        | 0.125mg                              |
| Triprolidine                       | R06AX07                        | (150)                    | Somnolence and fatigue are adverse effects with “Not Known” frequency” (SmPC)                          | 2.5mg                                |
| Valganciclovir                     | J05AB14                        | HPRA Search              | Fatigue and asthenia are “Common” adverse effects. (SmPC)                                              | 900mg                                |

| International Non-Proprietary Name | ATC Code | Source for Consideration | Reason for Inclusion                                                                                 | Minimum Effective Daily Dose |
|------------------------------------|----------|--------------------------|------------------------------------------------------------------------------------------------------|------------------------------|
| Valproic Acid                      | N03AG01  | (143, 150)               | Somnolence is a “Common” adverse effect. Sedation is noted as a potential adverse effect. (SmPC)     | 1000mg                       |
| Varenicline                        | N07BA03  | HPRA Search              | Somnolence and fatigue are a “Common” adverse effect (SmPC)                                          | 2mg                          |
| Vigabatrin                         | N03AG04  | HPRA Search              | Somnolence and fatigue are “Very Common” adverse effects (SmPC)                                      | 1000mg                       |
| Vinorelbine                        | L01CA04  | HPRA Search              | Fatigue is a “Very Common” adverse effect. (SmPC)                                                    | Per m <sup>2</sup>           |
| Zaleplon                           | N05CF03  | (143, 150)               | Somnolence is a “Common” adverse effect. (SmPC)                                                      | 5mg                          |
| Zolpidem                           | N05CF02  | (143, 150, 164)          | Drowsiness during the following day, reduced alertness and fatigue are common adverse effects (SmPC) | 5mg                          |
| Zonisamide                         | N03AX15  | (161)                    | Somnolence is a “Very Common” adverse effect (SmPC) Fatigue is a “Common” adverse effect (SmPC)      | 300mg                        |
| Zopiclone                          | N05CF01  | (143, 164)               | Drowsiness, reduced alertness and fatigue are noted as adverse effects (SmPC)                        | 3.75mg                       |

## Appendix 6 Anticholinergic Cognitive Burden Scale Inventory and Scores

| INN                            | ATC Code           | ACB Score | Notes |
|--------------------------------|--------------------|-----------|-------|
| Alprazolam                     | N05BA12            | 1         |       |
| Alverine                       | A03AX08            | 1         |       |
| Amisulpride                    | N05AL05            | 1         |       |
| Amitriptyline                  | N06AA09            | 3         |       |
| Aripiprazole                   | N05AX12            | 1         |       |
| Atenolol                       | C07AB03            | 1         |       |
| Atropine                       | S01FA01            | 3         |       |
| Baclofen                       | M03BX01            | 1         |       |
| Bendroflumethiazide            | C03AA01            | 1         |       |
| Benperidol                     | N05AD07            | 1         |       |
| Benzatropine                   | N04AC01            | 3         |       |
| Biperiden                      | N04AA02            | 3         |       |
| Captopril                      | C09AA01            | 1         |       |
| Carbamazepine                  | N03AF01            | 2         |       |
| Cetirizine                     | R06AE07            | 1         |       |
| Chlorphenamine                 | R06AB04            | 3         |       |
| Chlorpromazine                 | N05AA01            | 3         |       |
| Chlortalidone                  | C03BA04            | 1         |       |
| Cimetidine                     | A02BA01            | 1         |       |
| Citalopram                     | N06AB04            | 1         |       |
| Clomipramine                   | N06AA04            | 3         |       |
| Clozapine                      | N05AH02            | 3         |       |
| Codeine                        | N02AA59<br>R05DA04 | 1         |       |
| Cyproheptadine                 | R06AX02            | 2         |       |
| Desloratidine                  | R06AX27            | 1         |       |
| Diazepam (oral)                | N05BA01            | 1         |       |
| Dicycloverine<br>(Dicylcomine) | A03AA07            | 3         |       |
| Digoxin                        | C01AA05            | 1         |       |
| Diphenhydramine                | R06AA02            | 3         |       |
| Dipyridamole                   | B01AC07            | 1         |       |

| INN                 | ATC Code | ACB Score | Notes                                                                                  |
|---------------------|----------|-----------|----------------------------------------------------------------------------------------|
| Dosulepin           | N06AA16  | 2         | Added from Anticholinergic Review<br>(141)<br>Moderate anticholinergic effect<br>(231) |
| Doxazosin           | C02CA04  | 1         |                                                                                        |
| Doxepin             | N06AA12  | 3         |                                                                                        |
| Escitalopram        | N06AB10  | 1         |                                                                                        |
| Fentanyl            | N02AB03  | 1         |                                                                                        |
| Fesoterodine        | G04BD11  | 3         |                                                                                        |
| Flupentixol         | N05AF01  | 1         |                                                                                        |
| Fluphenazine        | N05AB02  | 1         |                                                                                        |
| Furosemide          | C03EB01  | 1         |                                                                                        |
| Haloperidol         | N05AD01  | 1         |                                                                                        |
| Hydrochlorothiazide | C03EA01  | 1         |                                                                                        |
| Hydroxyzine         | N05BB01  | 3         |                                                                                        |
| Hyoscine            | A03BB01  | 3         |                                                                                        |
| Ipratropium         | R03BB01  | 1         |                                                                                        |
| Levocetirizine      | R06AE09  | 1         |                                                                                        |
| Loperamide          | A07DA03  | 1         |                                                                                        |
| Loratadine          | R06AX13  | 1         |                                                                                        |
| Mebeverine          | A03AA04  | 1         |                                                                                        |
| Metoprolol          | C07AB02  | 1         |                                                                                        |
| Mirtazapine         | N06AX11  | 1         |                                                                                        |
| Morphine            | N02AA01  | 1         | Added from Anticholinergic Review<br>(141)                                             |
| Nefopam             | N02BG06  | 2         |                                                                                        |
| Nifedipine          | C08CA05  | 1         |                                                                                        |
| Olanzapine          | N05AH03  | 3         |                                                                                        |
| Oxybutynin          | G04BD04  | 3         |                                                                                        |
| Oxycodone           | N02AA05  | 1         | Added from Anticholinergic Review<br>(141)                                             |
| Paroxetine          | N06AB05  | 3         |                                                                                        |
| Pericyazine         | N05AC01  | 3         |                                                                                        |
| Prednisolone        | H02AB06  | 1         |                                                                                        |
| Prochlorperazine    | A04A     | 1         |                                                                                        |
| Procyclidine        | N04AA04  | 3         |                                                                                        |



