Exploring the Biopsychosocial Risk Factors for Dementia in People Ageing with Down Syndrome

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

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2026

Declaration

I declare that this thesis has not been submitted as an exercise for a degree at this or any other university and it is entirely my own work. I confirm that the work has been completed in full compliance with relevant university policies, including the Academic Integrity Policy, the Trinity Policy on Good Research Practice, and the guidance on AI and GenAi in Teaching, Learning, Assessment and Research.

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“If a man will begin with certainties, he shall end in doubts; but if he will be content to begin with doubts, he shall end in certainties”

Bacon and Montagu (1857)

“All scientific knowledge that we have of this world, or will ever have, is as an island in the sea of mystery”

Raymo and Richardson (1998)

“The larger the island of knowledge, the longer the shoreline of wonder”

Gleiser (2014)

Dedication

This PhD thesis is dedicated to my family. To my husband Damien for his patience and support for family life during particularly busy periods, and for listening to a lot of PhD related chat that he surely had no interest in! To my sons James and Dara for the joy they gave me in watching them grow into young men over the past few years. Most importantly, to my two Labradors, Bran and Sam, who have sat beside me and given quiet canine encouragement to my endeavours; you have been my constant companions throughout.

R.I.P. Bran 17/03/2014 – 7/10/2025

You were the very best boy

I miss you

Summary

There remains a gap in the conceptualisation of dementia risk and subsequent modelling of dementia risk factors for those ageing with Down syndrome. This is particularly pertinent given the significant likelihood of Down syndrome related Alzheimer's Disease (DSAD) developing in this population with age (Andrews et al., 2022; Firth et al., 2018; Fonseca et al., 2019). The aim of this thesis is to explore the influence of various biopsychosocial factors on the risk of developing dementia in a sample of people ageing with Down syndrome. The research objectives include exploring if people ageing with Down syndrome have a different biopsychosocial risk factor profile for dementia, examining if generic dementia risk factors emerge as statistically significant for this population and if there is a cumulative effect of these risk factors on age of dementia diagnosis in the sample.

A lagged logistic regression model is used to test the longitudinal influence of dementia risk factors on subsequent risk of dementia diagnosis in the sample. Linear regression modelling is used to assess the influence of cumulative risk factor totals on age of dementia diagnosis in the sample. Almost half (44%) of participants in the study had developed dementia by the fourth wave of data collection (2007-2020), with a median age of diagnosis of 52.7 years, broadly in line with international findings (Fortea et al., 2021; Iulita et al., 2022). This study finds that two data models can predict, with a high degree of sensitivity and specificity, who has a dementia diagnosis in the sample, based on their biopsychosocial risk profile. Individual risk factors found to be significant predictors of dementia diagnosis are living in a congregated setting, physical inactivity and social isolation.

A different dementia risk factor profile is found to be present for persons ageing with Down syndrome than the extant profile for the general ageing population. The demographic factor of residential setting also reveals a difference in lived ageing experience; people with Down syndrome are living within service-provided and/or more congregated settings from an earlier age. A more individualised look at participant profiles reveals the relative clustering of biopsychosocial factors of concern, indicating the importance of a good understanding of the presenting risk profile for dementia for this population.

This thesis research adds a unique contribution to further understanding the life experience of people ageing with Down syndrome, with a particular focus on how various biopsychosocial factors may influence their dementia risk in later life.

Acknowledgements

I began my PhD research in September 2019. In March 2020, Covid restrictions began, ushering in a strange and isolated period of life for all of us. Then, just as Covid restrictions were finally easing in January 2022, I received an entirely unexpected diagnosis of breast cancer. It has been a long and challenging road to reach the submission stage of this thesis, and this section serves as a thank you to all of those who supported me along the way. Truly, it takes a village!

Firstly, a huge thank you to my PhD supervisors. Professor McCarron- you supported me from the very beginning of my research, believing in me at times when I didn't believe in myself, and always being an inspiration. Professor McCallion- I enjoyed your challenging queries and robust debates, but your kindness and mentorship always shone through too. Dr. de Vries- thank you for your macro level insights and practical thoughtful advice. Dr. McGlinchey- I am truly blessed to have had you as my Principal Supervisor. You are a person of exceptional integrity, ability and kindness and I have learned so much from our conversations on all those Friday mornings through the years.

Thanks to the wider TCAID team for your support and input at various points, particularly Dr. Louise Lynch, Dr. Rosemary Monaghan, Dr. Niamh Mulryan and Professor Fintan Sheerin. Thanks to the Statistics team of Dr. Caitriona Ryan and Aviejay Paul for your support and expertise, even if I didn't manage to learn R in the end! Special thanks to the Administration team, including Gavin Dann, June O'Reilly and Marie-Pierre Lavergne, for unstinting kindness and support throughout the years.

Thanks to my work colleagues Dawn Hunt and Pauline Smyth for your unfailing support and encouragement throughout. I feel privileged to also consider you my friends.

Thanks to the oncology teams in the Blackrock (Galway) Clinic and the Bon Secours Hospital, Galway. Words can't do justice to the gratitude I feel to Mr. Karl Sweeney and Professor Maccon Keane for your compassion, expertise and support during my breast cancer treatments and ongoing follow-up care. This enabled me to continue my PhD research despite the challenging personal circumstances.

A final thanks to all the IDS-TILDA participants, families and supporters whom I met during the research. It was a privilege to witness the generosity with which you shared your life experience of ageing with Down syndrome in Ireland.

Publications and Conference Presentations

Publications

Allen, A. P., McGlinchey, E., Fallon, M., McCallion, P., & McCarron, M. (2023). Cognitive reserve and dementia risk management in people with an intellectual disability. *International Journal of Geriatric Psychiatry*, *38*(4). https://doi.org/10.1002/gps.5906

Chen, Y., Allen, A. P., Fallon, M., Mulryan, N., McCallion, P., McCarron, M., & Sheerin, F. (2022). The challenges of mental health of staff working with people with intellectual disabilities during COVID-19—A systematic review. *Journal of Intellectual Disabilities*, *0*(0). https://doi.org/10.1177/17446295221136231

Fallon, M. & McGlinchey, E. (2025). Supporting development of a national intellectual disability memory service in Ireland. In R. Brady, J. Varkonyi-Sepp, & J. Smith (Eds.), *The Palgrave handbook of consultancy in health psychology*, Palgrave Macmillan.

Sheerin, F., Allen, A. P., Fallon, M., McCallion, P., McCarron, M., Mulryan, N., & Chen, Y. (2023). Staff mental health while providing care to people with intellectual disability during the COVID-19 pandemic. *British Journal of Learning Disabilities*, *51*(1), 80-90. https://doi.org/10.1111/bld.12458 **

Sheerin, F., Fallon, M., Daly, L. (In Press). Growing Older with Intellectual Disability. In S. Abdulla, D. Marsden (Eds.), *Fundamentals of learning disability nursing*, Wiley Publishing.

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Beresford-Webb, J. & Zaman, S. H. (Eds.) (2024). CAMDEX-DS-II (2nd ed.). Pavilion Publishing. https://pavpub.com/camdex-ds-ii

Invited Speaker

Brain Health Presentation, LD COP HSE Wales Multidisciplinary team ONLINE 2021

Promoting Brain Health Across the Lifespan, NIDMS Masterclass, ONLINE 2021

Ageing and Intellectual Disability Annual Workshop Delivery, Open Training College, 2018-Present

Dementia Risk Factors Presentation, Brothers of Charity Services West Region Senior Management Group, 2024

Brain Health and Wellbeing in Adulthood, Leitrim Down syndrome Ireland, 2025

Creative Brain Health Conference, Roscommon, 2025

Dementia/Brain Health online webinar, Brothers of Charity Services Limerick, 2025

Conferences

Sixth IASSID Europe Congress, ONLINE 2021

Fallon, M., McGlinchey, E., McCallion, P., & McCarron, M. (2021, July). Developing a biopsychosocial model of cognitive decline in people aging with intellectual disability. Journal of Applied Research in Intellectual Disabilities, 34 (5), 1305. Online.

Seventh IASSID World Congress, 2024

Fallon, M., McCallion, P., McCarron, M. & McGlinchey, E. (2024). Exploring the biopsychosocial risk factors for dementia in Irish people ageing with Down syndrome.

Psychology, Health and Medicine Conference

Fallon, M., McGlinchey, E., McCallion, P., & McCarron, M. (2021). Using health psychology theory to inform research into cognitive decline in people with intellectual disability. Poster Presentation.

T21RS International Conference, 2024, Rome

Fallon, M., McCallion, P., McCarron, M. & McGlinchey, E. (2024). An Exploration of Biopsychosocial Risk Factors for Dementia in Irish People Ageing with Down syndrome. Abstract accepted, did not travel.

Trinity Health and Education International Research Conference

Fallon, M., McGlinchey, E., McCallion, P., & McCarron, M. (2021). Developing a biopsychosocial model of cognitive decline in people ageing with intellectual disability. Online.

Fallon, M., McCallion, P., McCarron, M. & McGlinchey, E. (2025). Exploring the biopsychosocial risk factors for dementia in Irish people ageing with Down syndrome.

Peer Reviewer

BMC Medical Geriatrics, Clinical Psychology Today, Journal of Intellectual Disabilities, Journal of Policy and Practice in Intellectual Disabilities.

*** This article was one of the most downloaded articles of the period 1st January 2022-31st December 2022 in this journal ***

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Abbreviations

AD	Alzheimer's Disease
APOE	Apolipoprotein
APP	Amyloid Precursor Protein
AT(N)	Amyloid Tau (Neurodegeneration) Model
ATC	Anatomical Therapeutic Chemical Classification
AUD	Alcohol Use Disorder
BMI	Body Mass Index
BDNF	Brain Derived Neurotropic Factor
BPS	Biopsychosocial
Brain-PAD	Brain Predicted Age Difference
CAPI	Computer Assisted Personal Interview
CI	Confidence Interval
CS	Case Study
DABNI	Down Alzheimer Barcelona Neuroimaging Initiative
df	Degrees of Freedom
DSAD	Down syndrome related Alzheimer's Disease
EEG	Electroencephalography
FINGER	Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability
GLMM	Generalised Linear Mixed Models
HSE	Health Service Executive
IDS-TILDA	The Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing
IGF-1	Insulin-like Growth Factor
IPAQ	International Physical Activity Questionnaire
LIBRA	Dutch Lifestyle for Brain Health Index
MAR	Missing at Random
MER	Mixed Effects Regression
MICE	Multiple Imputation by Chained Equations
MNAR	Missing Not at Random
MRI	Magnetic Resonance Imaging
NHATS	National Health and Ageing Trends Study

NIDD	National Intellectual Disability Database
OR	Odds Ratio
p	Probability
PA	Physical Activity
PAF	Population Attributable Fraction
PET	Positron Emission Tomography
PIQ	Pre-Interview Questionnaire
PPI	Patient and Public Involvement
SI	Social Isolation
SOC	Selective Optimisation with Compensation Model
SP	Social Participation
SPSS	IBM Statistical Package Version 28.0.1.1 (15)
SSRI	Selective Serotonin Reuptake Inhibitor
TCAID	Trinity Centre for Ageing and Intellectual Disability
TILDA	The Irish Longitudinal Study on Ageing
VIF	Variance Inflation Factor
WHO	World Health Organisation

Chapter 1: Introduction

1.1 Research Context

Down syndrome is the most common genetic cause of intellectual disability, with an estimated 6 million people presenting with the condition globally (Antonarakis et al., 2020). Lifespan for people with Down syndrome has greatly increased in the last century but a ceiling continues to be placed on life expectancy through a significantly increased genetic risk of developing Alzheimer's Disease (AD) (Andrews et al., 2022; Firth et al., 2018; Fonseca et al., 2019; Fortea et al., 2021; Iulita et al., 2022; McCallion & McCarron, 2004). There remains a gap in the conceptualisation of dementia risk and subsequent modelling of dementia risk factors for those ageing with Down syndrome. Robust dementia risk models have been developed for the general population, including those from differing socio-economic and ethnic backgrounds (Alshahrani et al., 2024; Livingston et al., 2024; Livingston et al., 2020; Livingston et al., 2017). These have included consideration of factors specific to these populations, such as lower incomes, inequitable healthcare access, infant malnutrition, higher exposure to pollutants and lifestyle stressors, that may also impact upon brain health and dementia risk over the lifespan (Alshahrani et al., 2024).

Given the differing life experiences of those ageing with a pre-existing disability, a varying dementia risk profile may pertain to those ageing with Down syndrome. Attention has been paid to reviewing the literature on potential risk and resilience factors for this population in recent times (Boyle et al., 2025). However, there remains a need for a dementia risk model to be developed and tested for this population. This requires an exploration of how risk profile may differ from the general population, including consideration of risk factors that may be more specific to this population. This information needs to be drawn from the biopsychosocial life experience of those ageing with Down syndrome.

1.2 Theoretical Background

This thesis is grounded in a positive psychology approach to ageing, emphasising the importance of a broad conceptualisation of positive ageing, including subjective and objective experiences, self-determination and meaningful engagement in one's life and community (Bar-Tur, 2021; Izal et al., 2019; Kleineidam et al., 2019). This approach to ageing is particularly applicable and meaningful for those ageing with a lifelong disability (de Vries & McGlinchey, 2023; Heller & van Heumen, 2021).

Underpinning this theoretical approach are operationalised constructs of positive ageing across various domains of functioning, including physical, cognitive and psychosocial functioning (Annele et al., 2019; Fernández-Ballesteros et al., 2019). This broad biopsychosocial conceptualisation offers an inclusive approach to the life experience of people ageing with Down syndrome.

1.3 Aim of Thesis

The aim of this thesis is to explore the influence of various biopsychosocial factors on the risk of developing dementia in a sample of people ageing with Down syndrome.

1.4 Objectives of Thesis

1. To examine if people ageing with Down syndrome have a different biopsychosocial risk factor profile for dementia than their peers in the general community.
2. To examine if dementia risk factors from the generic Lancet dementia model (Livingston et al., 2020) emerge as statistically significant, forming an initial predictive model for this cohort.
3. To examine if there is a cumulative effect of risk factors on age of dementia diagnosis.
4. To explore if the findings provide any recommendations towards positive ageing supports for people with Down syndrome, including brain health promotion as they age.

1.5 Significance of this Research

This thesis addresses under-explored questions in the literature, researching the biopsychosocial experience of those ageing with Down syndrome and particularly how these biopsychosocial factors influence dementia risk.

1.6 Ontological and Epistemological Approach

Ontology refers to an individual's view of the world and assumptions about the nature of reality whilst epistemology is the approach to gaining further knowledge about that reality (Baldwin et al., 2014). These approaches support the researcher to explore gaps in existing knowledge and decide on how best to research these (Baldwin et al., 2014). All research is subjective and based on assumptions and interpretations, depending on where the researcher positions themselves ontologically and epistemologically within the field (Jackson, 2013).

The ontological approach to this research was informed by a positive psychology lens in exploring the biopsychosocial experience of ageing in people with Down syndrome. This shifts the focus from deficits and losses to strengths and meaning as one ages (Heller & van Heumen, 2021). The importance of psychological and social well-being, as well as physical well-being is now being highlighted, with positive psychology emphasising the development of resilience in these domains across the lifespan to support positive ageing (Bar-Tur, 2021; Izal et al., 2019). The breadth of psychological theory and research has much to offer to inform the approach of meaningful and positive supports for people with intellectual disability, including those ageing with Down syndrome (de Vries & McGlinchey, 2023).

A positive psychology approach to ageing and disability emphasises the importance of people having self-determination and autonomy in making their own ageing life choices and the diversity of processes inherent within this (Heller & van Heumen, 2021). This approach is also aligned with person-centred approaches to supporting those with intellectual disability (O'Brien, 1992). These are particularly important themes in support work for people with Down syndrome, given the historical disenfranchisement of this population and the lack of decision-making power about their own lives (Franits, 2005). Positive ageing encompasses both subjective and objective outcomes of ageing such as longevity, mental and physical health, cognitive efficacy, satisfaction with life and social connections (Baltes & Baltes, 1990; Bowling, 1993). This ontological perspective conceptualises ageing as an experience that can be objectively measured through exploration of the biopsychosocial factors involved in the ageing process for a population group.

The epistemological approach is objectivist, seeking to elucidate the reality of the ageing experience for people with Down syndrome through a careful measurement of biopsychosocial factors associated with ageing and brain health. The objectivist approach assumes an external reality that can be discovered (in this case, the biopsychosocial ageing factors) using appropriate measurement tools (Feast & Melles, 2010). Whilst this is a data-driven approach, due cognisance of potential interactions between subjective and objective ageing elements needs to be kept in mind to avoid an overly reductionistic approach to people's lived reality (Ashcroft & Van Katwyk, 2016). Interpretation of findings will mention concepts such as autonomy, choice, loneliness and perceptions of ageing as subjective elements that may interact with the measured biopsychosocial factors.

1.7 Brief Chapter Overview

This section gives a brief overview of each chapter within the thesis, enabling a summative review of the contents.

1.7.1 Literature Review: Chapter 2

The literature review enables exploration of the existing theoretical framework in the field and any gaps existing (Jackson, 2013). It supports positioning of my research questions within the existing knowledge base and the identification of a unique contribution to knowledge that can be made, based on my own ontological and epistemological perspectives.

An overview of the ageing experience of people with Down syndrome will be given, framed within a positive psychology lens, underpinned by biopsychosocial ageing theory. There will be a specific focus on cognitive ageing/dementia risk for people with Down syndrome, due to their significantly increased chance of developing AD. The biopsychosocial dementia risk factors contained within the Lancet Dementia Model will be individually reviewed (Livingston et al., 2020). Differing incidence and prevalence of these risk factors between the general ageing population and those ageing with Down syndrome will be explored, based on existing epidemiological literature. The pathophysiological influences of these risk factors leading to cognitive decline and dementia will be reviewed, with a focus on these pathways in those ageing with Down syndrome, and their relative increased or decreased risk regarding each factor, based on existing research.

1.7.2 Methodology: Chapter 3

The Methodology Chapter outlines the design of the research to objectively evaluate the biopsychosocial elements of the ageing experience in this sample of people with Down syndrome, particularly as it relates to their dementia risk. This chapter explains the choices of variable derivation, modelling and analysis made and the reasons for these choices.

Ethical and data collection procedures and the process of deriving the demographic and dementia risk factors of the participant sample are reported. Initial demographic analysis procedures are outlined. Information is given on building the lagged logistic regression model used to test the longitudinal influence of dementia risk factors on subsequent risk of dementia diagnosis in the sample. Testing of assumptions, procedures for dealing with missing data in the model and power analysis calculations are given for this procedure. Linear regression modelling is used to assess the influence of cumulative risk factor totals on age of dementia diagnosis in the sample. Power analysis calculations and testing of assumptions are given for this procedure.

1.7.3 Results: Chapter 4

This chapter gives details of the results obtained from logistic regression modelling and analysis. A high percentage of participants in the study had developed dementia by the fourth wave of data collection (2007-2020), with a median age of diagnosis of 52.7 years, broadly in line with international findings (Fortea et al., 2021; Iulita et al., 2022). This study finds that two data models can predict, with a high degree of sensitivity and specificity, who has a dementia diagnosis in the sample, based on their biopsychosocial risk profile. Individual risk factors found to be significant predictors of dementia diagnosis are living in a congregated setting, physical inactivity and social isolation.

A different dementia risk factor profile is found to be present for persons ageing with Down syndrome than the extant profile for the general ageing population. The demographic factor of residential setting also reveals a difference in lived ageing experience; people with Down syndrome are living within service-provided and/or more congregated settings from an earlier age.

A more individualised look at participant profiles reveals the relative clustering of biopsychosocial factors of concern, indicating the importance of a good understanding of the presenting risk profile for dementia for this population. This also highlights the importance of a focus on supporting positive ageing for people with Down syndrome, integrating supports for physical, mental, cognitive and social wellbeing throughout their lives. Special attention can be paid to those risk factors emerging as more prevalent in this population, with some of these factors potentially more influential in driving cognitive decline, over and above the accepted genetic determinants for Down syndrome-associated Alzheimer's Disease (DSAD).

1.7.4 Discussion: Chapter 5

The aim of this thesis is to explore the influence of various biopsychosocial factors on the risk of developing dementia in a sample of people ageing with Down syndrome. It will examine the ageing experience of a sample population with Down syndrome in Ireland, through the lens of positive psychology and using the framework of the Lancet dementia risk model to examine biopsychosocial risks to cognitive health. These study findings suggest future potentially useful avenues of research. They need to be tested and replicated in a larger sample to have greater confidence in potential predictive risk factors. The differing risk factor profile for this population found in comparison to the general ageing population can inform the development of biopsychosocial interventions to address brain health across the lifespan. Key study findings are

summarised and related to the existing body of literature, along with highlighting of potential limitations in the study. The unique contribution to knowledge made by this research will be discussed, along with recommendations for policy, research and practice.