| INN             | ATC Code                      | ACB Score | Notes                     |
|-----------------|-------------------------------|-----------|---------------------------|
| Promazine       | N05AA03                       | 3         |                           |
| Promethazine    | R06AD02                       | 3         |                           |
| Quetiapine      | N05AH04                       | 3         |                           |
| Ranitidine      | A02BA02                       | 1         |                           |
| Risperidone     | N05AX08                       | 1         |                           |
| Scopolamine     | A04AD01                       | 3         |                           |
| Solifenacin     | G04BD08                       | 3         |                           |
| Sulpiride       | N05AL01                       | 1         |                           |
| Theophylline    | R03DA04                       | 1         |                           |
| Tiotropium      | R03BB04                       | 1         |                           |
| Tizanidine      | M03BX02                       | 2         |                           |
| Tolterodine     | G04BD07                       | 3         |                           |
| Trazodone       | N06AX05                       | 1         |                           |
| Trifluoperazine | N05AB06                       | 3         |                           |
| Trimipramine    | N06AA06                       | 3         |                           |
| Trospium        | G04BD09                       | 3         |                           |
| Venlafaxine     | N06AX16                       | 1         |                           |
| Warfarin        | B01AA03                       | 1         |                           |
| Zuclopenthixol  | N05AF05                       | 2         |                           |
| Alimemazine     | R06AD01                       | 1         | Not reported in IDS-TILDA |
| Amantadine      | N04BB01                       | 2         | Not reported in IDS-TILDA |
| Amoxapine       | N06AA17                       | 3         | Not reported in IDS-TILDA |
| Asenapine       | N05AH05                       | 1         | Not reported in IDS-TILDA |
| Belladonna      | A03BA04<br>A03CB02<br>A06AB30 | 2         | Not reported in IDS-TILDA |
| Brompheniramine | R06AB01                       | 3         | Not reported in IDS-TILDA |
| Carbinoxamine   | R06AA08                       | 3         | Not reported in IDS-TILDA |
| Cinnarizine     | N07CA02                       | 1         | Not reported in IDS-TILDA |
| Clemastine      | R06AA04                       | 3         | Not reported in IDS-TILDA |
| Clidinium       | A03CA02                       | 1         | Not reported in IDS-TILDA |
| Clorazepate     | N05BA05                       | 1         | Not reported in IDS-TILDA |
| Colchicine      | M04AC01                       | 1         | Not reported in IDS-TILDA |
| Cyclobenzaprine | M03BX08                       | 2         | Not reported in IDS-TILDA |
| Darifenacin     | G04BD10                       | 3         | Not reported in IDS-TILDA |
| Desipramine     | N06AA01                       | 3         | Not reported in IDS-TILDA |

| INN                                            | ATC Code | ACB Score | Notes                     |
|------------------------------------------------|----------|-----------|---------------------------|
| Dimenhydrinate (in combination with cyclizine) | N07CA52  | 3         | Not reported in IDS-TILDA |
| Disopyramide                                   | C01BA03  | 1         | Not reported in IDS-TILDA |
| Flavoxate                                      | G04BD02  | 3         | Not reported in IDS-TILDA |
| Fluvoxamine                                    | N06AB08  | 1         | Not reported in IDS-TILDA |
| Hydralazine                                    | C02DB02  | 1         | Not reported in IDS-TILDA |
| Iloperidone                                    | N05AX14  | 1         | Not reported in IDS-TILDA |
| Isosorbide mononitrate                         | C01DA14  | 1         | Not reported in IDS-TILDA |
| Levomepromazine (Methotrimeprazine)            | N05AA02  | 2         | Not reported in IDS-TILDA |
| Lofepramine                                    | N06AA07  |           | Not reported in IDS-TILDA |
| Loxapine                                       | N05AH01  | 2         | Not reported in IDS-TILDA |
| Meclozine                                      | R06AE05  | 3         | Not reported in IDS-TILDA |
| Meperiden/Pethidine                            | N02AB02  | 2         | Not reported in IDS-TILDA |
| Methocarbamol                                  | M03BA03  | 3         | Not reported in IDS-TILDA |
| Molindone                                      | N05AE02  | 2         | Not reported in IDS-TILDA |
| Nortriptyline                                  | N06AA10  | 3         | Not reported in IDS-TILDA |
| Orphenadrine                                   | N04AB02  | 3         | Not reported in IDS-TILDA |
| Oxcarbazepine                                  | N03AF02  | 2         | Not reported in IDS-TILDA |
| Paliperidone                                   | N05AX13  | 1         | Not reported in IDS-TILDA |
| Perphenazine                                   | N05AB03  | 3         | Not reported in IDS-TILDA |
| Pimozide                                       | N05AG02  | 2         | Not reported in IDS-TILDA |
| Propantheline                                  | A03AB05  | 3         | Not reported in IDS-TILDA |
| Propiverine                                    | G04BD06  | 3         | Not reported in IDS-TILDA |
| Quinidine                                      | C01BA01  | 1         | Not reported in IDS-TILDA |
| Triamterine                                    | C03DB02  | 1         | Not reported in IDS-TILDA |
| Trihexyphenidyl                                | N04AA01  | 3         | Not reported in IDS-TILDA |
| Ziprasidone                                    | N05AE04  |           | Not reported in IDS-TILDA |

Appendix 7 Sedative Medications added to Sedative Load Inventory

| INN                    | ATC Code | Notes on Sedation as an Adverse Effect                                                                                                                                         | Sedative Load Group, 2003 (143) | Sedative Load Group, 2011 (144) | Maudsley, 2015 (231) | Selected Group |
|------------------------|----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|---------------------------------|----------------------|----------------|
| <b>Agomelatine</b>     | N06AX22  | Somnolence & fatigue are “Common” adverse effects. (SmPC)                                                                                                                      | Group 3                         | Group 2                         | +                    | Group 2        |
| <b>Amisulpride</b>     | N05AL05  | Somnolence is a “Common” adverse effect (SmPC)                                                                                                                                 | Group 1                         | Group 1                         | -                    | Group 1        |
| <b>Aripiprazole</b>    | N05AX12  | Somnolence, sedation & fatigue are “Common” adverse effects (SmPC)                                                                                                             | Group 1                         | Group 2                         | -                    | Group 2        |
| <b>Benperidol</b>      | N05AD07  | No mention of sedation as an adverse effect (medicines.org.uk SmPC)                                                                                                            | Group 1                         | Group 1                         | +                    | Group 1        |
| <b>Benzatropine</b>    | N04AC01  | No mention of sedation as an adverse effect (New Zealand SmPC)                                                                                                                 | Group 2                         |                                 |                      | Group 2        |
| <b>Clozapine</b>       | N05AH02  | Drowsiness & sedation are “Very Common” adverse effects. Fatigue is a “Common” adverse effect (SmPC)                                                                           | Group 2                         | Group 2                         | +++                  | Group 1        |
| <b>Doxepin</b>         | N06AA12  | Drowsiness is noted as an adverse effect (SmPC)                                                                                                                                | Group 1                         | Group 1                         | +++                  | Group 1        |
| <b>Eslicarbazepine</b> | N03AF04  | Somnolence is a “Very Common” adverse effect. Sedation is an “Uncommon” adverse effect (SmPC)                                                                                  | Group 2                         | Group 2                         |                      | Group 2        |
| <b>Flupentixol</b>     | N05AF01  | Somnolence is a “Very Common” adverse effect. Asthenia & fatigue are “Common” adverse effects. (SmPC)                                                                          | Group 1                         | Group 1                         | +                    | Group 1        |
| <b>Fluphenazine</b>    | N05AB02  | Somnolence & lethargy are noted as adverse effects (SmPC)                                                                                                                      | Group 1                         | Group 1                         | +                    | Group 1        |
| <b>Haloperidol</b>     | N05AD01  | No mention of sedation in SmPC.                                                                                                                                                | Group 1                         | Group 1                         | +                    | Group 1        |
| <b>Hydroxyzine</b>     | N05BB01  | Somnolence is a “Very Common” adverse effect. Fatigue is a “Common” adverse effect. Asthenia is an “Uncommon” adverse effect. Sedation is a “Not Known” adverse effect. (SmPC) | Group 1                         |                                 |                      | Group 1        |
| <b>Lacosamide</b>      | N03AX18  | Somnolence & Fatigue are “Common” adverse effects (SmPC)                                                                                                                       | Group 2                         | Group 2                         |                      | Group 2        |