1.7.5 Conclusion: Chapter 6

Overall conclusions arising from the research are outlined. This brief section summarises the broader implications of the findings and points a way forward for future research.

1.8 Unique Contribution to Knowledge

This thesis uniquely contributes to the knowledge base on the lived ageing experience of a sample of people with Down syndrome through an examination of the influence of a range of biopsychosocial risk factors on Alzheimer's disease onset. It is the first study to use a longitudinal nationally representative dataset to build a predictive model of dementia risk factors in people ageing with Down syndrome and to compare this preliminary modelling to the Lancet Commission model of modifiable risk factors identified for the general ageing population. It offers an insight into the life experience of people ageing with Down syndrome in Ireland in recent years, signposting areas of potential intervention to promote positive ageing into the future.

"…. for my once tender body old age now
Has seized: my hair's turned white in place of black.
My heart's grown heavy; my knees will not support me
That once on a time were fleet for the dance as fawns.
This state often I regret - but what's to be done
Being human, there's no way not to grow old…"
From Sappho, Female Ancient Greek Poet (Gilleard, 2007)

Chapter 2: Literature Review

2.1 Approach to the Literature Review

Given the broad conceptual overview required for this research and the diverse and wide-ranging epidemiological and biopsychosocial studies requiring review, a narrative review approach was adopted (Baumeister & Leary, 1997; Byrne, 2016; Ferrari, 2015; Siddaway et al., 2019). A comprehensive review of the literature within the structure of a narrative review was undertaken, enabling connections and comparisons to be made across a wide range of literature themes, summarising into a cohesive and integrative whole (Baumeister & Leary, 1997; Siddaway et al., 2019).

Themes of interest for research were initially identified and then search questions were constructed around these themes e.g. how have psychological ageing models evolved to incorporate biopsychosocial elements? Keywords were chosen for each question to support definition of and searching for the concepts/themes (Ferrari, 2015). Each question then guided a search of academic databases and grey literature for relevant articles to build an overview of the area. Recent systematic reviews, meta-analyses and state-of-the-research type articles were particularly useful in guiding study selection for review, filtering for significance, quality and relevance. For epidemiological data for each risk factor, searches were undertaken for studies relevant to those ageing in the general population and then focused on those ageing with Down syndrome more specifically. In some cases, time filters were employed where up to date epidemiological information was required or to narrow down a very wide search field. Common findings arising between studies on a theme were gathered along with gaps or inconsistencies in the literature, critically analysing and synthesising the literature findings to provide an overview of the field. See Appendix A for sample of search strategy keywords.

2.2 Ageing with Down syndrome

Down syndrome is diagnosed in approximately 1 in 650-1000 live births worldwide and comprises approximately 12 to 15% of all of those living with intellectual disability in developed countries (Bittles et al., 2007; De Graaf et al., 2017). Down syndrome is caused by various degrees of trisomy in chromosome 21 (Torr et al., 2010), with more than 600 genes overexpressed as a result (Lott & Head, 2019). It is the most common cause of intellectual disability, with a prevalence of 4.9 people per 10,000 in the European population (Antonarakis et al., 2020). It is estimated that there are currently more than 400,000 people with Down syndrome in Europe and 5.8 million in the world population (Fortea et al., 2021; Iulita et al., 2022). The typical syndromic presentation was originally described by Dr. John Langdon Down, Cornwall, UK in the mid-1800s (Down, 1867).

Life expectancy of people with Down syndrome has increased greatly in recent years (De Graaf et al., 2017; McCallion & McCarron, 2004; Torr et al., 2010) due to greater community living opportunities and increased access to appropriate health supports across the lifespan, including cardiac surgery to correct congenital heart defects (Bittles & Glasson, 2004; Glasson & Bittles, 2008). It is calculated that the life expectancy of people with Down syndrome has increased by an average of 0.94 life years per calendar year since the middle of the last century (Bittles & Glasson, 2004). The average life expectancy of a person with Down syndrome has risen from 9 years of age in 1929 to 25 years in 1983 to 60 years in 2020 (Bittles & Glasson, 2004; Tsou et al., 2020).

However, this increase in longevity may not be matched by a corresponding healthy ageing process, with the risk of death for people with Down syndrome significantly increasing after the age of 40 (Glasson & Bittles, 2008; Torr et al., 2010). Several genes in the body are affected by the triplication of chromosome 21, affecting the function of many bodily systems and the overall health of a person with Down syndrome (Antonarakis et al., 2020; De França Bram et al., 2019; Torr et al., 2010). People with Down syndrome begin to age more prematurely than their peers with the onset of chronic age-related diseases happening at an earlier age, often from age 45 onwards, including a significantly increased risk of developing early-onset Alzheimer's Disease (AD) (Covelli et al., 2016; De França Bram et al., 2019; Firth et al., 2018; Fonseca et al., 2019; Fortea et al., 2021; Gensous et al., 2020; Hatzidimitriadou & Milne, 2005; Iulita et al., 2022; Krinsky-McHale, 2008; Roy-Vallejo et al., 2020; Torr et al., 2010; Zigman, 2013). People with Down syndrome and their families/carers are now encountering both the challenges and opportunities that arise with navigating the ageing process.

2.2.1 An Inclusive Experience of Positive Ageing?

Successful ageing has been operationalised as freedom from disease/disability, optimal cognitive and physical functioning and active engagement with daily life (Rowe & Kahn, 1997). Critiques of this construct include the fact that only a small minority of those ageing can fully achieve this, often excluding the life experience of many of those ageing with lifelong or acquired disability (Foster & Walker, 2021; Glass, 2003; Martin et al., 2015). The use of the term "successful ageing" has also been criticised, implying that the goal is to successfully age based on individual effort, with a judgement of those who may not 'successfully age' (Foster & Walker, 2021; Richardson et al., 2011). Positive ageing will be the preferred term used throughout this dissertation.

Baltes and Baltes (1990) developed the Selective Optimisation with Compensation (SOC) Model of successful (positive) ageing across the lifespan. This model offers a more flexible definition of positive ageing, outlining how people can compensate for cumulative losses as they age through using strategies of selection to optimise their remaining functioning whilst continuing to achieve personal goals. Carstensen (1992) developed socio-emotional selectivity theory, which suggests that people reduce their social circles in an adaptive response to ageing, prioritising deeper social connectivity. This approach is consistent with the SOC model in theorising that older adults become more selective in social relationships to optimise social capital. Further enhancement of this multidimensional modelling of positive ageing includes the proactive adaptation to the normative stressors of ageing using internal coping and external social support resources (Kahana et al., 2003). These models focus on *how* people can successfully age rather than *what* is required to successfully age, acknowledging the importance of psychological and social, as well as biological, resources (Foster & Walker, 2021). However, it can be queried how relevant these models are for those with lifelong disabilities as they negotiate the challenges of ageing with pre-existing functional capacity issues. The concept of retention of optimal functioning may have less relevance for their lived reality.

Further conceptualisation in positive ageing theory has continued into this century with the recognition that there are both subjective and objective dimensions defining this construct (Kahana et al., 2014; Martin et al., 2015). A two-factor model of ageing incorporates both objective and subjective definitions of positive ageing, combining the psychosocial approach of life satisfaction and death acceptance with the biomedical approach of maintaining optimal functioning (Glass, 2003; Pruchno et al., 2010).

Individual community members' definitions of positive ageing have been found to be multidimensional, encompassing numerous domains of health, including physical, functional, psychological and social (Phelan et al., 2004). Psychosocial factors such as engagement (e.g. in social activities) and personal resources (e.g. attitude to ageing) are frequently cited factors involved in positive ageing, with depression as a negative indicator (Cosco et al., 2013; Jeste et al., 2010). Research consistently shows that older adults report higher levels of subjective well-being and life satisfaction and lower levels of negative affect than younger adults, with these self-reports of positive affect continuing to improve with age (Diehl et al., 2020). Similarly, people ageing with intellectual disability have been found to have a positive view of the ageing process, with the majority reporting good health and that their life has stayed the same or improved with age (Burke et al., 2014).

Adults aged 60-75 have been shown to have significant inter-individual differences in relation to cognitive and physical functioning, life satisfaction and well-being and social connectedness, highlighting the heterogeneity of biopsychosocial ageing outcomes (Diehl et al., 2020; Gerstorf et al., 2020). Qualitative studies with older people have shown that the participants have a significantly higher rating of their level of positive ageing than objective measures might indicate, with many participants rating themselves as ageing well alongside having significant physical disabilities (Montross et al., 2006; Strawbridge et al., 2002). Those ageing often view psychosocial variables as being integral to positive ageing, rather than solely focusing on the physical aspects, with lay definitions of positive ageing highlighting psychosocial aspects also, such as resilience, wisdom and optimism (Depp et al., 2010).

There are calls for a "new narrative of ageing", challenging previously established narratives that ageing losses are irreversible, that the experience of ageing is uniformly negative and that those ageing have no control over their ageing processes (Diehl et al., 2020, p. 582). This new ageing paradigm encompasses biological, psychological and social aspects of ageing. An important intervention strategy promoting positive ageing is educating middle-aged adults about the adoption of health-promoting biopsychosocial behaviours as they age, prior to the onset of age-related functional decline (Diehl et al., 2020). A more holistic approach to promoting health through the life course is indicated, using broad health promotion and preventative health strategies rather than just targeting treatments for individual chronic health conditions as they arise with ageing (Diehl et al., 2020; Olshansky et al., 2007).

Minority and marginalised populations require more research into the biopsychosocial elements of their ageing to understand how the adoption of health behaviours may influence or modulate their ageing process (Diehl et al., 2020). There are challenges in constructing a definition of positive ageing that is broad enough to encompass the wide range of lived realities of people ageing, including those with a lifelong disability (Depp et al., 2010). A focus on cognitive and emotional health of those ageing, in addition to physical health, and the risk factors influencing these, has been proposed as another broader approach to evaluating positive ageing status in the population (Depp et al., 2010)

A recent systematic review of healthy ageing interventions with people with intellectual disability (covering biopsychosocial elements) found only 5 randomised control trials worldwide with small sample sizes, highlighting a significant need for more research in this area (Santos et al., 2021). It is recognised that clinical and health psychologists have an important role to play in researching critical lifespan interventions to promote healthy ageing, including examining the diverse positive ageing support needs of minority populations (Arnett et al., 2020; Diehl et al., 2020; Johnson & Acabchuk, 2018). This research will lead to more informed positive ageing support policies that can meet the needs of all ageing cohorts, including those ageing with intellectual disability.

Challenges of Ageing in this Population. Transitioning to older age can be a difficult time for people with Down syndrome, as they may not have the opportunity to formally transition through a planned retirement stage, simply remaining at home with less opportunities to engage in social and community activities and roles. Older people in the general population will have the opportunity to deepen important social networks and relinquish those that are less important to them (the socio-emotional connectivity theory of ageing); people ageing with Down syndrome may lack agency and opportunity in this regard and experience loneliness and depression as they lose existing friendships and social networks (Duvdevany & Arar, 2004). These differences in social networks/social capital may impact how people with intellectual disability experience the ageing process (Gangadharan et al., 2009). Domains of quality of life that are important to people of all ages with Down syndrome include: choice-making ability, meaningful community presence and engagement, respect and gaining/maintaining competence (Ee et al., 2022; O'Brien, 1992). These domains are central to O'Brien's (1992) Five Accomplishments Model for enhancing quality of life for people with disabilities.

As people with Down syndrome age and develop higher support needs, there may be a risk of moving to a more congregated or institutional setting. Recent housing scoping reviews have

found that those with increasing medical support needs/frailty or within the severe/profound range of intellectual disability are more likely to move out of family homes and to live in more institutionalised or congregated settings (Roebuck, 2021). It also found higher levels of illness, sedentary behaviour, challenging behaviours, social isolation and loss of skills in those living in more congregated settings (Roebuck, 2021). A review of Irish residents' experiences in various types of service-provided accommodation found lowest social contacts with friends and family and less community employment or volunteering options within congregated settings, compared to group homes or personalised support living arrangements (McConkey et al., 2016).

Irish disability housing policy proposes a move away from congregated settings towards living in small homes within a community, with Irish national standards for residential services firmly promoting community-based living arrangements for people with disabilities (Health Service Executive, 2011; Ryan, 2017). Many people with intellectual disability continue to live in congregated settings (Ribenfors et al., 2025). People with intellectual disability report social exclusion and lack of community integration across all housing types, however, indicating that positive social experiences need supporting regardless of residential setting (Roebuck, 2021).

Research across the world has shown that, even in community group homes, people with Down syndrome may not be able to exercise free will and meaningful choices and may not have choices with whom they live (Gjermestad et al., 2017; McConkey et al., 2019; Murphy & Bantry-White, 2021; O'Donovan et al., 2021; Ribenfors et al., 2025). People with Down syndrome value living within a community location and having autonomy over their own life decisions in their home (Ribenfors et al., 2025). The type of residence people with Down syndrome live in has been found to influence their age of dementia diagnosis and length of post-diagnostic survival (Pounds et al., 2025). Type of residence can be included in research into dementia risk as a potentially influencing factor more specific to this population (Pounds et al., 2025).

Biopsychosocial Approach to Positive Ageing. People with Down syndrome can age successfully with a wide variation in onset of cognitive and physical decline. An interesting case study of a gentleman with Down syndrome aged 70 has been described, who exhibited no measured decline in cognitive functioning over the previous 16-year period and was ageing well with no significant health conditions (Krinsky-McHale, 2008). These authors recommend further exploration of the variability in successful ageing in this population to formulate interventions to promote healthy ageing for all people with Down syndrome. Positive ageing in people with Down syndrome, as in the general population, is influenced by numerous biopsychosocial factors (Gangadharan et al., 2009).

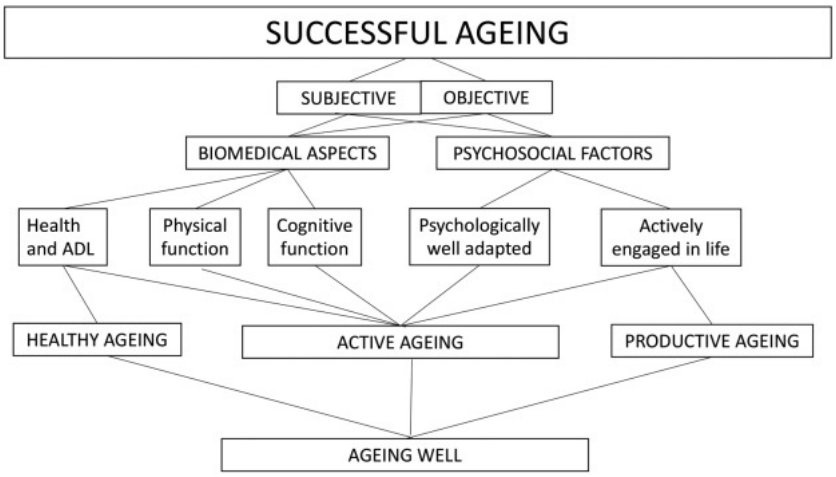
Taking a truly inclusive biopsychosocial approach to positive ageing with Down syndrome requires an understanding of the complex dynamic intersections of these processes across the lifespan (Heller & Harris, 2011). A person ageing ***into*** disability can often have different support needs and service access requirements than a person ageing ***with*** a disability who may age prematurely and require earlier access to geriatric services and supports. There exists an opportunity to promote positive ageing for all, including people with Down syndrome, through the development of biopsychosocial interventions for positive ageing in these populations.

A biopsychosocial model (Figure 2.1) has been proposed to support a positive ageing process, emphasising optimising wellbeing and adaptive functioning, that is eminently suitable for those with or without lifelong disabilities (Fernández-Ballesteros et al., 2019). Constructing a model of positive ageing involves incorporating subjective and objective measures of physical health, social engagement and psychological wellbeing as core components (Kleineidam et al., 2019). Newer models of positive ageing have examined the concept as relates to those with significant disabilities e.g. chronic illness (Young et al., 2009). Important themes emerging are maintaining physical and cognitive functioning as one ages, along with active social engagement in community and a positive attitude towards ageing with life satisfaction and purpose (Annele et al., 2019). A review of studies on positive ageing found that 13 out of 29 definitions had indicators of cognitive functioning, highlighting the importance of this construct in positive ageing (Depp & Jeste, 2006).

This model (see Figure 2.1), in emphasising psychosocial factors such as having a purpose and choices in the ageing process and meaningful social engagement, echoes the important domains of quality of life for people with Down syndrome (O'Brien, 1992). It is a holistic and nuanced approach to positive ageing, with a positive psychology focus, that can encompass the life experience of people ageing with Down syndrome. It will serve as an overarching framework to the research in this thesis, with a focus specifically on cognitive functioning as people with Down syndrome age, given their significantly increased risk of Alzheimer's Disease.

Figure 2.1

Dimensions of successful ageing



Note: The biopsychosocial dimensions of successful ageing. From: "Definitions of successful ageing: A brief review of a multidimensional concept" by Annele et al. (2019), *Acta Biomedica Atenei Parmensis*, 90 (2), Figure 1, p. 360. https://doi.org/10.23750/abm.v90i2.8376. Copyright 2019 by Mattioli Health.

2.3 Alzheimer's Disease

2.3.1 Dementia Demographics and Diagnosis

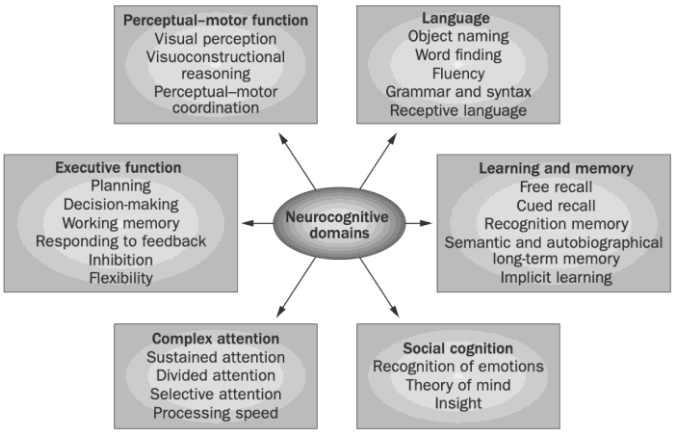
Recent projected prevalence of dementia cases globally is 152.8 million cases (range 130.8-175.9) by 2050 (GBD Dementia Forecasting Collaborators, 2022). Alzheimer's disease (AD) is the most common type of dementia, comprising up to an estimated 70% of dementia cases worldwide (Santabárbara et al., 2021). Significantly more women than men are diagnosed with AD, with up to two-thirds of AD cases being women (Nianogo et al., 2022).

Dementia and cognitive decline are now referred to by the widely influential Diagnostic and Statistical Manual of Mental Disorders as being within a cluster of neurocognitive disorders, with the defining features being that these disorders are primarily cognitive in nature and are acquired throughout life, representing a decline from previous level of functioning (Sachdev et al., 2014). Dementia is referred to as 'major neurocognitive disorder' with cognitive decline being referred to as 'mild neurocognitive disorder', which may or may not lead on to a more severe loss of cognitive functioning (Sachdev et al., 2014). Key domains of cognitive functioning can be affected in these disorders, as outlined in Figure 2.2. Domains of cognitive functioning may be differentially affected by various subtypes of dementia.

Dementia can be defined as a neurological disorder that progressively affects memory and other cognitive functions to such an extent that it significantly interferes with the person's ability to undertake activities of daily living (American Psychiatric Association, 2013; World Health Organization, 2022a). Significant progressive decline for any type of dementia can be expected in learning and memory, executive functioning, receptive and expressive communication, motor skills and ability to undertake activities of daily living (American Psychiatric Association, 2013). The significant decline in functioning is reported by the person themselves and / or an informant who knows them well, assessed using standardised neuropsychological instruments (American Psychiatric Association, 2013; British Psychological Society, 2015). Dementia of various sub-types may then be specified from the assessed clinical presentation of the condition: one such commonly presenting dementia sub-type is AD.

Figure 2.2

Domains of cognitive functioning affected by neurocognitive disorders



Note: The six domains of cognitive functioning affected by dementia. From: "Classifying neurocognitive disorders: the DSM-5 approach" by Sachdev et al. (2014), *Nature Reviews Neurology*, 10 (11), Figure 2, p.636. https://doi.org/10.1038/nrneurol.2014.181. Copyright 2014 by Macmillan Publishers Ltd.