| INN                    | ATC Code | Notes on Sedation as an Adverse Effect                                                                                                                                    | Sedative Load Group, 2003 (143) | Sedative Load Group, 2011 (144) | Maudsley, 2015 (231) | Selected Group |
|------------------------|----------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|---------------------------------|----------------------|----------------|
| <b>Melatonin</b>       | N05CH01  | Melatonin is indicated as monotherapy for the short-term treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 or over. (SmPC) | Group 1                         |                                 |                      | Group 1        |
| <b>Metoclopramide</b>  | A03FA01  | Somnolence is a “Very common” adverse effect. (SmPC)                                                                                                                      | Group 2                         |                                 |                      | Group 2        |
| <b>Pericyazine</b>     | N05AC01  | No mention of sedation as an adverse effect (medicines.org.uk SmPC)                                                                                                       | Group 1                         | Group 1                         |                      | Group 1        |
| <b>Procyclidine</b>    | N04AA04  | No mention of sedation in SmPC.                                                                                                                                           | Group 2                         |                                 |                      | Group 2        |
| <b>Scopolamine</b>     | A04AD01  | Somnolence is a “Very Common” adverse effect. (SmPC)                                                                                                                      | Group 2                         |                                 |                      | Group 2        |
| <b>Sumatriptan</b>     | N02CC01  | Drowsiness is a “Common” adverse effect. (SmPC)                                                                                                                           | Group 2                         |                                 |                      | Group 2        |
| <b>Theophylline</b>    | R03DA04  | No mention of sedation in SmPC.                                                                                                                                           | Group 2                         |                                 |                      | Group 2        |
| <b>Topiramate</b>      | N03AX11  | Somnolence & fatigue are “Very Common” adverse effects. Sedation is a “Common” adverse effect (SmPC)                                                                      | Group 2                         | Group 2                         |                      | Group 2        |
| <b>Triazolam</b>       | N05CD05  | Somnolence is a “Common” adverse effect. (SmPC)                                                                                                                           | Group 1                         | Group 1                         |                      | Group 1        |
| <b>Trifluoperazine</b> | N05AB06  | Lassitude & drowsiness are noted as adverse effects (SmPC)                                                                                                                | Group 1                         | Group 1                         | +                    | Group 1        |
| <b>Ziprasidone</b>     | N05AE04  | Sedation, somnolence, fatigue & asthenia are “Common” adverse effects. (SmPC)                                                                                             | Group 1                         | Group 2                         | +                    | Group 2        |
| <b>Zonisamide</b>      | N03AX15  | Somnolence is a “Very Common” adverse effect (SmPC) Fatigue is a “Common” adverse effect (SmPC)                                                                           | Group 2                         | Group 2                         |                      | Group 2        |
| <b>Zuclopenthixol</b>  | N05AF05  | Somnolence is a “Very Common” adverse effect. Asthenia & fatigue are “Common” adverse effects (SmPC)                                                                      | Group 1                         | Group 1                         |                      | Group 1        |

| INN                                                          | ATC<br>Code | Notes on Sedation as an Adverse Effect | Sedative<br>Load<br>Group,<br>2003<br>(143) | Sedative<br>Load<br>Group,<br>2011<br>(144) | Maudsley,<br>2015<br>(231) | Selected<br>Group |
|--------------------------------------------------------------|-------------|----------------------------------------|---------------------------------------------|---------------------------------------------|----------------------------|-------------------|
| Key: +++, high incidence/severity; + low; -, very low, none. |             |                                        |                                             |                                             |                            |                   |

Appendix 8 Sedative Medications included in Reference Sedative Load Inventory (161)

| <b>INN</b>              | <b>ATC Code</b> | <b>Notes on Sedation as a Potential Adverse Effect</b>                                                           | <b>Sedative Load Group, 2003 (143)</b> | <b>Sedative Load Group, 2011 (144)</b> | <b>Sedative Load Group, 2015 (161)</b> | <b>Maudsley, 2015 (231)</b> | <b>Selected Group</b> |
|-------------------------|-----------------|------------------------------------------------------------------------------------------------------------------|----------------------------------------|----------------------------------------|----------------------------------------|-----------------------------|-----------------------|
| <b>Alprazolam</b>       | N05BA12         | Sedation & somnolence are “Very Common” adverse effects. Asthenia & fatigue are “Common” adverse effects. (SmPC) | Group 1                                | Group 1                                | Group 1                                |                             | Group 1               |
| <b>Amitriptyline</b>    | N06AA09         | Drowsiness & fatigue are noted as adverse effects (SmPC)                                                         | Group 1                                | Group 1                                | Group 1                                | +++                         | Group 1               |
| <b>Baclofen</b>         | M03BX01         | Sedation & somnolence are “Very Common” adverse effects (SmPC). Fatigue is a “Common” adverse effect (SmPC)      | Group 2                                |                                        | Group 2                                |                             | Group 2               |
| <b>Biperiden</b>        | N04AA02         | Drowsiness is a “Rare” adverse effect (SmPC)                                                                     | Group 2                                |                                        | Group 2                                |                             | Group 2               |
| <b>Bromazepam</b>       | N05BA08         | Somnolence & fatigue are reported adverse effects (SmPC)                                                         | Group 1                                | Group 1                                | Group 1                                |                             | Group 1               |
| <b>Buprenorphine</b>    | N02AE01         | Somnolence is a “Very Common” adverse effect. Fatigue is an “Uncommon” adverse effect (SmPC)                     | Group 2                                | Group 2                                | Group 2                                |                             | Group 2               |
| <b>Carbamazepine</b>    | N03AF01         | Somnolence & fatigue are “Very Common” adverse effects.(SmPC)                                                    | Group 2                                | Group 2                                | Group 2                                |                             | Group 2               |
| <b>Chlordiazepoxide</b> | N05BA02         | Drowsiness, drowsiness during the day, reduced alertness and fatigue are noted as adverse effects (SmPC)         | Group 1                                | Group 1                                | Group 1                                |                             | Group 1               |

| INN                     | ATC Code | Notes on Sedation as a Potential Adverse Effect                                            | Sedative Load Group, 2003 (143) | Sedative Load Group, 2011 (144) | Sedative Load Group, 2015 (161) | Maudsley, 2015 (231) | Selected Group |
|-------------------------|----------|--------------------------------------------------------------------------------------------|---------------------------------|---------------------------------|---------------------------------|----------------------|----------------|
| <b>Chlorphenamine</b>   | R06AB04  | Fatigue is a “Common” adverse effect (SmPC)                                                | Group 3                         |                                 | Group 2                         |                      | Group 2        |
| <b>Chlorpromazine</b>   | N05AA01  | Sedation & drowsiness are noted as adverse effects (SmPC)                                  | Group 1                         | Group 1                         | Group 1                         | +++                  | Group 1        |
| <b>Citalopram</b>       | N06AB04  | Somnolence is a “Very Common” adverse effect. Fatigue is a “Common” adverse effect. (SmPC) | Group 2                         | Group 2                         | Group 2                         | -                    | Group 2        |
| <b>Clobazam</b>         | N05BA09  | Drowsiness is noted as an adverse effect in the SmPC.                                      | Group 1                         | Group 1                         | Group 1                         |                      | Group 1        |
| <b>Clomipramine</b>     | N06AA04  | Fatigue & somnolence are “Very Common” adverse effects (SmPC)                              | Group 1                         | Group 1                         | Group 1                         | ++                   | Group 1        |
| <b>Clonazepam</b>       | N03AE01  | Somnolence & fatigue are noted as adverse effects (SmPC)                                   | Group 2                         | Group 2                         | Group 1                         |                      | Group 1        |
| <b>Clonidine</b>        | C02AC01  | Sedation is a “Very Common” adverse effect. (SmPC)                                         | Group 3                         |                                 | Group 2                         |                      | Group 2        |
| <b>Codeine</b>          | R05DA04  | Tiredness is noted as an adverse effect (SmPC)                                             | Group 2                         |                                 | Group 2                         |                      | Group 2        |
| <b>Dextromethorphan</b> | N07XX59  | Somnolence is a “Not Known” adverse effect. (SmPC)                                         |                                 |                                 | Group 2                         |                      | Group 2        |
| <b>Diazepam</b>         | N05BA01  | Fatigue, drowsiness and alertness decreased are noted as adverse effects. (SmPC)           | Group 1                         | Group 1                         | Group 1                         |                      | Group 1        |
| <b>Dihydrocodeine</b>   | N02AA08  | Drowsiness is noted as an adverse effect (SmPC)                                            | Group 2                         | Group 2                         | Group 2                         |                      | Group 2        |
| <b>Domperidone</b>      | A03FA03  | Somnolence is a “Very Rare” adverse effect. (SmPC)                                         |                                 |                                 | Group 2                         |                      | Group 2        |
| <b>Dosulepin</b>        | N06AA16  | Sedation is a “Common” adverse effect. Drowsiness is an “Uncommon” adverse effect (SmPC)   | Group 1                         | Group 1                         | Group 1                         | +++                  | Group 1        |

| INN                  | ATC Code | Notes on Sedation as a Potential Adverse Effect                                                                 | Sedative Load Group, 2003 (143) | Sedative Load Group, 2011 (144) | Sedative Load Group, 2015 (161) | Maudsley, 2015 (231) | Selected Group |
|----------------------|----------|-----------------------------------------------------------------------------------------------------------------|---------------------------------|---------------------------------|---------------------------------|----------------------|----------------|
| <b>Duloxetine</b>    | N06AX21  | Somnolence is a “Very Common” adverse effect. Fatigue & lethargy are “Common” adverse effects (SmPC)            | Group 3                         | Group 2                         | Group 2                         | -                    | Group 2        |
| <b>Escitalopram</b>  | N06AB10  | Somnolence & fatigue are “Common” adverse effects (SmPC)(                                                       | Group 2                         | Group 2                         | Group 2                         | -                    | Group 2        |
| <b>Fentanyl</b>      | N02AB03  | Somnolence & fatigue are “Common” adverse effects (SmPC)                                                        | Group 2                         | Group 2                         | Group 2                         |                      | Group 2        |
| <b>Fluoxetine</b>    | N06AB03  | Fatigue is a “Very Common” adverse effect. Somnolence is a “Common” adverse effect. (SmPC)                      | Group 2                         | Group 2                         | Group 2                         | -                    | Group 2        |
| <b>Flurazepam</b>    | N05CD01  | Somnolence & fatigue are “Common” adverse effects (SmPC)                                                        | Group 1                         | Group 1                         | Group 1                         |                      | Group 1        |
| <b>Gabapentin</b>    | N03AX12  | Somnolence & fatigue are “Very Common” adverse effects.(SmPC)                                                   | Group 2                         | Group 2                         | Group 1                         |                      | Group 1        |
| <b>Lamotrigine</b>   | N03AX09  | Somnolence & tiredness are “Common” adverse effects (SmPC)                                                      | Group 2                         | Group 2                         | Group 2                         |                      | Group 2        |
| <b>Levetiracetam</b> | N03AX14  | Somnolence is a “Very Common” adverse effect. Lethargy, fatigue & asthenia are “Common” adverse effects. (SmPC) | Group 2                         | Group 2                         | Group 2                         |                      | Group 2        |
| <b>Lofepramine</b>   | N06AA07  | Drowsiness is a “Rare” adverse effect (SmPC)                                                                    | Group 1                         | Group 1                         | Group 1                         | +                    | Group 1        |