Recent staging guidelines from the Alzheimer's Association highlight the importance of defining AD from biological indicators (biomarkers) rather than relying on clinical presentation, to improve early diagnosis and detection (Jack et al., 2024). Cognitive changes in AD exist on a continuum of progressive severity, from presymptomatic through to a full clinical presentation. Relevant biomarkers can be measured at a much earlier stage in the disease progression than is possible with clinical assessment, leading to earlier and more targeted interventions in the disease process (Jack et al., 2024). Concerns about relying solely on biological indicators for AD have been raised by the International Working Group of Alzheimer Europe. They advocate for a clinical-biological approach to assessing AD, with AD only diagnosed once definite early-stage clinical features are assessed as being present (Dubois et al., 2024). This is due to concerns that a higher rate of 'false positive' diagnoses may be made based on biological indicators alone, where progression to clinical AD may not happen; rather, these people should be viewed as being at risk for possible later development of AD (Dubois et al., 2024).

2.3.2 Physiological Pathways of Alzheimer's disease

The amyloid hypothesis of Alzheimer's Disease was first proposed in the 1990s, suggesting that an accumulation of the beta amyloid protein in the brain leads to a cascade of neurological dysfunction culminating in cognitive decline and, ultimately, the clinical attributes of AD (Glenner & Wong, 1984; Hardy & Higgins, 1992; Selkoe, 1991). Evidence to support this hypothesis has been based on such factors as the presence of amyloid plaques (post-mortem/neuroimaging) in patients with AD, the genetics of familial AD and the occurrence of excessive amyloid in the brains of people ageing with Down syndrome, exhibiting the clinical features of AD (Bruni et al., 2020; Drachman, 2014; Harrison & Owen, 2016). Whilst familial AD is a relatively uncommon form of AD (less than 1% of all cases), Down syndrome related Alzheimer's Disease (DSAD) affects almost all individuals ageing with Down syndrome and is the most prevalent form of genetic AD (Falgàs et al., 2025). Studying the disease process in DSAD offers a significant opportunity to study the preclinical asymptomatic stages of AD and the progression into clinical expression of the disease, supporting more targeted and earlier intervention options (Barroeta et al., 2025; Falgàs et al., 2025).

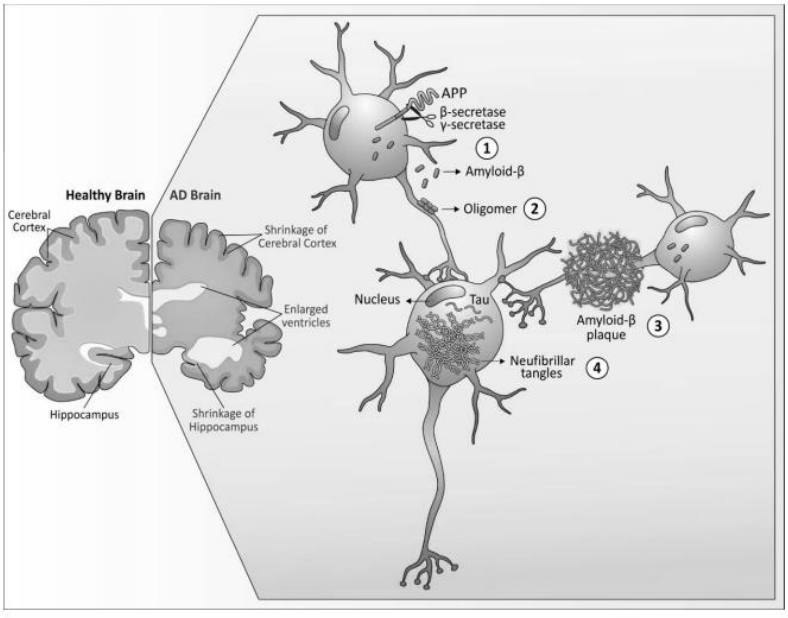
Tau protein pathology, causing lesions and tangles in the brain, is also a hallmark of AD symptomatology (Iqbal et al., 2016). Amyloid plaques initially form in the cerebral cortex and then progress to formations in the hippocampus, striatum and cerebellum, whilst tau neurofibrillary tangles form in neurons connecting into these brain areas (Gomez et al., 2020). See Figure 2.3 overleaf. A higher rate of tau accumulation relative to amyloid deposition earlier in the AD disease

process has been found in people with DSAD rather than other forms (Fu et al., 2025). Higher levels of tau in this population have been linked to earlier memory impairment prior to full blown clinical expression of AD and is another biomarker of note for measurement (Fu et al., 2025).

Research is showing the importance of inflammatory processes in brain ageing. Post-mortem brain studies of those who have died with AD have found increased inflammatory biomarkers (Grande et al., 2020). Changes in microglial function early in the disease process, leading to neuroinflammation, have been found through recent genome studies to raise the risk of dementia onset, with microglial activity being important in clearing beta amyloid plaques (Bruni et al., 2020; Falgàs et al., 2025). Increased oxidative stress in neurons and astrocytes leads to altered function and increased neurodegeneration (Ponroy Bally & Murai, 2021). The expression of the Apolipoprotein E gene (APOE) has also been shown to be important in influencing levels of beta amyloid, levels of tau and neuroinflammation in neurodegeneration, with APOE ε4 particularly significant in raising the risk of AD (Bruni et al., 2020; Jack et al., 2024). It has recently been suggested that APOE4 homozygotes are a genetically determined form of AD (Fortea et al., 2024).

Figure 2.3

Progression of Alzheimer's disease



Note: From "Down syndrome and AD: Common molecular traits beyond the amyloid precursor protein" by Gomez et al. (2020), *Aging*, 12 (1), Figure 1, p. 1012. https://doi.org/10.18632/aging.102677. Copyright 2020 by Impact Journals Ltd.

Biomarkers. Recent scientific advances have meant that blood-based biomarkers for AD are now accessible, in addition to the use of neuroimaging and spinal fluid assays, enhancing the diagnostic process (Jack et al., 2024). “Core biomarkers” for AD examine levels of Amyloid and Tau and can be differentiated into those that are abnormal at an earlier stage in the onset of AD, when no symptoms may present (“Core 1” biomarkers, generally amyloid detection) and those that are detectable at a later stage in AD presentation when symptomatology is present (“Core 2” biomarkers, generally tau detection) (Jack et al., 2024, p. 4). It is now proposed that these Core 1 blood-based biomarkers may be sufficient in themselves to indicate a diagnosis of AD, prior to any symptoms presenting, meaning this is a biologic rather than a clinical presentation diagnosis, earlier in the course of the disease (Jack et al., 2024). However, as previously mentioned, the diagnostic threshold of AD continues to be debated, in terms of a clinical or clinical-biological presentation or only a biological presentation being accepted as the diagnostic standard, particularly as many populations may not currently have access to biomarker assessment and evaluation (Petersen et al., 2023). Others have highlighted that changes in neuropathology as measured by biomarkers are not sufficient for a diagnosis of AD without an accompanying symptomatic presentation assessed clinically (Dubois et al., 2024; Petersen et al., 2024). These individuals can be considered at risk for later diagnosis of AD, given the pattern of biomarkers positively confirmed (Dubois et al., 2024; Petersen et al., 2024).

A model for understanding the onset and progression of AD has been proposed, AT(N), outlining that increased amyloid (A) deposition occurs first in the brain, then tau protein (T) accumulates, along with other potential markers of neurodegeneration (N), with a long preclinical phase before the expression of clinical symptoms (Jack et al., 2016). This model is suitable for use with all populations with AD process and can be used independently of the staging process preferred (Alzheimer’s Association or International Working Group). The A and T biomarkers specifically measure AD related disease burden, but other non-AD neurodegenerative elements (N) may also be present, contributing to overall functional decline. Each biomarker is then rated as being present or absent to give an overall picture of contributors to the person’s neurodegenerative decline or risk of neurodegeneration (Jack et al., 2016).

The effects of cognitive reserve can also be examined using these biomarkers, showing later presentation of cognitive symptomatology in comparison to measured biomarkers in those with higher cognitive reserve (Jack et al., 2024). New medications have been developed showing promise in targeting amyloid and tau pathologies and slowing the progression of AD from an early stage in the disease process (Budd Haeberlein et al., 2022; Sims et al., 2023; Van Dyck et al., 2023).

Lifestyle interventions are recommended for those who may be presenting with positive biomarkers but are currently asymptomatic for AD (Dubois et al., 2024; Petersen et al., 2024).

It is accepted that the onset of AD dementia is based on the complex interaction of several physiological and lifestyle factors, with the preclinical phase of the disease possibly extending for longer than was previously suggested (Bruni et al., 2020; Harrison & Owen, 2016). Interventions to reduce the incidence and prevalence of AD in any population need to be targeted across the lifespan, with optimal stages of life for targeting of some risk factors (Grande et al., 2020).

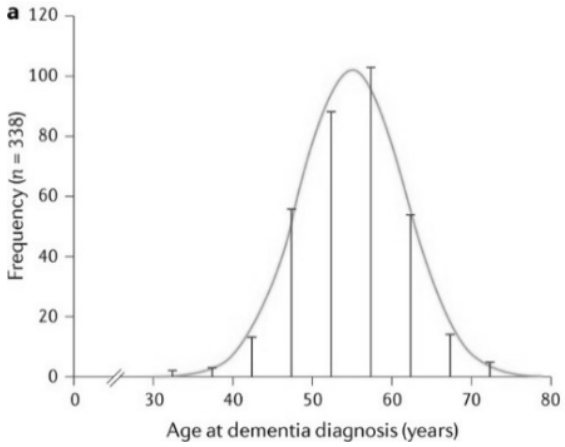
2.4 Down syndrome-related Alzheimer's disease (DSAD)

People with Down syndrome have a significantly increased risk for developing Alzheimer's Disease (AD), with almost full penetrance in this population with increasing age (Firth et al., 2018; Fonseca et al., 2020; Fortea et al., 2021; Videla et al., 2022). This is caused by the triplication of the amyloid precursor protein (APP) on chromosome 21 that is responsible for both Down syndrome and the over-production of the beta-amyloid plaque present in the aetiology of AD (see Figure 2.4 overleaf) (De França Bram et al., 2019; Fonseca et al., 2020; Fortea et al., 2018; Hartley et al., 2020; Hithersay et al., 2019; Iulita et al., 2022; Videla et al., 2022). Practically all people with Down syndrome will eventually develop the neuropathology of AD dementia if they live long enough, given the very strong genetic predisposition to the condition (Andrews et al., 2022). In fact, the Alzheimer's Association now classifies Down syndrome as a preclinical stage of AD, with the cumulative lifetime risk of the clinical expression of dementia in this population being over 95% (Barroeta et al., 2025; McCarron, 2017). Due to this genetic predisposition, there are greater numbers of people with DSAD than a more frequently cited population sub-group, people with autosomal dominant AD (Gomez et al., 2020; Hartley et al., 2015; McGlinchey et al., 2020; Snyder et al., 2020). The amyloid burden in the brains of people with Down syndrome has an accelerated progression in comparison to those in the general population with AD and those with sporadic AD (McVea et al., 2025; Stoltzner et al., 2000).

A meta-analysis of 44 studies of age of onset of AD with this population (N=2695 individuals) found a mean age of onset of 53.8 years (95% CI, P<.001, range 53.1-54.5) (Iulita et al., 2022). This study also found the mean estimate of age of death to be 58.4 years (95% CI, range 57.2-59.7 years, N=324) and the mean estimate of duration of AD to be 4.6 years (95% CI, range 3.7-5.5 years, N=226). This has led to a ceiling of life expectancy up to 20 years less for this population than those ageing in the general population (Iulita et al., 2022). Figure 2.4 overleaf shows a distribution of dementia diagnosis in a sample of people with Down syndrome with mean age of diagnosis of 55 years (Antonarakis et al., 2020).

Figure 2.4

Distribution of age of dementia diagnosis in people with Down syndrome



Note: Sample distribution of age of dementia diagnosis with a mean age of 55 years. From "Down syndrome" by Antonarakis et al. (2020), *Nature Reviews Disease Primers*, 6 (1), Figure 5, p.43. https://doi.org/10.1038/s41572-019-0143-7. Copyright 2020 by Springer Nature.

The Core 1 biomarkers for AD are also relevant to people with Down syndrome. The Alzheimer's Association Workgroup has recommended the use of the term 'pre-symptomatic AD' for those with a genetically driven high lifetime risk of developing clinical expression of AD, including those with autosomal dominant genetic variations and people with Down syndrome (Dubois et al., 2024; Petersen et al., 2024). Further research into the specific profile of biomarkers for these populations is also recommended. A comparison has been drawn with the progression of cancer from asymptomatic in situ (breast and gastric cancers) to steadily progressing cancer pathology and symptomatology over time, similar to the almost universal probability of developing AD in this population, moving from presymptomatic AD (biomarker profile) to the clinical presentation of AD (diagnostic threshold) (Dubois et al., 2024; Petersen et al., 2024).

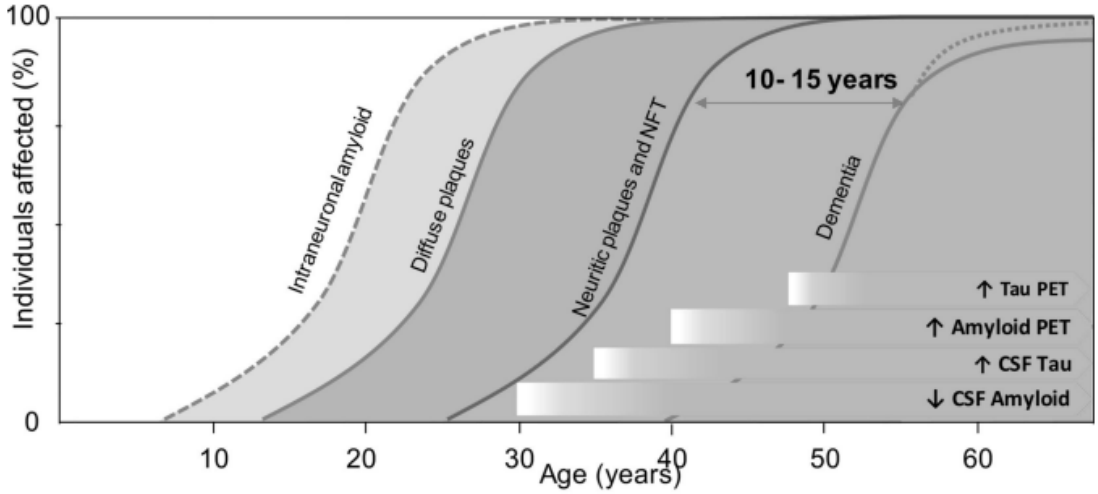
Brain changes indicative of the development of AD have been shown to be measurable in many cases from a young age in people with Down syndrome (Fortea et al., 2021). Using the AT(N) model, AD biomarkers in 388 participants with Down syndrome found a long preclinical phase of AD in this population, where indicative biomarkers are measurable over twenty years before clinically presenting symptoms (see Figure 2.5 overleaf). Increased astrocyte reactivity in the brains of those with Down syndrome also occurs prior to amyloid plaque formation, increasing the expression of APP protein, and may also play a role in neurodegeneration (Ponroy Bally &

Murai, 2021). People with Down syndrome have higher levels of neuronal oxidative stress which can damage neuronal functioning and cause increased neurodegeneration (Ponroy Bally & Murai, 2021).

Even with this increased genetic risk, people with Down syndrome do not currently have access to newer therapeutic drugs for treating dementia, such as monoclonal antibodies, with safety concerns around cerebral amyloid angiopathy being cited as a need to conduct clinical trials into toleration by this population (Rafii & Fortea, 2023). A recent bibliometric analysis of research trends in Down syndrome found a significant focus on the link between Down syndrome and AD in the last 20 years (Huang et al., 2024). Several European consortia are now working to investigate and further understand the pattern of clinical and biomarker changes in people with Down syndrome who develop AD, including the Down Alzheimer Barcelona Neuroimaging Initiative (DABNI), the Alzheimer's Biomarker Consortium for Down syndrome and Horizon 21 (Head & Ances, 2020; Rafii & Fortea, 2023; Videla et al., 2025). These consortia are also advocating for the inclusion of people with Down syndrome in clinical trials for dementia treatments (Rafii & Fortea, 2023).

Figure 2.5

Early onset Alzheimer's biomarkers in Down syndrome



Note: The age at which biomarkers for DSAD can be detected in people with Down syndrome. From: "Alzheimer's Disease associated with Down syndrome: a genetic form of dementia" by Fortea et al. (2021), *The Lancet Neurology*, 20 (11), Figure 1, p.931. https://doi.org/10.1016/S1474-4422(21)00245-3. Copyright 2021 by Elsevier Ltd.

Women in the general population, particularly those with the APOE4 gene, have been found to be at higher risk for AD onset, with higher levels of pathology found post-mortem (Andrews et al., 2022). It is recommended that the influence of gender be explored in terms of its influence on DSAD incidence and prevalence (Head & Ances, 2020). Women with Down syndrome on average enter earlier menopause between 44-46 years of age, with consequent loss of circulating oestrogen's protective effect on cognition (Coppus et al., 2010; Ejskjaer et al., 2006; Schupf et al., 2018; Schupf et al., 1997). With the early mean age of onset of AD in this population, there may be a greater risk for women with Down syndrome in more pronounced clinical expression of dementia, given the early reduction in oestrogen levels (Andrews et al., 2022; Schupf et al., 2018).

Women with Down syndrome present with higher levels of systemic inflammatory markers, such as interleukins 6 and 8, than men; neuroinflammation has been shown to be a risk factor for development of AD (Flores-Aguilar et al., 2020). There has been very limited research into gender differences in brain structure between men and women ageing with Down syndrome, with a need to examine differences in tau burdens and structural changes in the brain between pre- and post-menopausal women with Down syndrome (Andrews et al., 2022). Some studies have found gender differences in DSAD in this population, but a recent meta-analysis did not (Andrews et al., 2022; Iulita et al., 2023). A very recent study found higher levels of tau pathology in women with Down syndrome than men and more pronounced markers of small vessel cerebrovascular disease; it recommended that gender differences in AD onset and progression need to be evaluated in designing and interpreting clinical trials with this population (Andrews et al., 2025).

Level of intellectual disability does not appear to have a significant influence on average age of AD diagnosis in this population (Boyle et al., 2025). Similar ages for AD biomarker expression and similar rates of progression of AD symptomatology have been found across the various levels of intellectual disability (Hartley et al., 2023). However, it is acknowledged that there may be significant under-diagnosis of AD and at a later age for those with Down syndrome with more severe levels of intellectual disability; this is discussed in more detail below.

2.4.1 Clinical Presentation

The clinical presentation of dementia in people with Down syndrome may differ from that of the general population, particularly for those within the more severe range of functioning (British Psychological Society, 2015; Wissing et al., 2022b). There has been some debate on the early presentation of DSAD, with some studies finding evidence of a variety of behavioural and psychological symptoms of dementia presenting in the prodromal and early stages of the disease rather than short-term memory declines (de Oliveira & de Paula Faria, 2022; Lautarescu et al., 2017). Recent large scale prospective studies show impairment in memory and executive functioning as a key feature of prodromal decline into dementia for people ageing with Down syndrome, similar to the general population (Fonseca et al., 2020). These studies are using consensus validated direct neuropsychological testing instruments specifically designed for this population (such as the CAMCOG-DS-II), which may be leading to more sensitive and earlier assessment of the symptoms of prodromal decline, such as memory, verbal fluency and sustained attention (Firth et al., 2018; Videla et al., 2022).

A recent study analysed four cycles of biomarker and behaviour data from the Alzheimer-Biomarker Consortium Down syndrome and found an increase in repetitive behaviours, social withdrawal, depressive symptoms and changes in eating and energy patterns may appear prodromal to mild cognitive impairment and progression to DSAD (Jenkins et al., 2025). The understanding of dementia symptom expression and progression in people with Down syndrome continues to evolve. Research is ongoing into the most effective and sensitive testing for detecting prodromal cognitive decline and diagnosing AD in its earliest stages for people with Down Syndrome. The use of neuropsychological testing batteries in the diagnosis of AD in this population presents with difficulties (Benejam et al., 2020; Videla et al., 2022). These include variability of people's baseline cognitive abilities with concomitant need for longitudinal testing to measure change over time and the presence of floor effects in some testing instruments (Benejam et al., 2020; Hithersay et al., 2019; Videla et al., 2022).