| INN                  | ATC Code | Notes on Sedation as a Potential Adverse Effect                                                                                             | Sedative Load Group, 2003 (143) | Sedative Load Group, 2011 (144) | Sedative Load Group, 2015 (161) | Maudsley, 2015 (231) | Selected Group |
|----------------------|----------|---------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|---------------------------------|---------------------------------|----------------------|----------------|
| <b>Lorazepam</b>     | N05BA06  | Sedation, fatigue and drowsiness are “Very Common” adverse effects.(SmPC)                                                                   | Group 1                         | Group 1                         | Group 1                         |                      | Group 1        |
| <b>Lormetazepam</b>  | N05CD06  | Sedation & somnolence are “Common” adverse effects. Depressed level of consciousness is an adverse effect with “Not Known” frequency (SmPC) | Group 1                         | Group 1                         | Group 1                         |                      | Group 1        |
| <b>Mirtazapine</b>   | N06AX11  | Somnolence & sedation are “Very Common” adverse effects. Fatigue is a “Common” adverse effect” (SmPC)                                       | Group 2                         | Group 2                         | Group 1                         | +++                  | Group 1        |
| <b>Morphine</b>      | N02AA01  | Somnolence is a “Common” adverse effect.(SmPC)                                                                                              | Group 2                         | Group 2                         | Group 2                         |                      | Group 2        |
| <b>Nitrazepam</b>    | N05CD02  | Drowsiness & fatigue are “Common” adverse effects (SmPC)                                                                                    | Group 1                         | Group 1                         | Group 1                         |                      | Group 1        |
| <b>Olanzapine</b>    | N05AH03  | Somnolence is a “Very Common” adverse effect. Asthenia & fatigue are “Common” adverse effects (SmPC)                                        | Group 2                         | Group 2                         | Group 1                         | ++                   | Group 1        |
| <b>Oxycodone</b>     | N02AA05  | Somnolence is a “Very Common” adverse effect (SmPC)                                                                                         | Group 2                         | Group 2                         | Group 2                         |                      | Group 2        |
| <b>Paroxetine</b>    | N06AB05  | Somnolence is a “Common” adverse effect (SmPC)                                                                                              | Group 2                         | Group 2                         | Group 2                         | +                    | Group 2        |
| <b>Phenobarbital</b> | N03AA02  | The most frequent adverse effect following administration of phenobarbital is sedation. (SmPC)                                              | Group 2                         | Group 2                         | Group 1                         |                      | Group 1        |

| INN                 | ATC Code | Notes on Sedation as a Potential Adverse Effect                                                       | Sedative Load Group, 2003 (143) | Sedative Load Group, 2011 (144) | Sedative Load Group, 2015 (161) | Maudsley, 2015 (231) | Selected Group |
|---------------------|----------|-------------------------------------------------------------------------------------------------------|---------------------------------|---------------------------------|---------------------------------|----------------------|----------------|
| <b>Phenytoin</b>    | N03AB02  | Somnolence & drowsiness are noted as adverse effects (SmPC)                                           | Group 2                         | Group 2                         | Group 2                         |                      | Group 2        |
| <b>Prazepam</b>     | N05BA11  | Drowsiness is an adverse effect stated in the SmPC                                                    | Group 2                         | Group 1                         | Group 1                         |                      | Group 1        |
| <b>Pregabalin</b>   | N03AX16  | Somnolence is a "Very Common" adverse effect (SmPC)                                                   | Group 2                         | Group 2                         | Group 1                         |                      | Group 1        |
| <b>Primidone</b>    | N03AA03  | Drowsiness is a "Common" adverse effect (SmPC)                                                        | Group 2                         | Group 2                         | Group 2                         |                      | Group 2        |
| <b>Promethazine</b> | R06AD02  | Drowsiness is noted as an adverse effect. (SmPC)                                                      | Group 3                         |                                 | Group 1                         |                      | Group 1        |
| <b>Quetiapine</b>   | N05AH04  | Somnolence is a "Very Common" adverse effect (SmPC)                                                   | Group 2                         | Group 2                         | Group 1                         | ++                   | Group 1        |
| <b>Risperidone</b>  | N05AX08  | Somnolence, sedation & lethargy are "Common" adverse effects.                                         | Group 2                         | Group 2                         | Group 2                         | +                    | Group 2        |
| <b>Rotigotine</b>   | N04BC09  | Fatigue & asthenia are "Very Common" adverse effects. Somnolence is a "Common" adverse effect. (SmPC) | Group 3                         |                                 | Group 2                         |                      | Group 2        |
| <b>Sertraline</b>   | N06AB06  | Somnolence & fatigue are "Very Common" adverse effects. (SmPC)                                        | Group 2                         | Group 2                         | Group 2                         | -                    | Group 2        |
| <b>Sulpiride</b>    | N05AL01  | Sedation & drowsiness are "Common" adverse effects. (SmPC)                                            | Group 1                         | Group 1                         | Group 2                         | -                    | Group 2        |

| INN                  | ATC Code | Notes on Sedation as a Potential Adverse Effect                                                    | Sedative Load Group, 2003 (143) | Sedative Load Group, 2011 (144) | Sedative Load Group, 2015 (161) | Maudsley, 2015 (231) | Selected Group |
|----------------------|----------|----------------------------------------------------------------------------------------------------|---------------------------------|---------------------------------|---------------------------------|----------------------|----------------|
| <b>Temazepam</b>     | N05CD07  | Drowsiness during the day, reduced alertness and fatigue are noted as adverse effects (SmPC)       | Group 1                         | Group 1                         | Group 1                         |                      | Group 1        |
| <b>Tiagabine</b>     | N03AG06  | Somnolence is a “Very Common” adverse effect (SmPC)                                                | Group 2                         | Group 2                         | Group 2                         |                      | Group 2        |
| <b>Tizanidine</b>    | M03BX02  | Somnolence & fatigue are “Common” adverse effects (SmPC)                                           | Group 2                         |                                 | Group 2                         |                      | Group 2        |
| <b>Tramadol</b>      | N02AX02  | Somnolence & fatigue are “Common” adverse effect (SmPC)                                            | Group 2                         | Group 2                         | Group 2                         |                      | Group 2        |
| <b>Trazodone</b>     | N06AX05  | Drowsiness & fatigue are noted as adverse effects. (SmPC)                                          | Group 2                         | Group 2                         | Group 1                         | +++                  | Group 1        |
| <b>Trimipramine</b>  | N06AA06  | Drowsiness & sedation are noted as adverse effects. (SmPC)                                         | Group 1                         | Group 1                         | Group 1                         | +++                  | Group 1        |
| <b>Valproic Acid</b> | N03AG01  | Somnolence is a “Common” adverse effect. Sedation is noted as a potential adverse effect. (SmPC)   | Group 2                         | Group 2                         | Group 2                         |                      | Group 2        |
| <b>Venlafaxine</b>   | N06AX16  | Somnolence & fatigue are “Common” adverse effects. (SmPC)                                          | Group 2                         | Group 2                         | Group 2                         | -                    | Group 2        |
| <b>Zolpidem</b>      | N05CF02  | Drowsiness during the following day, reduced alertness & fatigue are common adverse effects (SmPC) | Group 1                         | Group 1                         | Group 1                         |                      | Group 1        |

| INN                                                          | ATC Code | Notes on Sedation as a Potential Adverse Effect                             | Sedative Load Group, 2003 (143) | Sedative Load Group, 2011 (144) | Sedative Load Group, 2015 (161) | Maudsley, 2015 (231) | Selected Group |
|--------------------------------------------------------------|----------|-----------------------------------------------------------------------------|---------------------------------|---------------------------------|---------------------------------|----------------------|----------------|
| <b>Zopiclone</b>                                             | N05CF01  | Drowsiness, reduced alertness & fatigue are noted as adverse effects (SmPC) | Group 1                         | Group 1                         | Group 1                         |                      | Group 1        |
| Key: +++, high incidence/severity; + low; -, very low, none. |          |                                                                             |                                 |                                 |                                 |                      |                |

# Appendix 9 Multivariate Analyses using three-level age categories

Multivariate analysis of polypharmacy and frailty using three-level age categories (n = 528)<sup>a</sup>

|                                                                                                                                                        | Pre-Frail            |               | Frail                 |                   |
|--------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|---------------|-----------------------|-------------------|
|                                                                                                                                                        | OR (95% CI)          | p             | OR (95% CI)           | p                 |
| <b>Polypharmacy</b>                                                                                                                                    |                      |               |                       |                   |
| No Polypharmacy                                                                                                                                        | 1 (reference)        |               | 1 (reference)         |                   |
| Polypharmacy                                                                                                                                           | 1.420 (0.841; 2.397) | 0.190         | 2.196 (1.024; 4.711)  | <b>0.043*</b>     |
| Excessive Polypharmacy                                                                                                                                 | 2.682 (1.244; 5.782) | <b>0.012*</b> | 7.764 (3.058; 19.712) | <b>&lt;0.001*</b> |
| <b>Age</b>                                                                                                                                             |                      |               |                       |                   |
| 44 – 49 years                                                                                                                                          | 1 (reference)        |               | 1 (reference)         |                   |
| 50 – 64 years                                                                                                                                          | 0.890 (0.522; 1.518) | 0.668         | 0.831 (0.405; 1.703)  | 0.612             |
| 65+ years                                                                                                                                              | 2.002 (0.863; 4.645) | 0.106         | 3.188 (1.202; 8.456)  | <b>0.020*</b>     |
| <b>Level of ID</b>                                                                                                                                     |                      |               |                       |                   |
| Mild                                                                                                                                                   | 1 (reference)        |               | 1 (reference)         |                   |
| Moderate                                                                                                                                               | 1.550 (0.905; 2.654) | 0.110         | 4.363 (1.753; 10.859) | <b>0.002*</b>     |
| Severe/Profound                                                                                                                                        | 2.078 (1.025; 4.213) | <b>0.043*</b> | 6.787 (2.410; 19.112) | <b>&lt;0.001*</b> |
| <b>Type of Residence</b>                                                                                                                               |                      |               |                       |                   |
| Independent/Community                                                                                                                                  | 1 (reference)        |               | 1 (reference)         |                   |
| Group Home                                                                                                                                             | 1.009 (0.597; 1.703) | 0.974         | 1.286 (0.665; 2.486)  | 0.455             |
| Residential Care                                                                                                                                       |                      |               |                       |                   |
| <sup>a</sup> Reference category: Robust. Data are adjusted odds ratio (OR). Cox and Snell r <sup>2</sup> is 0.126; Nagelkerke r <sup>2</sup> is 0.150. |                      |               |                       |                   |

Multivariate analysis of Drug Burden Index and frailty using three-level age categories (n = 528)<sup>a</sup>

|                                                                                                                                                                                                        | Pre-Frail            |       | Frail                 |                   |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|-------|-----------------------|-------------------|
|                                                                                                                                                                                                        | OR (95% CI)          | p     | OR (95% CI)           | p                 |
| <b>Drug Burden Index</b>                                                                                                                                                                               |                      |       |                       |                   |
| No Exposure                                                                                                                                                                                            | 1 (reference)        |       | 1 (reference)         |                   |
| Low Exposure                                                                                                                                                                                           | 1.115 (0.577; 2.155) | 0.745 | 1.455 (0.541; 3.912)  | 0.458             |
| High Exposure                                                                                                                                                                                          | 1.374 (0.761; 2.479) | 0.292 | 2.418 (1.004; 5.826)  | <b>0.049*</b>     |
| <b>Age</b>                                                                                                                                                                                             |                      |       |                       |                   |
| 44 – 49 years                                                                                                                                                                                          | 1 (reference)        |       | 1 (reference)         |                   |
| 50 – 64 years                                                                                                                                                                                          | 0.867 (0.507; 1.482) | 0.602 | 0.836 (0.408; 1.711)  | 0.624             |
| 65+ years                                                                                                                                                                                              | 1.881 (0.810; 4.368) | 0.142 | 3.091 (1.169; 8.174)  | <b>0.023*</b>     |
| <b>Level of ID</b>                                                                                                                                                                                     |                      |       |                       |                   |
| Mild                                                                                                                                                                                                   | 1 (reference)        |       | 1 (reference)         |                   |
| Moderate                                                                                                                                                                                               | 1.539 (0.895; 2.648) | 0.119 | 4.302 (1.733; 10.682) | <b>0.002*</b>     |
| Severe/Profound                                                                                                                                                                                        | 2.027 (0.998; 4.117) | 0.051 | 6.873 (2.448; 19.301) | <b>&lt;0.001*</b> |
| <b>Type of Residence</b>                                                                                                                                                                               |                      |       |                       |                   |
| Independent/Community                                                                                                                                                                                  | 1 (reference)        |       | 1 (reference)         |                   |
| Group Home                                                                                                                                                                                             | 0.987 (0.583; 1.670) | 0.961 | 1.318 (0.684; 2.542)  | 0.409             |
| Residential Care                                                                                                                                                                                       |                      |       |                       |                   |
| <sup>a</sup> Reference category: Robust. Data are adjusted odds ratio (OR). Model adjusted for number of non-DBI medicines; Cox and Snell r <sup>2</sup> is 0.121; Nagelkerke r <sup>2</sup> is 0.144. |                      |       |                       |                   |

Multivariate analysis of Anticholinergic Cognitive Burden and frailty using three-level age categories (n = 528)<sup>a</sup>

|                                                                                                                                                                                      | Pre-Frail            |               | Frail                 |                   |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|---------------|-----------------------|-------------------|
|                                                                                                                                                                                      | OR (95% CI)          | <i>p</i>      | OR (95% CI)           | <i>p</i>          |
| <b>Anticholinergic Cognitive Burden</b>                                                                                                                                              |                      |               |                       |                   |
| No Exposure                                                                                                                                                                          | 1 (reference)        |               | 1 (reference)         |                   |
| Low Exposure                                                                                                                                                                         | 0.925 (0.535; 1.597) | 0.779         | 1.663 (0.768; 3.601)  | 0.197             |
| High Exposure                                                                                                                                                                        | 1.031 (0.524; 2.026) | 0.930         | 1.698 (0.693; 4.160)  | 0.246             |
| <b>Age</b>                                                                                                                                                                           |                      |               |                       |                   |
| 44 – 49 years                                                                                                                                                                        | 1 (reference)        |               | 1 (reference)         |                   |
| 50 – 64 years                                                                                                                                                                        | 0.859 (0.503; 1.469) | 0.579         | 0.825 (0.402; 1.695)  | 0.601             |
| 65+ years                                                                                                                                                                            | 1.920 (0.828; 4.450) | 0.128         | 3.067 (1.160; 8.114)  | <b>0.024*</b>     |
| <b>Level of ID</b>                                                                                                                                                                   |                      |               |                       |                   |
| Mild                                                                                                                                                                                 | 1 (reference)        |               | 1 (reference)         |                   |
| Moderate                                                                                                                                                                             | 1.501 (0.873; 2.579) | 0.142         | 4.171 (1.675; 10.386) | <b>0.002*</b>     |
| Severe/Profound                                                                                                                                                                      | 2.038 (1.006; 4.131) | <b>0.048*</b> | 6.668 (2.376; 18.713) | <b>&lt;0.001*</b> |
| <b>Type of Residence</b>                                                                                                                                                             |                      |               |                       |                   |
| Independent/Community                                                                                                                                                                | 1 (reference)        |               | 1 (reference)         |                   |
| Group Home                                                                                                                                                                           | 0.977 (0.575; 1.659) | 0.931         | 1.297 (0.670; 2.513)  | 0.440             |
| Residential Care                                                                                                                                                                     |                      |               |                       |                   |
| <sup>a</sup> Reference category: Robust. Data are adjusted odds ratio (OR). Model adjusted for number of non-ACB medicines; Cox and Snell $r^2$ is 0.131; Nagelkerke $r^2$ is 0.157. |                      |               |                       |                   |