2.4.2 Assessment and Diagnosis

It is recommended that people with Down syndrome be supported to take part in proactive memory screening from an early age (30-35) to establish a baseline of their premorbid cognitive functioning which can serve as a comparison against any subsequent decline as they age (Burt et al., 2005; Hithersay et al., 2019; Lautarescu et al., 2017; Videla et al., 2022). The assessment process must include a comprehensive history taking, examination of both physical and mental health status and the use of validated standardised instruments to directly measure

cognitive and daily functioning with the person and indirectly through informant report (Auty & Scior, 2008; British Psychological Society, 2015). A review of the practice of UK clinical psychologists, however, reported difficulties in establishing dementia diagnoses in this population, citing a lack of normative data, lack of consistency in reports from informants and issues with variability of scoring between assessment tools (Auty & Scior, 2008).

Research is ongoing into best practice in diagnosing dementia in people with different levels of intellectual disability. More recent research has found that newer diagnostic instruments (CAMCOG-DS-II and modified cued-recall test) have high accuracy in diagnosing preclinical and AD in a sample of 567 adults with Down syndrome (mild-moderate intellectual disability) (Benejam et al., 2020). This diagnostic accuracy falls sharply for those with more severe/profound intellectual disability, due to their inability to undertake the tasks to the same level (Benejam et al., 2020). Several recent studies have used the CAMCOG-DS-II to assess early cognitive decline (Fonseca et al., 2020; Hartley et al., 2020; Videla et al., 2022) but there remain difficulties in assessing dementia for those with more severe levels of intellectual disability (Wissing et al., 2022a).

People with severe / profound intellectual disability represent a growing cohort of individuals presenting with dementia, due to increasing life expectancy. There are relatively few published studies examining the assessment of cognitive decline in people with severe/profound intellectual disability (Wissing et al., 2022b). Dementia may be under-diagnosed in this population due to the difficulties in using standardised neuropsychological testing, a need for high baseline levels of assistance with the activities of daily living and, frequently, multiple co-existing complex health conditions (Wissing et al., 2022a; Wissing et al., 2022b). The most frequently cited dementia symptom has been found to be a decrease in ability to take part in activities of daily living (82% cited), followed by a decrease in responsiveness (76% cited) in the cognitive and daily living activities domain (Wissing et al., 2022b). The authors note that the diagnosis of dementia in people with severe/profound intellectual disability remains complex, including the possibility of diagnostic overshadowing with other conditions (Wissing et al., 2022b).

Neuroimaging is also used to support diagnosis of dementia in people with Down syndrome. Neale et al. (2018) undertook a review of studies using various neuroimaging techniques and other modalities (Positron Emission Tomography PET; Magnetic Resonance Imaging MRI; Electroencephalography EEG & retinal imaging) and found that, despite some limitations, these techniques do show some promise for aiding diagnosis and therapeutic input for people with Down Syndrome at risk of, or who have developed, dementia. Participants with

Down syndrome with greater assessed levels of beta amyloid from neuroimaging displayed lower initial scores on episodic memory, visual attention and executive functioning and displayed faster rates of decline in these domains, even with controls for normal ageing (Hartley et al., 2020).

2.5 Towards a Biopsychosocial Conceptualisation of Dementia

"*Brain health can be defined as the state of brain functioning across cognitive, sensory, social-emotional, behavioural and motor domains, allowing a person to realize their full potential over the life course, irrespective of the presence or absence of disorders*".

(World Health Organization, 2022b, p. 2)

The interaction between psychosocial and biological processes in the development of dementia was initially outlined by Kitwood (1993) in his dialectical model of dementia, whereby dementia was presented as the sum of the interactions between personality, biography, physical health, neurological impairment, and social psychology of the individual. There has been further progression of this theory through the development of biopsychosocial models of dementia (Downs et al., 2008; Spector & Orrell, 2010). There is a continuing search for the neurobiological pathways that will enhance our understanding of how the various biopsychosocial variables influence the brain's progressive cognitive decline. This biopsychosocial conceptualisation of dementia onset and progression also aligns with positive ageing models in highlighting the importance of a wide range of biomedical and psychosocial factors involved in ageing well (Fernández-Ballesteros et al., 2019).

2.5.1 Structure of the Brain for Memory Processes

Memory processing involves acquiring, storing and retrieving information. Explicit memory is memory for specific facts and events whereas implicit memory is concerned with learned processes that are more automatic in nature e.g. driving. These types of memory can also be termed declarative and procedural memory skills. Given the complexity of these processes, many areas of the brain are involved. The hippocampus (limbic brain system) has been shown to have an important influence on many memory functions (episodic, autobiographical and contextual), memory processes (encoding, pattern recognition, declarative learning, retention), spatial navigation and discrimination (Genon et al., 2018). The hippocampus and cerebral cortex of patients with AD show atrophy which progresses over time, particularly in the entorhinal cortex which communicates extensively with the hippocampus (Kalat, 2015). The neurons in these areas of the brain deteriorate and release less acetylcholine, along with plaques and tangles of neurons forming containing the protein b-amyloid and tau (Kalat, 2015).

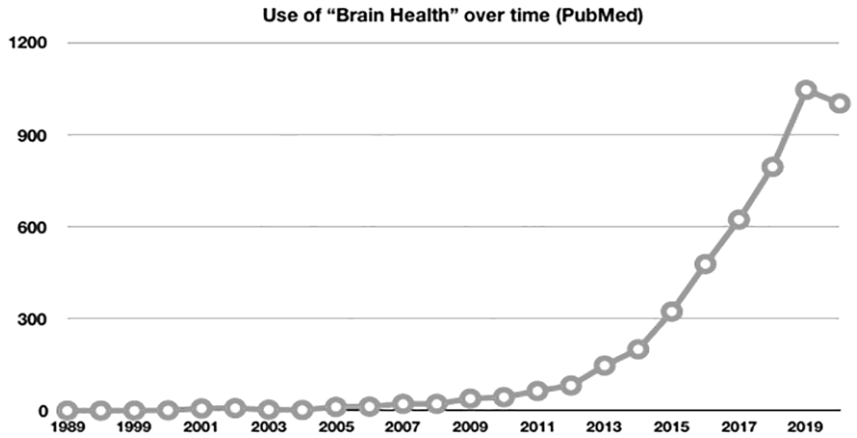
The prefrontal area of the brain is a newer system in our evolutionary processes and is central to the higher order functioning and executive processing of the brain. The prefrontal cortex is responsible for co-ordinating 'working memory' in the brain i.e. storing and manipulating information for language processing, problem solving, learning and planning (Funahashi, 2017). The prefrontal cortex integrates information from the rest of the brain systems to enable the complex cognitive processes that distinguish humans from many other animals. Damage to the lateral prefrontal cortex in dementia inhibits working memory, planning and executive processing. Damage to the orbitofrontal cortex leads to impulse control difficulties, risk taking behaviours and lack of mood control whilst damage to the medial prefrontal cortex damages the ability to monitor and correct errors (Fuster, 2019).

2.5.2 Brain Health

Brain health is an evolving concept. The term first appeared in studies in the 1980s, with an exponential increase in studies referencing brain health since then: see Figure 2.6 below for an overview (Chen et al., 2022; World Health Organization, 2022b). Initially, conceptualising brain health tended towards preservation of functioning and an absence of neurodegenerative conditions, but the construct has become more holistic over time, encompassing a biopsychosocial approach, covering several domains of functioning (Chen et al., 2022; World Health Organization, 2022b).

Figure 2.6

Increase in studies mentioning brain health



Note: Increase in research studies mentioning brain health since the 1980s. From: "Defining brain health: A concept analysis" by Chen et al. (2022), *International Journal of*

Geriatric Psychiatry, 37 (1), Figure 1, p.6. https://doi.org/10.1002/gps.5564. Copyright 2022 by John Wiley and Sons Publishers.

Research themes emerging include brain health conceptualised as a multidimensional construct with objective and subjective elements existing in a dynamic state across an individual's lifespan (Chen et al., 2022). The brain is the guiding centre of the body for all voluntary and involuntary functions, with brain health being vital in influencing overall physical and mental health (World Health Organization, 2022b). Optimising brain health can lead to better functioning across many life domains, including resilience, adaptability to meet challenges, enhanced social connectedness and more autonomy and independence throughout life (Chen et al., 2022; World Health Organization, 2022b). A person's brain health can be measured using neuroimaging to estimate the "brain age gap" between chronological age and brain age (Chen et al., 2022, p. 9) or through assessing key lifestyle pillars of brain health, as used in the Barcelona Brain Health Initiative and the Dutch Lifestyle for Brain Health Index (LIBRA) study (Cattaneo et al., 2020; Heger et al., 2021). However, given the broad multidimensional conceptualisation of brain health, it is difficult to fully measure this construct.

Brain changes with age have been studied in people with Down Syndrome. Researchers have found that, using measures of brain-predicted age difference (brain-PAD, chronological age subtracted from brain-predicted age), participants with Down Syndrome had significantly greater brain-PAD than healthy controls, indicating more rapid brain ageing than in the general population (Cole et al., 2017; Cole et al., 2019). They found that frontal (executive) functioning in the brain has been found to decline at a much earlier age in people with Down syndrome, with decline in functional scores after the age of 40 equivalent to the decline in functioning exhibited by those in the general population after age 70 (Appollonio et al., 2005; Ghezzo et al., 2014).

The dynamic nature of brain health across the lifespan has been shown to comprise neuronal plasticity in early life, efficient pruning of these connections in adolescence and younger adulthood progressing to senescence or loss of neuronal connections in later life (Patel et al., 2018; World Health Organization, 2022b). Many psychologists have highlighted the importance of midlife for integrating the learning of youth and foreshadowing the wisdom of old age. Studies have shown the importance of engaging in health behaviours across the biopsychosocial spectrum during midlife in supporting cognitive functioning and optimal health in older age (Lachman et al., 2015). The evidence strongly supports the importance of "midlife social, health and lifestyle activities" in promoting these successful outcomes in older age (Infurna et al., 2020, p. 479). Several biopsychosocial determinants influencing brain health across the lifespan have been

established in recent research (Cattaneo et al., 2020; Chen et al., 2022; Heger et al., 2021; Livingston et al., 2024; Livingston et al., 2020; Livingston et al., 2017; World Health Organization, 2022b).

2.5.3 Brain Network Theory

"*The brain is a highly complex, interconnected network that balances regional segregation and specialisation of function with strong integration*"

(Fornito et al., 2015, p. 159)

There is significant individual variation in cognitive ageing trajectories, with variation being a function of both prior cognitive ability and cumulative biopsychosocial impacts on brain health across the lifespan (Bettcher et al., 2019; Cabeza et al., 2018; Deary, 2012; Deary et al., 2009; Deery et al., 2023; Hendrie et al., 2006; Okely et al., 2019). Recent research on brain structure and function, using neuroimaging techniques, has led to a network theory of brain interconnections, with brain structures integrating locally processed information into the global processing network in an efficient way (Deery et al., 2023). The functioning of the brain, conceptualised through the application of network science, is now being mapped to try and predict patterns of dysfunction over time: the field of brain connectomics (Fornito et al., 2015).

As a person cognitively ages, their ability to globally process and integrate information is decreased, with both metabolic and structural changes contributing to this process (Deery et al., 2023). Deficits in one part of the brain network can spread to other linked elements through synaptic and axonal connections, leading to an accumulation of deficits spreading across the network (Fornito et al., 2015). Two hypotheses relating to cognitive compensation with age have been proposed: dedifferentiation and compensation (Grady, 2012). The dedifferentiation hypothesis proposes that the brain can recruit more diffuse areas to replace the activity of specific regions of the brain if their functioning is lessened, providing a type of plasticity to brain structure functioning (Deery et al., 2023; Fornito et al., 2015; Grady, 2012).

The compensation hypothesis proposes that the ageing brain compensates for lowered capacity in some areas of the brain by increased activity in other areas; this increased activity is often seen in the frontal lobe areas of the brains of older adults (Deery et al., 2023; Grady, 2012). The scaffolding theory of cognitive ageing proposes that the brain uses both dedifferentiation and compensation strategies to enable network reorganisation, reducing loss of functioning due to structural deficits (the underpinning scaffolding) in the ageing brain (Naik et al., 2017). Inter-individual differences in cognitive ageing may be mediated by more efficient deployment of

alternate networks or a more preserved glucose metabolism in the brain; these differences are often associated with the proxy indicators of cognitive reserve such as a higher level of education and / or career (Deery et al., 2023).

People with Down syndrome may have lowered functional connectivity across their brains, which may increase their susceptibility to, and progression of, AD dementia (DiProspero et al., 2022; Wilson et al., 2019). Recent neuroimaging studies have shown evidence of lower levels of white matter in frontal lobes and differing structural connectivity in people with Down syndrome (Saini et al., 2022), indicating the importance of an evolving understanding of how brain structure and functioning may be contributing to cognitive reserve and cognitive decline in this population.

Cognitive Reserve. Brain network theory further develops the concept of cognitive reserve (Stern, 2012; Stern et al., 2019), in proposing potential brain mechanisms that may compensate for reduced brain functioning, thereby delaying the clinical onset of mild cognitive impairment and dementia. Cognitive reserve is "a cumulative improvement [over the lifespan], due to genetic and/or environmental factors, of neural resources that mitigates the effects of neural decline caused by ageing or age-related disease" (Cabeza et al., 2018, p. 702). It is not possible yet to measure cognitive reserve directly and so proxies such as years of education and level of occupation are often used (Cabeza et al., 2018; Stern, 2021; Stern et al., 2020). Research is currently ongoing, including in the fields of molecular genetics and neuroimaging, to provide more biological indices of measurement of cognitive reserve (Stern et al., 2020).

The concept of degeneracy, or the ability of other areas of the brain to undertake the functioning of compromised areas, is thought to provide the neural underpinning of cognitive reserve (Fornito et al., 2015; Genon et al., 2018). Cognitive reserve has been called the "software" in comparison to brain reserve, the enhanced structural "hardware" within an individual's brain, with these features supporting brain maintenance and reducing cognitive decline with age (Stern, 2021; Stern et al., 2020, p. 7). A body of research now points to the fact that cognitive reserve may have a role to play in the reduction of susceptibility to neurodegenerative processes and loss of brain function as people age (Wagster and King, 2019; Gallagher et al., 2019; Burke et al., 2019).

A high percentage (20-40%) of normally functioning adults are found at autopsy to meet neuropathological criteria for a diagnosis of AD, despite not showing deterioration in functioning whilst alive (Bettcher et al., 2019; Boyle et al., 2013). Studies of the oldest old in the population (the Nun Study and the 100-Plus Study) show that some centenarians display little evidence of

cognitive decline in their lifetime, despite neurodegeneration found post-mortem, indicating that their cognitive reserve capacity was sufficient to minimise any decline (Qiu & Fratiglioni, 2018). In people with Down syndrome, similar post-mortem evidence of minimal or less-than-expected cognitive decline has been found, despite AD neuropathology being present (Boyle et al., 2025).

Meta-analysis of longitudinal studies found that higher cognitive reserve (measured either by proxies or residual variance estimations from neuropsychological testing) was associated with a 47% reduced risk of progression to mild cognitive impairment or dementia (Nelson et al., 2021). Interestingly, high cognitive reserve estimated through neuropsychological testing led to a higher relative risk reduction (62%) than proxy-measured high cognitive reserve (48%) (Nelson et al., 2021). It appears that mechanisms underlying cognitive reserve are broad ranging and consist of biologic and psychosocial factors combining to yield increased cognitive resilience to the neuropathology of AD (Burke et al., 2019). A wide variety of biopsychosocial factors may be influential in modifying cognitive reserve, including physical fitness, social engagement, lifestyle behaviours, vascular, metabolic and neuro-inflammatory factors and levels of stress (Song et al., 2022; Stern, 2021; Stern et al., 2019). Increasing focus on the individual factors and lifespan behavioural choices that may influence cognitive resilience are important in future research to develop targeted therapeutic interventions to reduce the individual and societal burden of cognitive decline in ageing populations worldwide (Austad et al., 2019; Song et al., 2022; White et al., 2019). Delaying the onset of AD by even two years can significantly lower the incidence of new AD cases and reduce the overall healthcare supports required for the ageing population (Jorm, 2002).

The evidence on modifiable risk factors in maintaining cognitive reserve and brain health is also relevant to people ageing with Down syndrome, given their risk of accelerated cognitive decline as they age and significantly increased susceptibility to developing dementia (Boyle et al., 2025). Researchers have begun to explore the biopsychosocial factors that may be related to “resistance” and “resilience” to DSAD (Boyle et al., 2025, p. 3). Less attention has been paid to the lifestyle factors influencing onset of dementia in this population than in the general population (Pounds et al., 2025). A recent narrative review exploring the evidence base for psychosocial determinants of AD in people with Down syndrome found a paucity of studies in this area and recommended that clinical longitudinal research be undertaken to more fully understand the risk factors pertaining to dementia in this population (Hamadelseed et al., 2022). It seems clear that a more nuanced biopsychosocial understanding of dementia development and onset across the lifespan is important for people ageing with Down syndrome.

2.6 Biopsychosocial Factors in AD

"*Memory loss doesn't begin according to a date on the calendar- it's determined in large part by all the choices we make and all the experiences we have along the way*".

Mosconi (2020, p. 27)

Age is the main risk factor for development of AD, with risk of the disease doubling every 5-6 years once a person reaches 65 (Grande et al., 2020; Qiu & Fratiglioni, 2018). In addition to physiological risk factors, lifestyle factors have also been found to be important in the risk of developing dementia with age. A review of worldwide meta-analyses estimated the Population Attributable Risk of AD for seven risk factors related to lifestyle (diabetes, hypertension and obesity in middle age, physical inactivity, depression, smoking, low level of education) and found that up to a third of AD cases worldwide could be caused by these potentially modifiable risk factors (Norton et al., 2014).

A review of the biodata of 196,383 people in the UK aged at least 60 years found that lifestyle factors (smoking, diet, physical activity and alcohol consumption) significantly influenced risk of dementia onset, even in those participants with higher genetic risk of dementia (Lourida et al., 2019). The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) found, using a randomised controlled trial, that interventions in lifestyle were effective in reducing the likelihood of dementia onset (Ngandu et al., 2015). It has been noted that the evidence base indicates that the timepoint for lifestyle modifications is important, with interventions for people in middle age being more effective in reducing risk of AD onset than interventions in later life (Bruni et al., 2020). As no cure or long-term effective treatment for AD and other types of dementia has been found (Grande et al., 2020), the importance of the biopsychosocial factors influencing the risk and timing of onset of dementia across the lifespan cannot be overstated.

The World Dementia Council (comprising the G8 nations) commissioned a summary of the evidence from meta-analyses, systematic reviews and Cochrane reviews on modifiable risk factors for cognitive decline and dementia (Baumgart et al., 2015). This review found strong evidence for several modifiable risk factors (low levels of physical activity, traumatic brain injury, diabetes, smoking, obesity and hypertension) and moderately strong evidence for the protective factors of healthy diet and lifelong learning to reduce cognitive decline. These authors also highlighted the importance of a multi-component intervention strategy to lessening the incidence of dementia. Another systematic review into the strength of evidence for prevention of AD found strong

evidence for very similar modifiable risk and protective factors, generally grouped into cardiovascular risk factors and lifestyle behaviours (Yu et al., 2020). The epidemiological evidence to reduce lifetime risk of dementia onset has been summarised into three preventative strategies: the body-mind connection (improving the health of the body particularly cardiovascular health and weight management), interventions to counteract brain ageing (maintaining and enhancing cognitive reserve through lifelong learning, social interactions, work and leisure activities) and lifespan health promotion (physical activity, no smoking, low alcohol consumption, good diet) (Grande et al., 2020).

A recent review of AD genetic and biopsychosocial influences found variances in the age of onset of biomarker expression and significant variances in the clinical expression of AD in people ageing with Down syndrome (Boyle et al., 2025). This review concludes that there is a need for longitudinal research into the impact of biopsychosocial factors, along with the development of more sensitive and specific validated assessment instruments for lifestyle behaviours for people with Down syndrome (Boyle et al., 2025). It also recommends exploring the profiles of those who appear to be more resilient and resistant to the onset of DSAD, along with taking a life-course approach to brain health and cognitive reserve in this population (Boyle et al., 2025).