Multivariate analysis of Sedative Load Model and frailty using three-level age categories (n = 528)<sup>a</sup>

|                                                                                                                                                                                     | Pre-Frail            |               | Frail                 |                   |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|---------------|-----------------------|-------------------|
|                                                                                                                                                                                     | OR (95% CI)          | <i>p</i>      | OR (95% CI)           | <i>p</i>          |
| <b>Sedative Load Model</b>                                                                                                                                                          |                      |               |                       |                   |
| No Exposure                                                                                                                                                                         | 1 (reference)        |               | 1 (reference)         |                   |
| Low Exposure                                                                                                                                                                        | 0.908 (0.490; 1.683) | 0.760         | 1.578 (0.641; 3.885)  | 0.321             |
| High Exposure                                                                                                                                                                       | 1.091 (0.606; 1.966) | 0.772         | 2.236 (0.959; 5.212)  | 0.062             |
| <b>Age</b>                                                                                                                                                                          |                      |               |                       |                   |
| 44 – 49 years                                                                                                                                                                       | 1 (reference)        |               | 1 (reference)         |                   |
| 50 – 64 years                                                                                                                                                                       | 0.848 (0.496; 1.450) | 0.547         | 0.813 (0.397; 1.666)  | 0.572             |
| 65+ years                                                                                                                                                                           | 1.806 (0.775; 4.208) | 0.171         | 2.982 (1.124; 7.912)  | <b>0.028*</b>     |
| <b>Level of ID</b>                                                                                                                                                                  |                      |               |                       |                   |
| Mild                                                                                                                                                                                | 1 (reference)        |               | 1 (reference)         |                   |
| Moderate                                                                                                                                                                            | 1.536 (0.895; 2.638) | 0.120         | 4.226 (1.703; 10.484) | <b>0.002*</b>     |
| Severe/Profound                                                                                                                                                                     | 2.076 (1.024; 4.210) | <b>0.043*</b> | 6.827 (2.442; 19.084) | <b>&lt;0.001*</b> |
| <b>Type of Residence</b>                                                                                                                                                            |                      |               |                       |                   |
| Independent/Community                                                                                                                                                               | 1 (reference)        |               | 1 (reference)         |                   |
| Group Home                                                                                                                                                                          | 0.979 (0.576; 1.663) | 0.937         | 1.294 (0.670; 2.501)  | 0.443             |
| Residential Care                                                                                                                                                                    |                      |               |                       |                   |
| <sup>a</sup> Reference category: Robust. Data are adjusted odds ratio (OR). Model adjusted for number of non-SL medicines; Cox and Snell $r^2$ is 0.126; Nagelkerke $r^2$ is 0.151. |                      |               |                       |                   |

## Appendix 10 Multivariate Analyses including Alzheimer's Disease/Dementia

Multivariate analysis of polypharmacy and frailty including adjustment for Alzheimer's disease/dementia (n = 497)<sup>a</sup>

|                                     | Pre-Frail             |               | Frail                  |                   |
|-------------------------------------|-----------------------|---------------|------------------------|-------------------|
|                                     | OR (95% CI)           | p             | OR (95% CI)            | p                 |
| <b>Polypharmacy</b>                 |                       |               |                        |                   |
| No Polypharmacy                     | 1 (reference)         |               | 1 (reference)          |                   |
| Polypharmacy                        | 1.259 (0.738; 2.150)  | 0.398         | 1.835 (0.821; 4.101)   | 0.139             |
| Excessive Polypharmacy              | 2.362 (1.085; 5.141)  | <b>0.030*</b> | 5.701 (2.155; 15.082)  | <b>&lt;0.001*</b> |
| <b>Age</b>                          |                       |               |                        |                   |
| 44 – 59 years                       | 1 (reference)         |               | 1 (reference)          |                   |
| 60+ years                           | 2.314 (1.243; 4.309)  | <b>0.008*</b> | 3.954 (1.875; 8.335)   | <b>&lt;0.001*</b> |
| <b>Level of ID</b>                  |                       |               |                        |                   |
| Mild                                | 1 (reference)         |               | 1 (reference)          |                   |
| Moderate                            | 1.561 (0.898; 2.714)  | 0.115         | 4.297 (1.638; 11.273)  | <b>0.003*</b>     |
| Severe/Profound                     | 2.370 (1.143; 4.914)  | <b>0.020*</b> | 7.681 (2.561; 23.034)  | <b>&lt;0.001*</b> |
| <b>Type of Residence</b>            |                       |               |                        |                   |
| Independent/Community               | 1 (reference)         |               | 1 (reference)          |                   |
| Group Home                          |                       |               |                        |                   |
| Residential Care                    | 0.912 (0.533; 1.562)  | 0.737         | 1.042 (0.521; 2.083)   | 0.908             |
| <b>Alzheimer's disease/dementia</b> |                       |               |                        |                   |
| No                                  | 1 (reference)         |               | 1 (reference)          |                   |
| Yes                                 | 3.752 (0.478; 29.466) | 0.209         | 11.773 (1.435; 96.614) | <b>0.022*</b>     |

<sup>a</sup> Reference category: Robust. Data are adjusted odds ratio (OR). Cox and Snell  $r^2$  is 0.151; Nagelkerke  $r^2$  is 0.181.

Multivariate analysis of Drug Burden Index and frailty including adjustment for Alzheimer's disease/dementia (n = 497)<sup>a</sup>

|                                     | Pre-Frail             |               | Frail                  |                   |
|-------------------------------------|-----------------------|---------------|------------------------|-------------------|
|                                     | OR (95% CI)           | p             | OR (95% CI)            | p                 |
| <b>Drug Burden Index</b>            |                       |               |                        |                   |
| No Exposure                         | 1 (reference)         |               | 1 (reference)          |                   |
| Low Exposure                        | 1.001 (0.505; 1.986)  | 0.998         | 1.434 (0.497; 4.142)   | 0.505             |
| High Exposure                       | 1.179 (0.634; 2.194)  | 0.602         | 1.992 (0.761; 5.217)   | 0.160             |
| <b>Age</b>                          |                       |               |                        |                   |
| 44 – 59 years                       | 1 (reference)         |               | 1 (reference)          |                   |
| 60+ years                           | 2.257 (1.211; 4.2058) | <b>0.010*</b> | 3.921 (1.868; 8.231)   | <b>&lt;0.001*</b> |
| <b>Level of ID</b>                  |                       |               |                        |                   |
| Mild                                | 1 (reference)         |               | 1 (reference)          |                   |
| Moderate                            | 1.551 (0.887; 2.711)  | 0.124         | 4.257 (1.626; 11.147)  | <b>0.003*</b>     |
| Severe/Profound                     | 2.323 (1.119; 4.822)  | <b>0.024*</b> | 7.825 (2.623; 23.346)  | <b>&lt;0.001*</b> |
| <b>Type of Residence</b>            |                       |               |                        |                   |
| Independent/Community               | 1 (reference)         |               | 1 (reference)          |                   |
| Group Home                          |                       |               |                        |                   |
| Residential Care                    | 0.902 (0.525; 1.548)  | 0.708         | 1.077 (0.540; 2.147)   | 0.833             |
| <b>Alzheimer's disease/dementia</b> |                       |               |                        |                   |
| No                                  | 1 (reference)         |               | 1 (reference)          |                   |
| Yes                                 | 3.670 (0.469; 28.752) | 0.216         | 11.544 (1.418; 94.012) | <b>0.022*</b>     |

<sup>a</sup> Reference category: Robust. Data are adjusted odds ratio (OR). Model adjusted for number of non-DBI medicines. Cox and Snell  $r^2$  is 0.147; Nagelkerke  $r^2$  is 0.176.

Multivariate analysis of Anticholinergic Cognitive Burden and frailty including adjustment for Alzheimer's disease/dementia (n = 497)<sup>a</sup>

|                                         | Pre-Frail             |               | Frail                  |                   |
|-----------------------------------------|-----------------------|---------------|------------------------|-------------------|
|                                         | OR (95% CI)           | p             | OR (95% CI)            | p                 |
| <b>Anticholinergic Cognitive Burden</b> |                       |               |                        |                   |
| No Exposure                             | 1 (reference)         |               | 1 (reference)          |                   |
| Low Exposure                            | 0.873 (0.491; 1.551)  | 0.643         | 1.609 (0.692; 3.742)   | 0.269             |
| High Exposure                           | 0.883 (0.437; 1.784)  | 0.730         | 1.884 (0.726; 4.893)   | 0.193             |
| <b>Age</b>                              |                       |               |                        |                   |
| 44 – 59 years                           | 1 (reference)         |               | 1 (reference)          |                   |
| 60+ years                               | 2.335 (1.251; 4.359)  | <b>0.008*</b> | 3.972 (1.887; 8.357)   | <b>&lt;0.001*</b> |
| <b>Level of ID</b>                      |                       |               |                        |                   |
| Mild                                    | 1 (reference)         |               | 1 (reference)          |                   |
| Moderate                                | 1.504 (0.860; 2.629)  | 0.153         | 4.145 (1.577; 10.894)  | <b>0.004*</b>     |
| Severe/Profound                         | 2.309 (1.114; 4.788)  | <b>0.024*</b> | 7.701 (2.582; 22.971)  | <b>&lt;0.001*</b> |
| <b>Type of Residence</b>                |                       |               |                        |                   |
| Independent/Community                   | 1 (reference)         |               | 1 (reference)          |                   |
| Group Home                              |                       |               |                        |                   |
| Residential Care                        | 0.891 (0.517; 1.536)  | 0.679         | 1.026 (0.512; 2.056)   | 0.942             |
| <b>Alzheimer's disease/dementia</b>     |                       |               |                        |                   |
| No                                      | 1 (reference)         |               | 1 (reference)          |                   |
| Yes                                     | 3.501 (0.445; 27.549) | 0.234         | 11.323 (1.380; 92.881) | <b>0.024*</b>     |

<sup>a</sup> Reference category: Robust. Data are adjusted odds ratio (OR). Model adjusted for number of non-ACB medicines; Cox and Snell  $r^2$  is 0.159; Nagelkerke  $r^2$  is 0.190.

Multivariate analysis of Sedative Load and frailty including adjustment for Alzheimer's disease/dementia (n = 497)<sup>a</sup>

|                                     | Pre-Frail             |               | Frail                  |                   |
|-------------------------------------|-----------------------|---------------|------------------------|-------------------|
|                                     | OR (95% CI)           | p             | OR (95% CI)            | p                 |
| <b>Sedative Load</b>                |                       |               |                        |                   |
| No Exposure                         | 1 (reference)         |               | 1 (reference)          |                   |
| Low Exposure                        | 0.835 (0.437; 1.595)  | 0.585         | 1.379 (0.521; 3.652)   | 0.518             |
| High Exposure                       | 1.003 (0.543; 1.852)  | 0.993         | 2.091 (0.843; 5.187)   | 0.112             |
| <b>Age</b>                          |                       |               |                        |                   |
| 44 – 59 years                       | 1 (reference)         |               | 1 (reference)          |                   |
| 60+ years                           | 2.209 (1.184; 4.121)  | <b>0.013*</b> | 3.880 (1.847; 8.151)   | <b>&lt;0.001*</b> |
| <b>Level of ID</b>                  |                       |               |                        |                   |
| Mild                                | 1 (reference)         |               | 1 (reference)          |                   |
| Moderate                            | 1.532 (0.877; 2.675)  | 0.134         | 4.175 (1.595; 10.926)  | <b>0.004</b>      |
| Severe/Profound                     | 2.365 (1.140; 4.906)  | <b>0.021*</b> | 7.909 (2.663; 23.491)  | <b>&lt;0.001*</b> |
| <b>Type of Residence</b>            |                       |               |                        |                   |
| Independent/Community               | 1 (reference)         |               | 1 (reference)          |                   |
| Group Home                          |                       |               |                        |                   |
| Residential Care                    | 0.896 (0.519; 1.544)  | 0.691         | 1.059 (0.530; 2.115)   | 0.872             |
| <b>Alzheimer's disease/dementia</b> |                       |               |                        |                   |
| No                                  | 1 (reference)         |               | 1 (reference)          |                   |
| Yes                                 | 3.714 (0.470; 29.332) | 0.213         | 11.874 (1.443; 97.689) | <b>0.021*</b>     |

<sup>a</sup> Reference category: Robust. Data are adjusted odds ratio (OR). Model adjusted for number of non-Sedative Load medicines; Cox and Snell  $r^2$  is 0.153; Nagelkerke  $r^2$  is 0.183.