2.6.1 The Lancet Commission Model of Brain Health

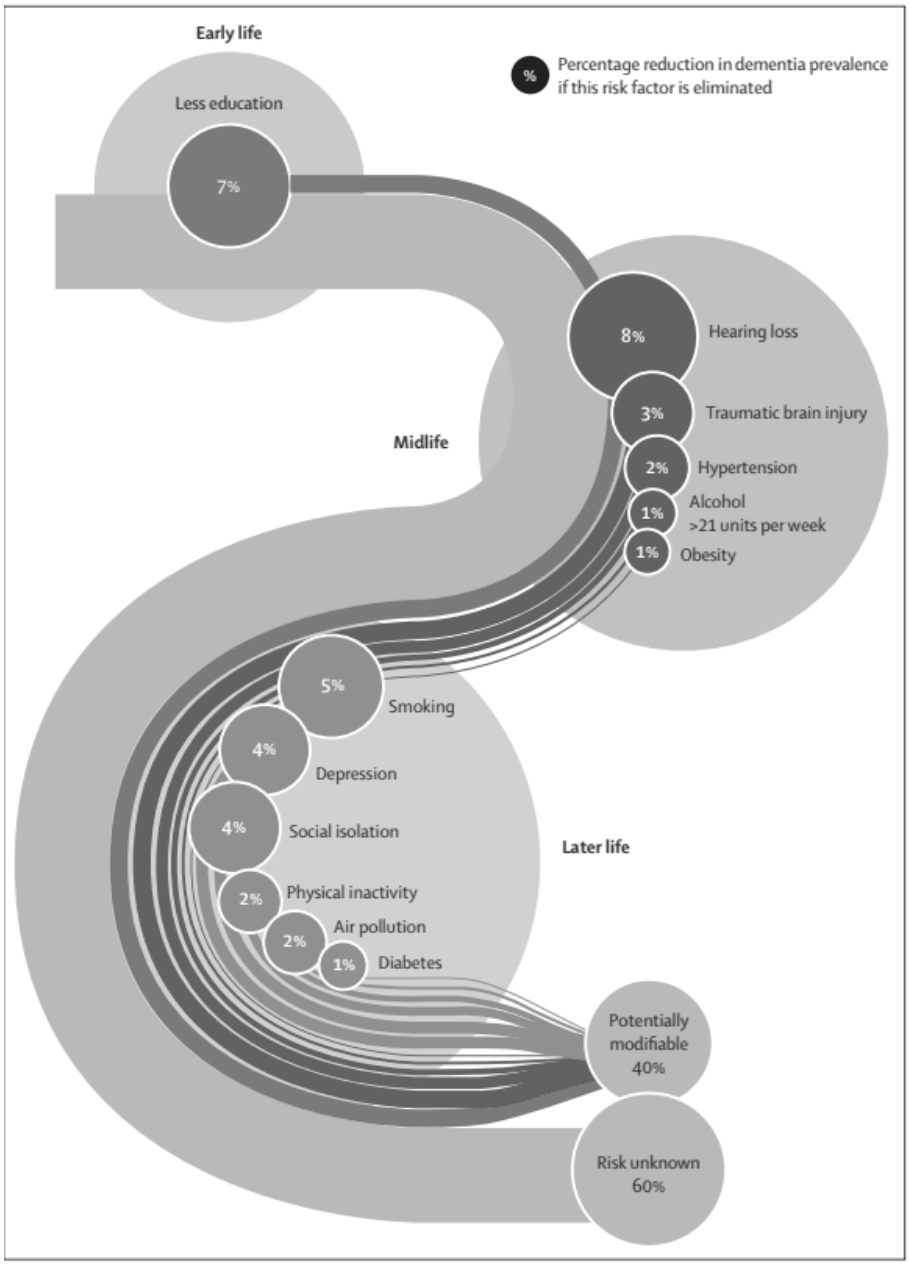
It is now recognised that dementia is multifactorial in its aetiology with lifespan risk factors spanning the biological, psychological and social domains (World Health Organization, 2019a). A Lancet Commission model of dementia risk factors, based on extensive meta-analysis review, represents the best current level of understanding of the complex biopsychosocial interactions leading to cognitive decline and dementia (Livingston et al., 2024; Livingston et al., 2020; Livingston et al., 2017). The Lancet Commission for Dementia Prevention, Intervention and Care, following an extensive review of the then extant literature on dementia, initially estimated that up to a third of dementia cases might be prevented if an identified 9 risk factors across the lifespan were modified (Livingston et al., 2017). The Commission then added an additional 3 significant modifiable risk factors following another literature review in 2020, leading to an estimated potential reduction or delay of dementia incidence by up to 40% for this model (Livingston et al., 2020). The Lancet Commission stresses the importance of targeting interventions to modifying these significant risk factors across the entire lifespan to reduce the incidence of dementia at population level. Another updated model of risk factors has recently been released by the Lancet Commission (Livingston et al., 2024), with the addition of two further risk factors, cholesterol and vision deficits.

Clear evidence exists for a multifactorial aetiology for AD and dementia in general, with several modifiable risk and protective biopsychosocial factors affecting different physiological pathways. The question arises as to what extent these biopsychosocial factors influence the risk of dementia of people ageing with Down syndrome, given the variance in "resistance and resilience" for DSAD beginning to be established for this population, with variable age of onset and differences in disease trajectory and progression rates at an intra-population level (Boyle et al., 2025, p. 3). Another question arising is the value or importance placed on a good quality of life being achieved by people with Down syndrome, throughout their life, to the end of their life, despite their elevated risk of DSAD. This is aligned to a positive psychology approach being taken to supports for this ageing population, emphasising a broad variety of domains of positive ageing, including objective and subjective experiences, with a focus on self-determination and active meaningful engagement in one's own life (Annele et al., 2019; Fernández-Ballesteros et al., 2019).

Each of the dementia risk factors included from the Lancet 2020 model in this research will be discussed in more detail in the next section, excepting acquired brain injury and air pollution levels, which were not available in this study's longitudinal dataset. An overview of the general epidemiology for each factor with a focus on the prevalence and incidence of each factor for those ageing with Down syndrome, potentially differing from the general ageing population, will be presented. The importance of each factor for brain health and the pathophysiological pathways leading to cognitive decline and dementia will be highlighted. This thesis research focuses on the 2020 version of the Lancet Model (Livingston et al., 2020), as the most recent Lancet model (Livingston et al., 2024) was released after the statistical analysis and modelling had been finalised for this research. See Figure 2.7 overleaf for an overview of the Lancet Commission Model used in this thesis. These modifiable factors sit firmly within a biopsychosocial approach to positive ageing and brain health. They offer a framework within which to examine the life experience of this sample of people ageing with Down syndrome and enable a specific focus on the impact of these factors on later DSAD diagnosis within this population.

Figure 2.7

Lancet Commission model of brain health



Note: Potentially Modifiable Risk Factors in Dementia. From: "Dementia prevention, intervention, and care: 2020 report of the Lancet Commission", by Livingston et al. (2020), *The Lancet*, 396 (10248), Figure 7, p.428. https://doi.org/10.1016/S0140-6736(20)30367-6. Copyright 2020 by Elsevier Ltd.

2.6.2 Education

The importance of education in preserving cognitive functioning is recognised with educational attainment used as a common proxy measure for cognitive reserve (Anatürk et al., 2021). It is measured as a 'static proxy' as most individuals complete their formal education before mid-life, with levels of educational attainment staying roughly the same over later life (Zahodne et al., 2019, p. 110). Estimates have been made that up to 19% of dementia incidence may be related to low levels of education (Norton et al., 2014). Higher levels of educational attainment were associated with significantly lower risk of developing dementia, with an odds ratio of 0.89 lower risk per year of education completed (Larsson et al., 2017). There is an estimated 7% reduction in later life risk of dementia with education in early life (Livingston et al., 2020).

Many older people in the general Irish population aged 60 plus have not progressed beyond junior cert level (56% of men, 51% of women), with very low rates of completion of third level education (21% for men, 20% for women), reflecting the historical lack of access to educational opportunities (FitzGerald et al., 2011). Those aged 25-29 have much higher levels of completion of third level degrees (38% for men, 54% for women) and few have only completed junior cert level or less (14% for men, 11% for women), indicating that the levels of cognitive reserve in the general population will increase as this cohort ages (FitzGerald et al., 2011).

However, this gradual increase in educational levels as a proxy for cognitive reserve may not be replicated in those with Down syndrome, where, despite improvements in educational access, significant gaps remain. There has been increased access to secondary school education for people with Down syndrome in this century (Aston, 2019), but those with more severe levels of disability face ongoing obstacles in their access to inclusive education and progression through levels of education (Alquraini & Gut, 2012; Olson et al., 2016).

A recent survey showed the majority of second level Irish students with an intellectual disability are in mainstream classes (55%), with 34% in smaller special classes within mainstream school and the remaining 12% in larger special classes (Aston, 2019). The older cohort of Irish people ageing with Down syndrome did not have access to such supports. Many may have no education or have only completed primary school education, in many cases in a segregated setting, with no records of their attendance in education. Findings from the Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing (IDS-TILDA) have shown low levels of educational attainment across all age bands and levels of intellectual disability in the sample with

only 3% of the participants reporting achieving higher than primary level education (McCarron, 2011).

Neuroimaging data to estimate brain age relative to the person's chronological age show higher levels of educational attainment are linked with a younger brain age (Anatürk et al., 2021). Education may delay the presentation symptoms of cognitive decline in the prodromal and early stages of dementia. Each one-year increase in education reduces dementia prevalence rates by 17% and a university degree adds an additional 2.30 years' delay in onset of cognitive decline and a 3.2% increase in life expectancy without cognitive decline (Clouston et al., 2020; Ozyigit, 2021). Lifelong learning opportunities may also contribute to maintaining cognitive reserve and reduce the risk of dementia; the evidence continues to evolve on this (Chan et al., 2018; Peeters et al., 2020; Staff et al., 2018; Wilson et al., 2013). Interestingly, some studies have found that the dementia-protective gains due to education tend to reach a plateau by late adolescence, with later life learning or relative job complexity contributing little extra difference to measured cognitive functioning for men in midlife (Kremen et al., 2019). However, progressing to university level education and working in a cognitively challenging occupation do appear overall to have significant influences on cognitive health over a lifespan (Livingston et al., 2024).

Despite progression of university access programmes in recent years, young Irish people with Down syndrome still have limited choices regarding higher educational opportunities; many still attend Health Service Executive (HSE) funded adult day services rather than higher educational settings (Aston, 2019). Recent data from the National Ability Supports System show that just 0.4% of 22,434 people registered with a disability were attending university at the time of recording (Casey et al., 2020). Irish people ageing with Down syndrome have access to local lifelong learning opportunities, however, these vary in standard and quality, with few accessing certified courses such as FETAC or QQI. It is therefore difficult to create a comparison across individuals with Down syndrome of the extent and intensity of their lifelong learning opportunities. Some research has examined the effects of computerised cognitive training on promoting cognitive reserve and executive functioning in individuals ageing with Down syndrome. Participation in an 8-week brain training programme significantly increased planning, working memory and inhibition for participants, all important components of executive functioning (McGlinchey et al., 2019).

The neurological underpinnings of this preservation of cognitive functioning have been investigated in relation to education's effects as a moderator on episodic memory and white and grey brain matter volumes. Higher levels of education may support episodic memory functioning,

despite progressive neurological dysfunction, through increased plasticity of brain network structures (Barulli & Stern, 2013). Educational attainment levels appeared to have a greater moderating influence on the association between episodic memory and brain matter volumes in earlier stages of cognitive impairment, consistent with what would be predicted by cognitive reserve theory (Mungas et al., 2018; Zahodne et al., 2019). It was also found across several studies that higher educational attainment levels can lead to faster brain atrophy at later stages of cognitive impairment; these authors suggest that episodic memory may have more construct validity as a predictor of cognitive reserve than education (Mungas et al., 2021). The use of education as a proxy for cognitive reserve needs to consider the disease stage of dementia (Zahodne et al., 2019).

2.6.3 Hearing Loss

"*The evidence on hearing aids reducing dementia risk is consistent and supportive*"

(Livingston et al., 2024, p. 10)

Hearing loss can be measured as the averaged loss of hearing tones at 1000, 2000 and 4000 Hertz, with hearing loss judged as present if there is loss of decibels of 25 or more in the best ear, as measured by pure tone audiometry (IASSIDD, 2019). There is an increased risk of hearing loss with ageing. Hearing loss amongst the world's population is increasing, with a prevalence of 32% in people aged 55 years and older (Livingston et al., 2017) and globally it is now the fourth leading cause of years lived with disability (Canli et al., 2017). Hearing impairment in the population increases significantly with age, with some reports of between 70 to 90% of people aged 85 + having some degree of hearing impairment (Maharani et al., 2018). Despite its prevalence, hearing impairment remains relatively untreated (Maharani et al., 2018).

Several meta-analyses in recent years have shown that hearing loss is associated with cognitive decline and/or dementia; in fact, after adjustment for age and cardiovascular risk factors, it was found that hearing loss can almost double the risk of developing dementia RR=1.94, 95% CI: 1.38-2.73 (Livingston et al., 2020; Livingston et al., 2017). Recent research has found a 16% increase in dementia risk with each 10-decibel reduction in hearing (Yu et al., 2024). The Lancet Commission has estimated that this equates to an 8 per cent reduction in onset risk of cognitive decline if hearing loss in midlife was reduced or compensated for (Livingston et al., 2020).

The physiological pathways through which hearing loss may affect cognitive decline are not yet fully established; it is speculated that hearing loss may add to the brain's "cognitive load",

induce depression and / or lessened social engagement or be a part of general central nervous system degeneration over time (Livingston et al., 2024; Livingston et al., 2017, p. 2680; Loughrey et al., 2018; Maharani et al., 2018). Another theory, the "cascade hypothesis", is that hearing loss may lead to less processing of sensory information by the brain, causing less brain stimulation and cognitive decline over time (Maharani et al., 2018, p. 1134; Okely et al., 2019). Magnetic resonance imaging (MRI) has found that hearing loss in midlife may lead to degeneration in the temporal lobe structures of the brain, including in the right hippocampus and left entorhinal cortex, which may be an indication of the later life neuropathological processes occurring in the brain in response to hearing loss (Armstrong et al., 2019). Laterality of hearing loss had an impact on the levels of temporal lobe neurodegeneration, with right sided hearing loss more significantly impactful (Armstrong et al., 2019).

Hearing loss has psychosocial implications, including for a person's well-being and social connectedness (Willems et al., 2021; World Health Organization, 2019a). It also affects the brain's ability to process information (Wilson et al., 2017). There is significant variation in the level of hearing loss people can develop as they age, influenced by lifestyle and health factors (Okely et al., 2019). Recent Irish Census data (Central Statistics Office, 2020) shows that 2.2% of the Irish population (N=103,676) reported having some type of hearing related disability, which represented an increase of 12.6% from 2011 Census. Hearing impairment incidence was related to increasing age, with only 1 in 100 Irish people reporting a hearing impairment up to age 42, then increasing to 1 in 10 people at age 77 and 1 in 4 at age 89.

People ageing with intellectual disability have been found to be at higher risk of developing hearing impairment, particularly people ageing with Down syndrome (Burke et al., 2019; Haveman et al., 2009; Meuwese-Jongejeugd et al., 2006; Willems et al., 2021). Paediatric studies have found many babies born with Down syndrome have conductive hearing loss (prevalence of up to 84%) (Bull, 2020). Almost 100% prevalence of hearing impairment in participants with Down syndrome by age 60 has been found (Bent et al., 2015; Meuwese-Jongejeugd et al., 2006; Willems et al., 2021).

Findings from the IDS-TILDA data wave 5 show that, although 87.5% of participants reported good, very good or excellent hearing, objective hearing testing showed a large percentage of hearing deficits within the sample. These measured hearing deficits were more pronounced in men, with 46.2% of older men having a hearing deficit and 23.1% of older women (McCarron, 2023). Men within the mild range of intellectual disability had higher measured hearing deficits than those within the moderate range overall whilst women within the moderate

range of intellectual disability had higher measured hearing deficits than women within the mild range (McCarron, 2023). These findings reveal a large level of unreported and under-assessed hearing difficulties in this population, including for people with Down syndrome.

Guidelines recommend that regular screening for hearing impairment for adults with Down syndrome should begin at age 30, due to progressive increase of hearing loss after this age (Lennox et al., 2002; Picciotti et al., 2017). Persistently low uptake of sensory screening (both vision and hearing) has been reported for Irish people with Down syndrome across the IDS-TILDA data waves (McCarron, Haigh, et al., 2017), with similarly low levels of screening for hearing loss reported in England for this population and low uptake of hearing aids when prescribed (Bent et al., 2015). Audiologists and GPs may lack the specialist skills required to adequately assess hearing loss in this population and may underestimate the need for hearing supports (Willems et al., 2021). Similarly, several studies have found that the person with intellectual disability or their carers may be unaware of the fact that they have a hearing loss (Willems et al., 2021). Hearing difficulties are often mis-attributed to the person exhibiting withdrawal, behaviour support needs or lacking motivation (IASSIDD, 2019).

Longitudinal population studies have found a significantly lower incidence of cognitive decline and dementia in those with hearing loss wearing hearing aids, than those not wearing hearing aids (Bucholc et al., 2021; Livingston et al., 2024; Livingston et al., 2020; Maharani et al., 2018; Yeo et al., 2023). Other studies have found a relationship between hearing aid use and lower levels of depression and anxiety with greater levels of social engagement (Maharani et al., 2018), again highlighting the psychosocial impact of hearing impairment. Compliance with hearing aid wearing when prescribed is low for people with Down syndrome (Coppens-Hofman et al., 2011).

The psychosocial impact of hearing loss on people ageing with Down syndrome is even more severe than on their peers in the general population, due to pre-existing communication and functional abilities due to their intellectual disability (Carvill, 2001). Due to the higher percentage of comorbidities and other sensory issues experienced by people with intellectual disability, any degree of hearing loss may disproportionately affect the functioning of this population, including raising the risk of cognitive decline and dementia, particularly given low compliance with wearing hearing aids (IASSIDD, 2019).

2.6.4 Hypertension

A large body of evidence is available highlighting the importance of cardiovascular health in healthy cognitive ageing and reducing the risk of dementia onset across the lifespan, including

from the well-known Rotterdam and Nun Studies (Fierini, 2020; Gorelick et al., 2011; Johansen et al., 2020). Hypertension in midlife poses a 2% increased modifiable risk of developing dementia, according to the Lancet model of risk factors for dementia over a lifespan (Livingston et al., 2024; Livingston et al., 2020). Global prevalence of hypertension in the general population is estimated at 24% for men and 20% in women, with a declining prevalence in higher income countries due to access to antihypertensive medication (Mills et al., 2020; Zhou et al., 2021). More men have high blood pressure than women (Zhou et al., 2021).

Chronic hypertension raises the risk for stroke and subsequent damage to areas of the brain (Johansen et al., 2020). A prospective longitudinal study assessing blood pressure, brain pathology and volume found no evidence of an association between blood pressure at any age and subsequent amyloid status in the brain (Lane et al., 2019). Higher blood pressure in midlife was found to be significantly associated with greater microvascular issues and smaller brain and hippocampal volumes by age 70, with the authors inferring from these findings that hypertension increases AD risk through vascular rather than amyloidogenic pathways in the brain.

Evidence suggests that hypertension in later life is not as big a risk factor for dementia; rather sustained high blood pressure levels over many years from midlife is a higher risk, impacting on grey and white matter integrity within the frontoparietal network responsible for executive functioning (Gottesman et al., 2017; Johansen et al., 2020; Sabia et al., 2019; Veldsman et al., 2020; Walker et al., 2019). The high prevalence of mixed dementia in the general population shows that mixed pathology may occur in many cases of dementia and may share underlying physiological pathways, including cardiovascular elements (Fierini, 2020). A recent meta-analysis of six large prospective community studies found that those who used any hypertensive medication had a 12% lower risk of any dementia and 16% lower risk of AD, with no specific hypertension medication performing better than the others in this regard (Ding et al., 2020).

Despite evidence of accelerated ageing in many organs and bodily systems, people with Down syndrome have significantly less risk of developing hypertension as they age, perhaps due to lower baseline blood pressure levels (Baksh et al., 2023; Rodrigues et al., 2011; Roy-Vallejo et al., 2020). Autopsies have found minimal evidence of atherosclerotic plaques in the blood vessels of people with Down syndrome compared to matched controls (Roy-Vallejo et al., 2020). There is also evidence of much lower blood pressure readings in this population (Parra et al., 2017; Roy-Vallejo et al., 2020). It has been found that two genes located on the over-expressed chromosome 21 in people with Down syndrome seem to play a role in regulating blood pressure (Roy-Vallejo et al., 2020), which may explain the apparent down-regulation of blood pressure in this population.

Lower prevalence of hypertension may indicate that this risk factor is less relevant to those ageing with Down syndrome. However, recent cross-sectional analysis of the impact of physical activity on the cognition of younger adults with Down syndrome found a strong association between lower systolic blood pressure and better memory and reaction time scores (Frank et al., 2023), showing that control of blood pressure, where necessary, remains important for the long-term cognitive functioning of people ageing with Down syndrome.

2.6.5 Alcohol & Smoking

Alcohol abuse is recognised as one of the leading influences on morbidity and mortality worldwide, with projections of a continuing increase until 2030 and beyond (Manthey et al., 2019; Shield et al., 2020; Wiegmann et al., 2020). A high level of alcohol consumption appears to increase the risk of dementia (Wiegmann et al., 2020). Brain autopsies of those who have died from alcoholism have shown atrophy and reduced brain volume, mainly white matter loss, with some MRI studies showing increasing loss of cerebral brain volume with increase in alcohol consumption (Wiegmann et al., 2020). High levels of alcohol consumption promote increased inflammatory processes in the central nervous system, increased thiamine deficiency and impact on cardiovascular health (Wiegmann et al., 2020). Alcohol may also reduce the ability of microglial cells to remove beta amyloid depositions in the brain, thereby promoting the progression of AD (Kalinin et al., 2018). Drinking more than 21 units of alcohol per week from middle age is associated with increased dementia risk, related to reduced brain volume (grey matter) (Livingston et al., 2020; Rehm et al., 2019). Excess alcohol consumption in midlife is estimated to increase dementia risk across the lifespan by 1% (Livingston et al., 2020).

Alcohol Use Disorder (AUD), within a mild, moderate or severe range, is the newer term coined by the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), covering both alcohol abuse and alcohol dependence (National Institute on Alcohol Abuse and Alcoholism, 2021). Men, younger cohorts, lower levels of education and household income and being divorced, separated and widowed were all found to increase the likelihood of having AUD (Glantz et al., 2020; Probst et al., 2020; Shield et al., 2020). The prevalence of AUD has been found to be 14.8% in the Irish adult population, one-seventh of the total population, with 13.6% of drinkers aged 65+ drinking alcohol at least 4 times per week (Mongan et al., 2021).

Findings of the influence of alcohol consumption on dementia risk are somewhat conflicting, however. There appears to be a J-shaped correlation between alcohol consumption and dementia risk, in that low to very moderate levels of consumption of alcohol appear to reduce

dementia risk in comparison to abstention or high levels of consumption, with a potential explanation being a somewhat protective effect of alcohol on *some* cardiovascular risk factors (Wiegmann et al., 2020). A meta-analysis of 15 prospective studies from countries around the world exploring alcohol consumption and dementia risk in 24,478 adults over 60 years found increased risk for those who abstained as compared to those with light to moderate consumption of alcohol (Mewton et al., 2023). The authors do state that a possible confounding factor in the analyses is that some abstainers may be former heavier drinkers, conferring a higher lifetime risk of dementia onset (Mewton et al., 2023). Studies that have adjusted for this as a potential confounder have found that there isn't excess mortality from dementia in the always-abstaining group (Livingston et al., 2024).

It is accepted that smoking is also a modifiable risk for dementia, with 14% globally of AD diagnoses potentially attributable to cigarette smoking (Barnes & Yaffe, 2011). Smoking has several systemic adverse effects on the body, including damaging the cardiovascular system, with a direct effect on the brain, including increased beta amyloid and loss of cortical tissue (Bruni et al., 2020). Smoking may lead to a decrease in brain volume through loss of grey and white matter, increased oxidative stress and inflammatory processes in the body and a decrease in cardiovascular/cerebrovascular health (Elbejjani et al., 2019; Swan & Lessov-Schlaggar, 2007). Smoking causes grey matter reduction in various parts of the brain, including the cerebellum, basal ganglia, the hippocampus, the thalamus and prefrontal cortical regions (Cox et al., 2019; Sutherland et al., 2016). Alcohol use may be a confounder in these findings, as other studies have found little impact on grey matter volumes in those who smoke and don't drink; heavy use of alcohol appeared to be the more significant impacting factor on brain volume decreases (Elbejjani et al., 2019; Mackey et al., 2019). However, analysis of MRI and other brain imaging data from smokers in the UK biobank, controlling for other confounders, showed a significant relationship between decrease of grey and white matter brain volume and smoking (Gray et al., 2020).

Despite a decrease in prevalence in recent decades, smoking rates remain high globally with an estimated 1.1 billion people smoking (Flor et al., 2021; World Health Organization, 2019b). Population studies in the US have found a decrease in smoking rates in older people aged 55+, from 16% in 1998 to 11% in 2018 (Hunt et al., 2023). Globally, smoking cigarettes is the leading cause of premature death, with over 8 million preventable deaths occurring each year; one in ten deaths are caused by smoking (Jafari et al., 2021; World Health Organization, 2023). Significant numbers of people also die worldwide each year from passive smoking (Lushniak et al., 2014). Rates of smoking are high in both genders (Jafari et al., 2021) and has also been found to lead to

an increased risk for AUD (McKee & Weinberger, 2013). Long-term smoking significantly increases the risk of many types of cancers, respiratory and cardiovascular diseases (Jha, 2020). Smoking contributes up to a 5% modifiable dementia risk in later life (Livingston et al., 2020).

Self-reported alcohol use and smoking by teenagers and young adults with mild and moderate intellectual disability was found to be lower than their peers in one study (Robertson et al., 2020); however, another study found evidence of higher alcohol and cigarette use in those living independently with intellectual disability than had previously been assumed (Swerts et al., 2017). People ageing with intellectual disability tend to be much lower consumers of alcohol or cigarettes than their peers in the general population, with rates of reported consumption continuing to decrease within an Irish context (Chapman & Wu, 2012; McCarron, 2011; McCarron, 2023; McGillicuddy, 2006; Pape et al., 2021). Therefore, these lifestyle risk factors may not be as relevant for this population.

2.6.6 Obesity

Obesity, the accumulation of adipose tissue in the body, and a larger waist circumference from midlife are recognised as a significant risk factor for later-life dementia, with further research needed to clearly identify the physiological pathways contributing to this increased risk (Livingston et al., 2024). An increased risk of dementia in those who are underweight has also been found, but it is suggested that this may be a prodromal sign of developing dementia (Livingston et al., 2024). It is accepted that visceral fat tissue raises the level of inflammation in the body and the risk of impairment of metabolic functioning, leading to metabolic diseases and subsequent neurodegeneration (Arnold et al., 2018; Moreau et al., 2021; Ruze et al., 2023; Tramutola et al., 2020). A 1% increased risk of dementia has been found from having obesity in midlife (Livingston et al., 2020).

Obesity is recognised as a complex condition that is multifactorial in origin and is one of the leading preventable causes of death in the developed world (Mahmoud et al., 2022; Ruze et al., 2023; Wang et al., 2020). Currently, one third of the global population is overweight or obese, with 35% of those aged 65 and older being obese (Lin & Li, 2021; McKee & Morley, 2021). By 2030, 78% of Americans are projected to be obese or overweight and it has been estimated that maximum obesity prevalence will be reached by 2054, initially in the UK and US and then in other European countries (Janssen et al., 2020; Wang et al., 2020). Gender differences have been found in obesity risk, with women at greater risk of developing obesity than men (Lin & Li, 2021; Melville et al., 2007). Obesity is associated with a range of adverse health outcomes, including metabolic

disorders, cardiovascular disease, increased cancer risk, diabetes, kidney and liver disorders and depression, with an estimation of 30% higher medical costs in treating those with obesity than those with normal BMI (Endalifer & Diress, 2020; Lin & Li, 2021; World Health Organisation, 2000).

There is a higher prevalence of obesity in people with Down syndrome than the general population, potentially driven by genetically influenced metabolic dysfunctions (Dierssen et al., 2020). It has been estimated that people with Down syndrome are two to four times more likely to be obese than their peers in the general population, with females with Down syndrome being more at risk of obesity (Moreau et al., 2021). Higher levels of C-reactive protein, dysfunction in insulin signalling, endocrine dysfunction (including increased leptin resistance) have all been found in this population, indicating impaired metabolic functioning and increased risk of obesity (Dierssen et al., 2020; Gutiérrez-Rojas et al., 2020; Moreau et al., 2021). Physical activity interventions alone are not sufficient to address obesity with this population; interventions with several additional components including counselling, lifestyle changes and diet are recommended (Salse-Batán et al., 2022).

Increasing insulin resistance in the brain, driven by metabolic dysfunction, is recognised as one potential pathway through which neurodegeneration may occur in this population (Dierssen et al., 2020; Tramutola et al., 2020). People with Down syndrome have increased brain insulin resistance, related to their impaired metabolic dysfunction, leading to an increased risk of cognitive decline and dementia (Dierssen et al., 2020). Markers indicating brain insulin resistance have been found in people with Down syndrome prior to the development of AD (Lott & Head, 2019; Tramutola et al., 2020). Metabolic dysfunction may act synergistically with the genetic tendency to develop AD in people ageing with Down syndrome, raising the risk for development of cognitive decline and dementia (Dierssen et al., 2020).

Measuring Obesity. Traditionally, Body Mass Index (BMI) has been used to measure obesity (BMI>30). Waist circumference measurements may give a better indication of visceral fat, therefore more strongly predicting future health risks (Wang et al., 2020). Class 1 obesity classification (BMI > 30) and / or waist circumference measurements of greater than 102 cm for men and 88 cm for women (indicating central obesity) predict metabolic and other health disorders (Janssen et al., 2002; World Health Organization, 2008). Waist circumference has been predicted from BMI, with findings that BMI ≥ 30 kg/m^2 (“obese”) corresponds to WC of 88 cm for women and 102 cm for men, and these waist measurements have been identified as greatly increasing the risk of adverse health outcomes along with BMI (Bozeman et al., 2012; Department of Health and Aged Care Australia, 2025; World Health Organization, 2008).

2.6.7 Depression

Clinically diagnosed depression, known as Major Depressive Disorder (hereafter referred to as depression), is a very common mental health condition worldwide with a significant impact on daily functioning and quality of life (Gutiérrez-Rojas et al., 2020). A recent systematic analysis found that there appears to be an increasing prevalence of depression being recorded worldwide, with estimated prevalence of 19.2% in the elderly population worldwide, higher in those in nursing homes (Jalali et al., 2024; Moreno-Agostino et al., 2021). The prevalence of mental health issues increases with age for both the general population and those with an intellectual disability (Sheerin et al., 2022). Longitudinal findings of those ageing in the general Irish population found a prevalence of 22.8% of depression in one wave of data recording, with objective and perceived social isolation being significant predictors of depression (Domènech-Abella et al., 2019).

Due to difficulties in clinical assessment and diagnosis, estimates of depression prevalence in those with intellectual disability vary widely, from very low to 39% (Scheirs et al., 2022). Depression prevalence in those with Down syndrome is estimated to range from 6-18% with 18.4% of those aged 36+ found to have diagnosed depression (Startin et al., 2020; Thom et al., 2021). People with Down syndrome have a four to fivefold increased risk of developing depression than their peers in the general population (Startin et al., 2020). An increased rate of proven risk factors for depression has been found in this population, including having a smaller total brain volume, smaller hippocampus, reduced serotonin levels, increased levels of hypothyroidism, indicating potentially higher rates of under-diagnosed depression (Thom et al., 2021; Walker et al., 2011).

Despite this increased risk of depression, several studies have shown low knowledge of depression symptomatology in this population and low confidence in making diagnoses by mental health professionals, in comparison to diagnoses for the general population (Hinde & Mason, 2020; Hsieh et al., 2020; Man et al., 2017; Werner & Stawski, 2012). Diagnostic overshadowing, a reliance on proxy reporting due to communication issues and a lack of suitable assessment instruments for those with higher levels of need, can all contribute to the difficulties in diagnosis of depression (Axmon et al., 2018; Hsieh et al., 2020; Sheerin et al., 2022; Thom et al., 2021). Some studies have found lower rates of diagnosed depression in those with higher levels of intellectual disability; however, it is unclear how much this is influenced by the difficulties in diagnosis in this population (Axmon et al., 2018). A systematic review of depression assessment for people with a severe to profound intellectual disability (IQ <35) found that this cohort were less likely to be diagnosed with depression than those with higher levels of ability, due to lack of validated screening instruments, need for proxy report and an atypical clinical presentation.

Research has found an association between depression and dementia in people ageing with Down syndrome, with depressive symptoms associated with dementia in this cohort being low mood, less appetite, weight loss and sleep difficulties (Dekker et al., 2015). Depression can be misdiagnosed as dementia, or vice versa, in this population (Cooper & Collacott, 1994). Research with DSAD biomarkers and/or psychometric testing has found increased depressive symptoms prodromal to development of clinical expression of dementia in this population (Ballard et al., 2016; Dekker et al., 2021; Jenkins et al., 2025; Urv et al., 2008). These include lethargy and apathy as early presenting symptoms (Jenkins et al., 2025).

Antidepressant Prescribing. Antidepressant prescribing rates for people ageing with intellectual disability have increased over the last decade. Between 2010-2018, prescription rates rose from 20.2% to 26.1% in older age groups, with a 15.4% prescription rate for men of all ages with intellectual disability and a 22.5% prescription rate for women of all ages with intellectual disability (Mehta & Glover, 2019). Similarly, prescription of antidepressants for people with intellectual disability in Scotland rose from 11.2% in 2004 to 19.1% in 2014, with the greatest rates of increase for women and people with mild intellectual disability (Henderson et al., 2020).

Whilst antidepressant prescriptions in the UK have also risen in the general population, the rate of increase has been higher in those with intellectual disabilities – prescription rates of 20.7% vs 10.3% (NHS Digital, 2021). The increase in actual diagnosis of depression is similar in both populations, meaning that the increased rate of antidepressants may be being prescribed to manage other conditions in people with intellectual disability, including managing challenging behaviours, combining with another psychotropic medication and to help people to cope with adverse life circumstances such as loneliness or social isolation (Branford & Shankar, 2022). Those older than 50 years with intellectual disability have a 3 times greater chance of being prescribed an antidepressant with an antipsychotic than their peers aged 18-25 years (National Health Service, 2019). Although efforts at deprescribing are continuing, antidepressants remain the most widely prescribed psychotropic for people ageing with intellectual disability in the UK (Branford & Shankar, 2022; Henderson et al., 2020).

A similar picture of prescribing patterns for this population has been found in Ireland. Almost one third of those aged over 65 with intellectual disability in an Irish representative sample reported antidepressant prescription, with those living in residential settings more likely to have a prescription (O'Dwyer et al., 2017). There was an increasing prescription of antidepressants with age in this population and a higher level of use than their peers in the general population (O'Dwyer et al., 2017). Under-prescribing of anti-depressant medication has also been found, with either no

prescription being made or no second medication trialled if the first is ineffective (Cooper & Collacott, 1994). Systematic studies of the benefit and efficacy of various types of anti-depressants are lacking in this population; a recent study found a beneficial effect of selective serotonin re-uptake inhibitors in treating depression in a small sample of adults with Down syndrome (Thom et al., 2021).

Depression as a Risk Factor for Dementia. It is estimated that 5-11% of cases of AD may have been caused by depression as the main risk factor (Norton et al., 2014). Depression can, however, also be a consequence of developing dementia, so there remains some query regarding the directionality/causality of the relationship between these two conditions (Almeida et al., 2017; Dafsari & Jessen, 2020). The Lancet Commission report stated that the link is probably bidirectional between the two conditions, based on a systematic review of the evidence (Livingston et al., 2020).

There is a large body of evidence showing a higher risk of developing dementia if one has depression (Almeida et al., 2017; Gatchel et al., 2019; Norton et al., 2014; Zeki Al Hazzouri et al., 2018). It is highlighted as a midlife risk factor needing treatment and management to reduce risk of later life cognitive decline and dementia (Livingston et al., 2024). Estimations have been made of a reduction of up to 4% in dementia incidence worldwide if antidepressants were fully utilised (as clinically indicated) in the management of depression (Mossello et al., 2008). This has implications for those ageing with Down syndrome, with potential under-diagnosis and under-treatment of the condition (Thom et al., 2021). People ageing with Down syndrome prescribed anti-depressants experienced a mean later age of onset of clinical expression of dementia, 53.75 years, than those not using anti-depressants prior to dementia diagnosis, 52.44 years (Tsiouris et al., 2014).

The effect of depressive symptomatology has been studied as a risk for dementia incidence. A large longitudinal population study found that low and moderate depressive symptoms were not associated with an independent raised risk of dementia over time, whereas high and increasing depressive symptoms were (Kaup et al., 2016). The authors recommended that a pattern of depressive symptoms over time more accurately informs dementia risk than an assessment of symptoms at just one time-point (Kaup et al., 2016). More severe depression and depression in later life leads to a higher risk of dementia, with depression acting as an “accelerating factor” in progression into Mild Cognitive Impairment through to the clinical expression of dementia (Dafsari & Jessen, 2020, p. 161).

Physiological pathways that may influence the action of this risk factor include the effect that depression has on reducing cerebral blood flow, including in the frontal lobe and limbic regions that are involved in memory in the brain (Cooper et al., 2020; Popa-Wagner et al., 2015). Depression has a similar effect to hypertension on cerebral small vessel disease and increases the risk of small brain infarcts (Wang et al., 2014; Zeki Al Hazzouri et al., 2018). Depression also has a substantial effect on the body's ability to regulate its immuno-inflammatory systems (Cuypers et al., 2021; Hakim, 2022). Increased levels of interleukins and C reactive proteins, along with reduced homeostatic regulation of the inflammatory systems in the body, have been found in chronic depression (Dafsari & Jessen, 2020; Hakim, 2022; Miller & Raison, 2016). Some antidepressant medications have anti-inflammatory properties, for example selective serotonin reuptake inhibitors (SSRIs) reduce microglial activity; this provides one possible physiological pathway whereby treatment for depression reduces the risk for dementia, as both share common inflammatory pathways (Hakim, 2022). Social support and reduction in social isolation can also reduce depression, showing the synergistic effect of various risk factors on dementia risk reduction (Murata et al., 2017; Xiang et al., 2021).

2.6.8 Social Isolation

"*The power of community to create health is far greater than any physician, clinic or hospital*"

(Hyman, 2012)

Social isolation can be conceptualised as an objective quantitative lack of social experiences and connections whilst loneliness is a more subjective perception of a felt lack of social experiences and connections (Cattan et al., 2019; Donovan & Blazer, 2020; Holt-Lunstad & Steptoe, 2022; World Health Organization, 2021). People may subjectively feel alone whilst in the company of others, or conversely, may not feel alone despite objectively small social networks (Reinhardt et al., 2021). Social isolation can occur at any stage in the lifespan (Coyle & Dugan, 2012; Newall & Menec, 2019; Rafnsson et al., 2020; Valtorta et al., 2016b). However, those who are elderly appear to be more vulnerable, with those who are oldest (age 80+) most vulnerable (Teo et al., 2023; Zhenrong et al., 2024). A prevalence rate of 25% for social isolation in the elderly has been found, with risk factors being aged 80+, living alone and having less education (Cudjoe et al., 2020; Teo et al., 2023). Not all older adults are socially isolated, with many older adults frequently citing good social connections as one of the most important dimensions of positive ageing (Cavanaugh & Krauss Whitboume, 1999; Newall & Menec, 2019). In contrast to the other risk factors, this variable required quite a detailed conceptual approach to derivation for this

study. The conceptual and measurement framework for this derivation was informed by the literature review findings outlined in this section.

Social isolation can be measured by assessing a person's social activities and network, including the frequency of these contacts (Cattan et al., 2019; Holt-Lunstad & Steptoe, 2022; National Academies of Sciences, 2020; Wilson et al., 2007). Historically, these variables were viewed as proxy measurements for what was assumed to be the underlying function and quality of these relationships. It is now understood that social isolation may strongly independently predict health and well-being and needs to be considered separately to measures of loneliness (Holt-Lunstad & Steptoe, 2022; Penninkilampi et al., 2018). The structural aspects of relationship networks (social isolation measures) have been found to remain more stable over time than the function and quality of these relationships (loneliness measures); hence these more stable aspects are likely to have a stronger influence on future health outcomes (Holt-Lunstad & Steptoe, 2022).

Social isolation and loneliness have been identified as major public health issues due to significant adverse health effects across the lifespan (Coyle & Dugan, 2012; Lubben, 2017). Due to similar underlying physiological pathways of influence, they may also have a synergistic effect on adverse health outcomes in those ageing (Beller & Wagner, 2018b; Holt-Lunstad & Steptoe, 2022; Lennartsson et al., 2021; Ward et al., 2021). The World Health Organisation identified social isolation and loneliness as increasing the risk of cardiovascular disease and stroke, mental health issues, cognitive decline and dementia with age (World Health Organization, 2021). These two concepts have historically often been combined in the literature, but more recent research has attempted to separate the two with objective social isolation being found to have a greater influence on mortality rates, physical health outcomes and rate of cognitive decline than loneliness (Beller & Wagner, 2018a, 2018b; Ejiri et al., 2021; Griffin et al., 2020; Holt-Lunstad & Steptoe, 2022). Social isolation as a health risk across the lifespan has been estimated as being comparable to smoking and obesity in its effects (Holt-Lunstad, 2018; Holt-Lunstad et al., 2010; Wang et al., 2023). Social isolation significantly increases all-cause mortality and dementia risk by approximately 50 per cent (National Academies of Sciences, 2020). It has been found to independently predict premature mortality in several large longitudinal population studies, with strong evidence that social isolation is associated with poorer cardiovascular and mental health outcomes (Holt-Lunstad & Steptoe, 2022).

Several direct and indirect physiological pathways have been proposed to explain this relationship between social isolation and health outcomes over the lifespan (Newall & Menec, 2019). Social isolation has been found to be associated with a higher resting heart rate, higher systolic blood pressure and a less good lipid profile, potentially leading to lessened cardiovascular health (Donovan & Blazer, 2020; National Academies of Sciences, 2020). Higher inflammatory markers in the body, such as C-reactive protein and fibrinogen, indicating longer-term adverse cardiovascular health outcomes, have been found in older adults who are socially isolated (Donovan & Blazer, 2020). The Irish Longitudinal Study on Ageing (TILDA) has found that a larger social network size is associated with lower (healthier) resting heart rate for participants and that those from a lower socio-economic background had a smaller social network size; this association was more pronounced for male participants in this study (McCrory et al., 2016). Research has also found evidence of social isolation reducing immune responses and raising inflammation in the body (Cole et al., 2015; Pressman et al., 2005; E. Walker et al., 2019).

Longitudinal UK biobank data has shown a link between inflammatory and antiviral protein immune-related networks with social isolation and loneliness, with a six-fold higher level of proteins found to be significantly associated with social isolation than those associated with loneliness (Shen et al., 2025). Depression was found to moderate the association between these protein networks and social isolation, but physical activity was not found to influence the association (Shen et al., 2025). Social isolation in that study was measured using three questions (living alone, seeing family or friends less than once per month, not participating in weekly activities), social isolation being present if the person scored 2 or 3.

Social Isolation and Older Adults with Down syndrome. The social networks of older age can often reflect the earlier life circumstances and transitions of individuals, and as such, adults ageing with Down syndrome may have smaller social networks due to less social engagement throughout their life course (Heller & van Heumen, 2013). Adults ageing with Down syndrome may face barriers in social participation and interaction, requiring support with communication and accessing community facilities (van Asselt-Goverts et al., 2015; Wilson et al., 2017). These adults may have smaller friendship networks and identified friends are more likely to be family members or paid staff supports (McCausland et al., 2021; van Asselt-Goverts et al., 2013; Wilson et al., 2017).

A systematic review examining the social networks of people with intellectual disability in the UK found that network sizes remained significantly lower and less diverse than those of their peers in the general population (Harrison et al., 2021). Most network members were family members, support staff or peers with an intellectual disability, with very few other types of network members. Adults living in community settings reported more satisfaction with and diversity within their social networks than those living in more institutional settings. Research in an Irish context also highlights the restricted range of social relationships people ageing with intellectual disability may have (McCausland, 2016; McCausland et al., 2018). IDS-TILDA longitudinal data found most self-reported best friends were composed of peers (63.2%), staff (15.9%) or family members (8.4%), with very few best friends identified outside of these categories (McCausland et al., 2021).

Being in employment can be a significant factor in enhancing social network numbers and diversity (Harrison et al., 2021). Voluntary work in one's community has been highlighted as being an important avenue of social inclusion for people with intellectual disability, particularly for those who may not be employed (Lindsay, 2016). Volunteering can provide important opportunities for participants to experience social inclusion and to meaningfully contribute to their community, being then an integral part of the community relationship networks (Melbøe & Hardonk, 2022).

Physical presence within a community, however, does not necessarily mean that the person with Down syndrome is engaging in meaningful social contact with others in the community; active rather than passive social engagement is required (Bigby & Wiesel, 2019; Harrison et al., 2021; van Asselt-Goverts et al., 2013). People with intellectual disability are often aware of and saddened by their lack of integration into normal community life, feeling a sense of powerlessness around this (Harrison et al., 2021). People with varying levels of intellectual disability may have different needs for social connections, based on their cognitive and communication abilities (Simplican et al., 2015).

In a poignantly titled Australian study "Known well by no-one", Bigby (2008) found that participants with intellectual disability did not form new relationships over a period of 5 years after leaving an institution and moving to community-based living. Over four waves of data collection with 24 participants, it was found that the frequency of family interactions reduced over time as parents died with only 38% having active family member involvement in their lives, few people made friends in their community and 62% had no-one outside the paid staff team who were actively involved in their lives. The stark message from this study was that "physical presence in the community does *not* equate with social inclusion *[author's italics]* and…the impact of social

exclusion may in fact be more pronounced as people with ID [intellectual disability] embark on the ageing process" (Bigby, 2008, p. 156).

Living in Congregated Settings. People ageing with Down syndrome are at risk of moving to a more congregated living setting as their needs increase, at an earlier age than their general ageing peers (Ribenfors et al., 2025; Roebuck, 2021). Research suggests a possible bidirectional relationship between living in an institutionalised setting and social isolation, with lessened ability to communicate, cognitive impairment, lack of choice and isolation from wider community being found to be risk factors (Boamah et al., 2021). The authors note existing social network scales may find it hard to measure social isolation in these settings as residents are surrounded by people but that the "social ecosystems" within these settings may not always be "conducive to strong social integration among residents" (Boamah et al., 2021, p. 628). Further research in this under-researched yet important area is recommended by the authors.

Social Isolation as a Risk Factor for Dementia. Higher levels of social interactions have been linked to greater cognitive reserve, with the suggestion that they require increased cognitive processing and/or the use of compensatory mechanisms in the brain (Fratiglioni & Wang, 2007; Grande et al., 2020; Qiu & Fratiglioni, 2018; Sommerlad et al., 2023; Vernooij-Dassen et al., 2021). The Lancet Commission acknowledges that social isolation may be prodromal to or co-occur with cognitive decline/dementia; it also presents evidence that social contact is both a direct risk factor for dementia and an indirect contributor through its effect on raised risk of hypertension, coronary heart disease and depression (Livingston et al., 2020). There is a relative risk of dementia from social isolation in later life of 1.6 (CI 95%, range 1.3-1.9) with this variable contributing 3.5 percent to overall risk as a weighted population attributable fraction (Livingston et al., 2020).

Whilst more longitudinal evidence is now accruing for the effects of loneliness on increased dementia risk, it has not yet reached the threshold for inclusion in the Lancet Commission model of brain health as a significant risk factor (Livingston et al., 2024; Livingston et al., 2020). A meta-analysis of studies involving 2.37 million participants has found evidence of social isolation being a significant risk factor for cognitive decline and dementia whilst loneliness was not found to be a risk factor (Penninkilampi et al., 2018). Social isolation is recognised as a risk factor for dementia, independent of loneliness (Evans et al., 2019; Shen et al., 2022).

Several studies have found links between social isolation in older people and onset of cognitive decline / dementia, with a potential bidirectional relationship existing between these two variables (Ejiri et al., 2021; Penninkilampi et al., 2018). Withdrawal from social engagement can be part of a broader set of apathetic behaviours related to the onset of dementia, with suggestions that reduced social activity may be prodromal to cognitive decline (Lanctôt et al., 2017; World Health Organization, 2019a). Higher levels of social leisure activities undertaken by a sample of those ageing with Down syndrome was found to moderate change in beta-amyloid levels in the brain and decline in episodic memory over a three-year period (Mihaila et al., 2019).

Varying adverse physiological pathways of influence on cognition arising from social isolation have been proposed, including reduced cognitive reserve due to lessened social activity, increased stress reactivity in the absence of social support with cumulative damage to the hippocampus, reduced ability for bodily repair and maintenance processes and/or possibly increased behavioural risk and poor lifestyle factors (Lubben, 2017; Penninkilampi et al., 2018; Sommerlad et al., 2023; World Health Organization, 2021). Biological studies have shown an association between higher levels of brain-derived neurotropic factor (BDNF) and higher levels of social support, with BDNF being protective in terms of enhancing neuroplasticity and repair (Salinas et al., 2017). UK biobank data has shown that social isolation contributes a significant additional risk for dementia onset, over and above an individual's genetic risk, with lower grey matter volume detected in temporal, frontal and hippocampal brain regions (Elovainio et al., 2022; Shen et al., 2022; Sommerlad et al., 2023). However, the exact physiological mechanisms of influence remain unclear (Shen et al., 2022).

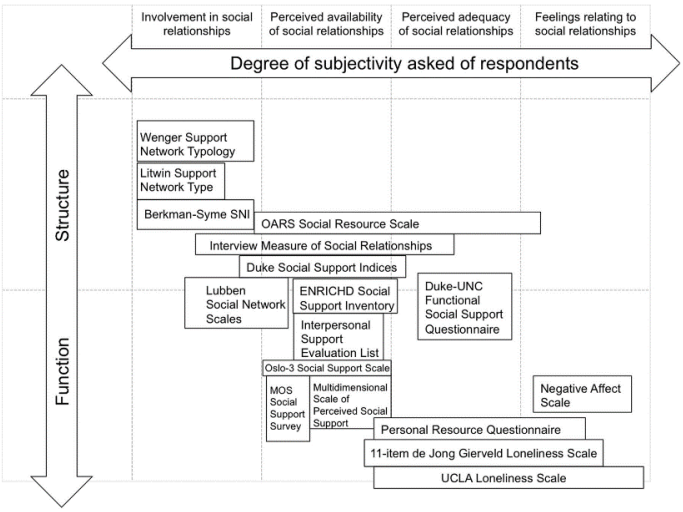
Social isolation measurements used in longitudinal studies are most frequently assessed as social activity (involvement in local clubs and other community groups, frequency of visits with family and friends, participation in voluntary work, attendance at religious and cultural activities) and social networks (number of people in the network, frequency of interaction with network, marital status and living arrangements) (Evans et al., 2019; Penninkilampi et al., 2018). There is heterogeneity in the measurement of some indicators (e.g. measurement of frequency of interactions, diversity of cultural and leisure activities) whereas other indicators are more specific in measurement and thus less varied across the studies (voluntary or paid work, number of people within social network and membership of social and community groups) (Evans et al., 2019).

Measurement of Social Isolation. A lack of operational definitions of social isolation and a lack of agreed standardised scales has been identified, leading to difficulties in comparability across studies (Courtin & Knapp, 2017; Ejiri et al., 2021; Newall & Menec, 2019; Valtorta et al., 2016a). A classification structure for the extant measurement scales has been proposed to aid researchers in choosing between functional (qualitative) and structural (quantitative) aspects of social connections and the degree of subjectivity required of participants in replying to each scale (Valtorta et al., 2016a). The social connection scales were mapped onto a diagram showing their relative focus on structure of social relationships (number and type of people connected with) vs. the function of social relationships (type of relationship with people connected with) and the degree of subjectivity required in replying to the scale (See Figure 2.8). This mapping provides a very useful overview for researchers in choosing measurement scales based on their operationalisation of the concepts of social isolation and loneliness. It enables comparison of measurement tools arising from different disciplines and places them into an overarching conceptual framework (Valtorta et al., 2016a).

Several well-validated scales are recommended by the Consensus Statement of National Academies of Sciences (2020) to measure social isolation, including the Berkman-Syme Social Network Index (Berkman & Syme, 1979) and the Steptoe Social Isolation Index (Steptoe et al., 2013). These scales measure the extent of contact a person may have in terms of intimate relationships, friends and family contact and broader community integration.

Figure 2.8

Continuum of objective to subjective social connection assessment tools



Note: Assessment tools for social connections measurement ranging in subjectivity. From: "Loneliness, social isolation and social relationships: What are we measuring? A novel framework for classifying and comparing tools", by Valtorta et al. (2016a), *British Medical Journal*, 6 (4), Figure 1, p.e010799. https:/doi.org/ 10.1136/bmjopen-2015-010799. Copyright 2016 by British Medical Association.

An objective social isolation typology has been developed (based on an adaptation of the Berkman-Syme Social Network Index) as part of the representative and longitudinal National Health and Ageing Trends Study (NHATS) in the US (Cudjoe et al., 2020). The authors formed a typology of objective social isolation composed of four domains: living arrangement (living with at least one other person), core discussion network size (talking to two or more people about important personal items in the past year), religious attendance (participating in organised religious services in the past month) and social participation (participating in other community activities in the past month, including voluntary work). Each participant received a score of 1 for each domain in which there was a positive answer. Scoring for participants overall was divided into the categories of severely socially isolated (sum score of zero), socially isolated (sum score of 1) or socially integrated (sum score of 2 or more). Approximately 25% of the study participants were adjudged to be socially isolated, based on this typology (Cudjoe et al., 2020).

The social isolation typology as outlined above is a good fit for the data collected across the first three waves of the IDS-TILDA study. The categories align well as both studies are nationally representative longitudinal studies of older adults, examining a broad range of indicators such as daily functioning, economic and health status and well-being. The NHATS social isolation typology investigates objective social isolation and so offers a clear conceptualisation of the concept, differentiating it from perceived social isolation / loneliness. This enables the researcher to examine the influence of social isolation on the dependent variable of cognitive decline, using a clearly defined measurement tool based on previous research and adaptation of a well-recognised and validated existing scale (Berkman-Syme Social Network Index). As most Irish people with intellectual disability have not been married, the adaptation of the question on marital status to living arrangement in the NHATS typology aligns well with the lived reality of people ageing with intellectual disability. It can be seen from the mapping framework (Valtorta et al., 2016a) that the Berkman-Syme Social Network Index and the NHATS typology are placed within the less subjective responses and the more structural focus of measurement scales of social isolation.

Difficulties arise in relation to measuring social isolation in people ageing with Down syndrome. As already mentioned, most people with intellectual disability historically have not gotten married. Their life experiences may be very different from the general population, in terms of the opportunity to form and develop meaningful social networks. They may live with others, but this may be a function of residing in a supported living or institutional setting and may not reflect a choice made of life companions. People ageing with Down syndrome may not have had the same opportunities to foster family and friendship links over the years, in comparison to their peers in the general population. Issues with communication and behaviour may mean that they find it more difficult to connect meaningfully with families and friends when they do meet socially.

There is a lack of research and a lack of standardised measurement approaches into the social networks and social isolation of this population (Harrison et al., 2021). There is a need to develop a validated social isolation scale for this population that considers the unique characteristics encompassing social isolation for this group and takes account of their unique life experiences throughout their lifespan. This will provide more accurate epidemiological data on rates of social isolation for this population, which is currently lacking.

2.6.9 Physical Inactivity

Physical activity can be defined as any activity a person engages in that raises their heart rate above its usual resting rate level, engages the skeletal muscles and increases energy expenditure (Caspersen et al., 1985; Daskalopoulou et al., 2017). This could be engaging in exercise (e.g. walking, swimming), routine household activities (e.g. gardening, cleaning) or community engagement (e.g. walking around shops at a brisk pace, employment tasks, cycling to work). It is accepted that physical activity greatly improves all aspects of health and reduces mortality from any cause (Bull et al., 2020; Donoghue et al., 2016). Recommended levels of physical activity for older adults are 150-300 minutes of moderate intensity or 75-150 minutes of vigorous intensity aerobic activity per week (Bull et al., 2020). Globally, up to 25% of the population is not sufficiently physically active, with up to one third of Irish adults not reaching physical activity recommendations (Bull et al., 2020; Donoghue et al., 2016; World Health Organization, 2020b). Studies worldwide have found increasingly low levels of daily physical activity as people age, some of which may be related to onset of illness or disability (Barnes et al., 2013; Koritsas & Iacono, 2016; Livingston et al., 2024; Marconi et al., 2018).

High rates of physical inactivity have been reported in older adults with one large meta-analysis reporting a prevalence rate of 43% (Silveira et al., 2022). Physical activity has an important role in positive ageing, reducing rates of obesity, chronic conditions, depression and cognitive decline (Daskalopoulou et al., 2017). Physical activity, along with smoking and alcohol, has been identified as one of the key determinants of healthy ageing (Peel et al., 2005). A stronger association across studies has been found of the influence of physical activity on biomedical models of healthy ageing (functional capacity, absence of disease) than psychosocial models (life satisfaction, social engagement) (Daskalopoulou et al., 2017).

Despite increases in physical activity levels over the years, just over 50% of people ageing with Down syndrome in Ireland are engaging in the recommended level of physical activity, with health issues being cited as the main reason for less activity (McCarron, 2023). High levels of sedentary behaviour have been reported in this population (Hilgenkamp et al., 2012; Hsieh et al., 2017; Lynch et al., 2021; Oreskovic et al., 2020). Higher support needs, living in a residential setting and being older have all been found to predict higher levels of physical inactivity in this cohort (Dairo et al., 2016). Gender differences have also been found, with women more likely than men to be physically inactive, as in the general population (Dairo et al., 2016; Westrop et al., 2019). Lower perceived self-efficacy, motivation and levels of social support have been found to influence these women's lower levels of physical activity (Edwards & Sackett, 2016).

Lower levels of social engagement have been found to be significantly associated with lower levels of physical activity in people with intellectual disability, including Down syndrome (Hsieh et al., 2015; Hsieh et al., 2017). Other barriers to exercise in this population are lack of access to transport, lack of social support and a dearth of accessible exercise options in their community (Mahy et al., 2010; Oreskovic et al., 2020). People with Down syndrome have been found to have lower levels of physical activity, poorer aerobic capacity and poorer muscle strength, agility and balance than their peers in the general population (Barnard et al., 2019; Mendonca et al., 2010). Higher levels of physical fitness in older adults with intellectual disabilities, including Down syndrome, is associated with significantly better mental and physical health and decreased mortality over a five-year period (Fleming et al., 2022; Oppewal & Hilgenkamp, 2019).

Measurement of physical activity levels in this population can be difficult with over – or under-reporting and reliance on proxy report of caregivers (Lynch et al., 2021). A comparison between an objective measurement of physical activity and self-reporting of physical activity by older adults with intellectual disability found only low to moderate agreement, with overestimation of moderate and vigorous activity levels and underestimation of lower intensity activity levels, highlighting potential inaccuracies in use of subjective/report-based measurements of this construct (Lynch et al., 2025).

Physical Inactivity as a Risk for Dementia. Research on physical inactivity and later life dementia risk is variable and complex, with a potentially bidirectional relationship between the two (Livingston et al., 2024; Livingston et al., 2020). There is evidence of a protective effect of physical activity against the onset of AD, with a relative risk for dementia from physical inactivity in later life of 1.4 (range 1.2-1.7 at 95% CI) (Livingston et al., 2020). Adults with normal cognitive function are strongly recommended to engage in regular moderate physical activity to reduce the risk of cognitive decline, with more evidence for aerobic exercise rather than resistance training in this regard (Carta et al., 2021; Consorti et al., 2021; Duzel et al., 2016; World Health Organization, 2019a). Older adults who engage in regular physical activity have been found to have better cognitive functioning than those who are less active, even with the same degree of neuropathology due to dementia (Fleming et al., 2025).

Physical inactivity has been identified as a “key modifiable factor for accelerated ageing and dementia” along with having significant influences on levels of other important dementia risk factors such as levels of depression, diabetes, obesity and hypertension (Tari et al., 2025, p. 1093). There is a lack of clarity in the literature, however, as to what level/intensity and duration of exercise is required to produce positive health benefits in those ageing, considering what is

practical for an ageing population with potential comorbidities to achieve in terms of regular exercise (Carta et al., 2021).

An association between physical activity and increased executive functioning has been found in adolescents and young adults with Down syndrome, including improvements in reaction time, attention switching, cognitive planning, working memory and semantic language fluency (Chen et al., 2015; Chen & Ringenbach, 2016; Holzapfel et al., 2016; Ptomey et al., 2018; Ringenbach et al., 2016). A number of these studies used assisted cycling therapy as the exercise intervention, originally developed for people with Parkinson's Disease (Ringenbach et al., 2013). It has been suggested that this therapy this may be a useful intervention for adults ageing with Down syndrome to reduce risk of cognitive decline and AD, as it has been shown to promote neurogenesis (Ringenbach et al., 2015).

Positive changes in white matter and hippocampal volume in the brain, along with better global cognitive functioning, have been observed with increased levels of physical activity in this population (Fleming et al., 2021; Peven et al., 2022). A significant association was found between engaging in moderate or high levels of exercise and lower levels of assessed changes in memory, personality, behaviour and everyday living skills over a testing period of two years in adults with Down syndrome (Pape et al., 2021). It is recommended that other biopsychosocial variables that may interact with or moderate the effect of physical activity on the brains of this population be explored (Pape et al., 2021). A recent study found that adults with Down syndrome who engaged in higher levels of physical activity had less measured cognitive decline than those who were less active, even with similar levels of amyloid in their brains (Fleming et al., 2025). Higher levels of physical activity were not, however, associated with a lower overall amyloid burden in the brain, unlike findings for those ageing in the general population. Study authors query if the genetically driven amyloid accumulation for people with Down syndrome is stronger than the protective effect of physical activity or if other biomarkers for DSAD (e.g. tau pathology) may be more reduced by higher levels of physical activity (Fleming et al., 2025).

Whilst the effect of physical activity on both protection of brain structures and promotion of neuronal plasticity is now appreciated, more research is required about the underlying physiological pathways through which this is enacted (Consorti et al., 2021; Steventon et al., 2020; Stillman et al., 2016). Some potential mechanisms have been elucidated which may explain the association. Skeletal muscle, when exercised, produces myokines which have a neuroprotective function in the brain, including promoting neurogenesis and angiogenesis in the hippocampus (Barbalho et al., 2020; Consorti et al., 2021; Di Liegro et al., 2019; Steventon et al., 2020). Physical

activity may lead to increased cerebral blood flow and improved operation of the Blood-Brain-Barrier, limiting permeability of damaging substances to the brain (Consorti et al., 2021; Gligoroska & Manchevska, 2012; Mela et al., 2020; Prakash et al., 2015; Steventon et al., 2020; Vecchio et al., 2018). Aerobic exercise has been shown to increase the levels of brain-derived neurotrophic factor (BDNF) and insulin-like growth factor (IGF-1) in the brain, influencing increased neurogenesis and spatial memory operations (Di Liegro et al., 2019; Duzel et al., 2016; Parrini et al., 2017; Prakash et al., 2015; Stillman et al., 2016; Vecchio et al., 2018). Physical activity lowers inflammation in the brain, through increased microglial activity and enhances structural and functional connectivity along with synaptic plasticity, increased BDNF secretion and increased hippocampal neurogenesis, all of which can reduce with age and contribute to neurodegeneration (Tari et al., 2025). Numerous beneficial physiological mechanisms for brain health are activated through increased physical activity (Tari et al., 2025).

2.6.10 Diabetes

Globally, it is estimated that 10.5% of adults have diabetes, projected to rise to a prevalence of 12.2% by 2045, with the greatest relative increase expected to occur in middle-income countries (Sun et al., 2022). A recent UK population-based study found a threefold increase in incidence of diabetes between 1990-2020, based on electronic health records (Aslam et al., 2022). A diabetes prevalence rate of 6.4% has been reported in the ageing Irish population (Cominetti et al., 2022). Type 2 diabetes represents approximately 90% of all diabetes diagnoses (Tyrer et al., 2020).

A mixed picture of the relevant prevalence of diabetes in people with Down syndrome in comparison to those in the general population presents itself. Some studies have found higher diabetes rates in people with Down syndrome, particularly in women, with prevalence estimates varying from four to ten times greater than the general population (Aslam et al., 2022; Flygare Wallén et al., 2018; McVilly et al., 2014). However, a recent large scale retrospective epidemiological study found a significantly lower rate of all types of diabetes in people with Down syndrome (10.4%) than in age-matched controls (13.2%) (Baksh et al., 2023).

Adults with Down syndrome have more visceral (abdominal) fat distribution than their peers in the general population and increased visceral fat levels contribute to increased systematic inflammation, a primary driver of type 2 diabetes (Moreau et al., 2021). They also have increased incidence of non-alcoholic fatty liver disease, which promotes insulin resistance in the body (Loomba et al., 2012). Some genes that are over-expressed in Down syndrome may also contribute

to hyperglycemia and insulin resistance (Aslam et al., 2022). The incidence of type 2 diabetes is twice as high in people with Down syndrome who are obese than those who are overweight or normal weight (Aslam et al., 2022). Recent clinical guidelines recommend screening for Type 2 diabetes in this population every 3 years from the age of 30 years, whilst those who are obese should be screened every 2 to 3 years from the age of 21 years (Tsou et al., 2020). People with intellectual disability, including Down syndrome, have been found to have a lesser ability to report symptoms or to self-manage their diabetes, with adequate screening and management supports being very important for this population (House et al., 2018; Taggart et al., 2018).

Diabetes as a Risk Factor for Dementia. A diagnosis of diabetes in midlife confers a 60% increased risk of developing any type of dementia and a 40% increased risk of developing nonvascular dementia for both genders (Chatterjee et al., 2016). Women with diabetes were found to have a significantly greater risk (18%) of developing vascular dementia than men with diabetes (Chatterjee et al., 2016). Diabetes was found independently associated with cognitive decline over a six-year period in an ageing Irish population sample (Cominetti et al., 2022). A 1% increase in lifetime risk of developing dementia from diabetes onset in later life was found in the Lancet model (Livingston et al., 2020). Similarly to hypertension, new evidence is emerging that diabetes onset in midlife is a higher risk factor for developing dementia than diabetes onset later in life; suggesting that duration of the illness may have a systemic and neurodegenerative effect (Livingston et al., 2024).

Insulin contributes to synaptic plasticity and learning and memory processes in the brain (Verdile et al., 2015). Glucose metabolism and neuronal development in the brain is regulated by insulin signalling; dysregulation of this process results in increased inflammation in the brain (Carlsson, 2010; Dierssen et al., 2020; Kubis-Kubiak et al., 2020; Makino et al., 2021). Type 2 diabetes contributes to a reduction in existing cognitive reserve and a lowered ability to deal with cerebrovascular incidents (Pal et al., 2018). Diabetes also adversely affects the microvascular structure in the brain, including capillary membrane thickening, microinfarcts and generalised atrophy, with resulting reduced cerebral blood flow (Carlsson, 2010). Hypertension and diabetes have a synergistic effect on increasing cognitive decline and risk of dementia, as does depression and diabetes (Chow et al., 2022; Feinkohl et al., 2015; Pal et al., 2018; Whitelock et al., 2021).

Brain insulin resistance is present in the brains of people with Down syndrome prior to AD neuropathology, with higher levels of neuroinflammation present from a young age; representing a shared clinical feature between metabolic disorders and AD (Dierssen et al., 2020). Several markers of dysregulated insulin pathway functioning are shared between younger people with

Down syndrome and those diagnosed with AD (Dierssen et al., 2020). This brain insulin resistance may support the development of both the metabolic disorder of diabetes and the neurodegenerative disorder of AD in this population (Head et al., 2018; Tramutola et al., 2020). The genetic cause for Down syndrome may lead to a higher risk for development of diabetes which in turn may contribute to the higher risk for DSAD in later life (Dierssen et al., 2020).

2.7 Conclusion

Positive ageing covers many aspects of a person's life, including maintenance of cognitive functioning/brain health. This is particularly pertinent to the population ageing with Down syndrome, given their significantly increased dementia risk. The Lancet model of dementia risk reduction (Livingston et al., 2020) has not been tested in this population to date. Those ageing with Down syndrome and living with dementia may also benefit from reducing these risk factors.

Many of the biopsychosocial risk factors for dementia have a synergistic or mediating effect on each other in their effects on brain health, contributing to a complex picture of the psychophysiological processes through which neurodegeneration leading to dementia occurs over time. Given the significantly elevated genetically driven risk people with Down syndrome have of developing AD, there may be less overall influence on their dementia risk from the risk factors outlined by the Lancet Commission (Livingston et al., 2024; Livingston et al., 2020; Livingston et al., 2017). This cohort also present with a differing risk profile to the general population, with lower rates of smoking and alcohol use, lower levels of hypertension and educational attainment and higher levels of physical inactivity, obesity, hearing loss and depression, some of these related to their underlying syndromic profile. This means the Lancet brain health model may not directly map onto the life experience of this population. There is a need to investigate the biopsychosocial dementia risk profile of the ageing population with Down syndrome, using the Lancet risk factor framework, to develop more specific recommendations for this group to support positive ageing and brain health.

The aim of this thesis is to explore the influence of various biopsychosocial factors on the risk of developing dementia in a sample of people ageing with Down syndrome. It will examine if the data in this sample shows a differing risk profile than that pertaining to the general population, as appears to be indicated by the evidence base in this literature review. It will examine if modifying these risk factors can slow the onset of dementia in this population, despite their genetic inheritance. Findings from this research will help to signpost supports for reducing dementia risk and supporting positive ageing for people with Down syndrome.

Chapter 3: Methodology

"Time is the best diagnostician"

(Martin & Romero Ortuño, 2019, p. 481)

3.1 Introduction

Positive ageing is a complex process, encompassing many biological, psychological and social determinants across the lifespan. Longitudinal studies give stronger evidence of causal association than the snapshot in time provided by cross-sectional approaches. National longitudinal studies of ageing support the investigation of early indicators of health conditions from an earlier stage in the lifespan, e.g. midlife, thus enabling more effective health promoting interventions at an earlier age (Martin & Romero Ortuño, 2019). Several longitudinal ageing studies have provided evidence of important modifiable risk factors across the life span for dementia, with these studies incorporating a holistic biopsychosocial approach to exploring ageing and brain health (Martin & Romero Ortuño, 2019). Findings from these longitudinal national ageing studies support governments and health care providers in anticipating future needs and health challenges of an ageing population, including health promoting interventions to support positive ageing (Kaiser, 2013).

The Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing (IDS-TILDA) captures the life experience of people ageing with intellectual disability in Ireland, with longitudinal data across 5 waves on health and lifestyle factors that may influence healthy brain ageing. The richness of this data source and the fact that it is nationally representative means that it offers the opportunity for in-depth study of the factors affecting health and patterns of morbidity and mortality over time in this population (McCarron et al., 2022). Variables for this study were derived from IDS-TILDA across the first 4 waves over a period of 11 years from 2009 – 2020.

The research aim is to explore the influence of various biopsychosocial factors on the risk of developing dementia in a sample of people ageing with Down syndrome. Ten dementia risk factors, based on the Lancet dementia risk factor model (Livingston et al., 2020), were derived from longitudinal data collected from this Irish population sample. These ten independent variables were: no educational attainment, hearing loss, hypertension, depression, diabetes, obesity, smoking, frequent alcohol consumption, social isolation and physical inactivity. The ten

independent variables were tested using logistic lagged regression analysis for their longitudinal influence on the dependent variable of clinical diagnosis of dementia.

This Methods section will:

- Give an overview of the Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing (IDS-TILDA), including an overview of the values framework, ethics procedures, participant sampling and sample retention across waves of data collection.
- Describe the data collection procedures, including this researcher's contribution, this study's research sample and the data used in this study from the research waves.
- Describe the methods used to derive the independent variables (dementia risk factor profiling and demographics of sample)
- Describe methodology for the derivation of demographic factors, dementia diagnosis (dependent variable) and dementia risk factors (independent variables).
- Describe the statistical analyses used to develop the modelling (including chi-squared analyses and lagged logistic and linear regression analyses).

3.2 The Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing (IDS-TILDA)

The Irish Longitudinal Study on Ageing (TILDA) was set up in 2009 to collect nationally representative data on the health and social care needs of older people in Ireland, with the aim of collecting longitudinal waves of this data every few years. The Intellectual Disability Supplement to TILDA, named IDS-TILDA, began collecting data in 2009 on the health and social care needs of a representative sample of older people ageing with intellectual disability in Ireland (McCarron et al., 2022). This is the only longitudinal study on ageing in people with intellectual disability that can directly compare the ageing experience of people with an intellectual disability to the general population with the most recent published data wave being Wave 5 in 2023 (McCarron, 2023; McCarron et al., 2022).

IDS-TILDA study aims (McCarron et al., 2022) include:

1. Understanding the health status and needs of people ageing with intellectual disability
2. Gaining insight into use of health care services by people ageing with intellectual disability
3. Identifying differences in health between those ageing with intellectual disability and those ageing in the general population in Ireland, by comparing findings with the TILDA study
4. Informing development of health policy and service provision at national level

IDS-TILDA collects data on a broad range of biopsychosocial indicators across six domains (McCarron et al., 2022). The conceptual framework has remained intact across each wave; however, some questions have been revised or deleted, following consultation with the expert panel. A health fair to measure objective health indicators was added in Wave 2, which added to the rigour of the study (see Appendix B for conceptual framework overview). The health fair is held in addition to the interview information collected and gives participants the opportunity to have objective health indicators measured, including cognitive and cardiovascular functioning, mobility, gait, vision and hearing.

3.2.1 Values underpinning IDS-TILDA conceptual framework

Several values are integral to the development and delivery of the longitudinal waves of IDS-TILDA. These include the importance of inclusion of people with intellectual disability in the design and development of the study, along with the importance of fully informed consent to participate in the research (see Appendix C for overview of values framework).

3.2.2 Ethical Approval for IDS-TILDA data collection

The rights of study participants to be treated with dignity and respect and to have their welfare protected is a central ethical tenet of research (World Health Organization, 2020a). Research involving vulnerable participants, such as IDS-TILDA, must be even more ethically rigorous to ensure that the principles of informed consent, benefits outweighing risks for participants and fair sampling procedures are sufficiently adhered to (McCausland et al., 2024).

Initially, an IDS-TILDA study protocol was developed with reference to internal and external stakeholders, including a Scientific Advisory Board, and engagement with people with intellectual disabilities themselves (Public and Patient Involvement-PPI) (McCausland et al., 2024). This detailed protocol was then sent for review and approval by the Trinity College (TCD) Faculty of Health Sciences Research Ethics Committee as well as the ethics committees of the disability service organisations supporting potential study participants (McCausland et al., 2024). From Wave 4, an extra ethics application was sent to the National Health Research Consent Declaration Committee regarding the process to facilitate consent for a person with a higher level of disability who may not be able to provide informed consent for themselves (McCarron et al., 2022; McCausland et al., 2024).

3.2.3 Participants in Original IDS-TILDA Research Sample

The original sample for IDS-TILDA was drawn from the National Intellectual Disability Database (NIDD). The NIDD was set up in 1995 to collect information on the demographic profile

of all people with intellectual disability in Ireland and their level of support need and utilisation of service provision. Audits have found the accuracy of the information collected by the NIDD to be good (Dodd et al., 2010), hence it is deemed a nationally representative database for sampling.

Initially, 1800 potential participants were selected from all those aged over 40 on the NIDD through the release of their personal identification numbers to the study. This preserved the confidentiality of those invited to participate until they decided to take part in the study. Wave 1 of IDS-TILDA recruited 753 participants from this original participant sample, with 150 of these having Down syndrome (McCarron et al., 2022), all of whom were invited to participate in future waves, if possible and consenting. Potential participants were given the option to consent to participate in the research with the aid of accessible consent materials; if this was not possible, proxy consent by a family member/legal guardian was sought (McCarron et al., 2022). The Wave 1 original sample of N= 753 made up 8.9% of the total population of people aged over 40 with intellectual disability in Ireland with representative demographic and geographic characteristics (McCarron et al., 2022).

3.2.4 Retention Across Sample Waves

Retention of participants with intellectual disability across waves of data collection is vital in longitudinal research designs to support greater understanding of changes in patterns of health and wellbeing over time, supporting the power of the research to make statistical inferences and increasing the generalisability of the results (McCarron et al., 2022). Studies have found that several retention strategies can be incorporated into longitudinal study design, including study reminders, minimising participation burden, emphasising the benefits for participations and incorporating PPI (Abshire et al., 2017; Crocker et al., 2018; Teague et al., 2018; Tomlinson et al., 2019). Strategies to encourage health agencies and services to continue to support participants to engage with longitudinal data collection include communicating study benefits for participants, sharing research findings and policy implications and connecting with a key stakeholder in each agency to support study participation (Pinto et al., 2018).

There was good retention across Waves 1-4 of IDS-TILDA data collection (2009-2020). Just over two-thirds of the original sample was still participating in Wave 4 (N=506, 67.2%). Most of the attrition in the sample was due to death (N=172, 69.6%), with only one third of the attrition due to withdrawal from the study (N=75, 30.5%). This means that only approximately 10% of the original sample attrition was due to withdrawal by Wave 4 and represents a very high retention rate of participation for a longitudinal study (McCarron et al., 2022).

3.3 Data Collection Procedures

There were three main elements in data collection for each wave (McCarron et al., 2022). Each element had secure data collection and storage procedures attached, to meet the highest standards of confidentiality and safety of data for participants.

1. Participants (with their supporters and/or their proxy respondents if necessary) took part in a face-to-face interview with a Field Researcher using a Computer Assisted Personal Interview (CAPI) programme on a laptop. Information was inputted during the interview and resulting data uploaded to secure data retention system, overseen by a data co-ordinator.
2. Participants and their supporters filled out a Pre-Interview Questionnaire (PIQ) before the face-to-face interview. This information was given a study identification number to ensure anonymity and posted via secure courier to the data co-ordinator.
3. From Wave 2, a Health Fair, measuring objective health indicators, has been carried out on every second wave of IDS-TILDA data collection. This Health Fair was facilitated by trained specialist nurses and all information collected was returned to data co-ordinator.

3.3.1 Researcher Contribution to Data Collection

I interviewed 31 participants in Wave 4 as a field researcher. Each participant was interviewed with the full CAPI protocol and set of questions for Wave 4. I received 3 days training from experts in the field in administering the CAPI protocol and training from people with intellectual disability on how to undertake the interviews.

An awareness of the dynamic nature of process consent (Kadam, 2017) always informed my approach during the interview process collecting the personal data of each participant. I only proceeded with interviews if the person expressed a willingness to participate throughout the process. I was aware at all times of the importance of this process being a positive experience for participants and their supporters, both as promoting good practice during the interview and to promote retention of participation across the waves. I was able to use my existing clinical interview skills to maximise participation and relaxation of participants during each interview. Every effort was made to hold interviews at a time, location and pace that suited each participant and their supporters.

3.3.2 Participants in this Research Sample

In Wave 1 of IDS-TILDA there were 150 people with DS out of a total sample of 753. These participants formed the research sample for this study across Waves 1 – 4 of IDS-TILDA. The IBM

SPSS Statistics package Version 28.0.1.1 (15) was used for data recording and analysis. Table 3.1 gives an overview of baseline demographic information from Wave 1.

Table 3.1

Baseline demographic profile of participants in Wave 1

Total and Missing N for each variable is presented, along with Variable Sub-Group n and percentage

Variable		Total N	n	%	Missing n
Gender		**150**			0
	Male		65	43.3	
	Female		85	56.7	
Age Bands		**150**			0
	40-49		81	54	
	50-59		56	37.3	
	60+		13	8.7	
Level of ID		**139**			11
	Mild		21	15.1	
	Moderate		76	54.7	
	Sev/Prof		42	30.2	
Residential Status		**149**			1
	Ind/Family		30	20.1	
	Group		63	42.3	
	Congregated		56	37.6	
Dementia Diagnosis		**150**			0
	Yes		14	9.3	
	No		136	90.7	

3.3.3 Use of Data within the Waves

Constant Demographic Data (Gender and Level of Intellectual Disability) was obtained for Participants from Wave 1, with Residential Status recorded for each wave. Dependent Variable of having a Dementia Diagnosis was recorded for each Wave, up to Wave 4, with total sample comprising of the people who were reported as having been diagnosed across one of the data collection waves.

The Independent Variables of Dementia Risk Factors are derived from the first three waves of data collection (Waves1-3) to provide lagged variables for the lagged logistic regression model. Educational attainment to young adulthood, being a constant across the waves, was taken

from Wave 1 data. This aligns with the Lancet model of dementia risk with level of education attained in childhood being treated as an early life risk factor for dementia later in the lifespan.

3.4 Derivation of Demographic Factors

The Gender, Level of ID and Residential Status of each participant was recorded by the interviewer during each CAPI interview. Gender and Level of ID from Wave 1 was taken as the demographic variables for the model, given that these factors remain constant in a person's life. Gender was coded as 1 for male and 2 for female. Level of ID was coded as reported within the Mild (1), Moderate (2) or Severe/profound (3) range of functioning. These were inputted into the Master Dataset containing information on independent and dependent variables for the model across all the waves for each participant with Down syndrome (N=150).

Residential Status may have changed across the waves for participants, so a variable of Residential Status was derived for each participant for each wave to reflect this. Three categories of residential status were recorded: living independently/family home, living in a community group home setting or living in a more congregated residential setting (coded 1,2,3 for SPSS). Three residential status variables, capturing each person's residential setting in each wave, were derived.

3.5 Derivation of Dementia Diagnosis

Participants who were diagnosed with Dementia at any point in Waves 1-4 were coded as 1, whilst those who were not diagnosed with Dementia throughout the data collection waves were coded as 0. The Wave in which each person received a diagnosis was also recorded coding of 1-4 to denote the relevant wave. Those who did not receive a diagnosis in any wave were inputted as missing for this variable.

3.6 Derivation of Dementia Risk Factors

The following risk factors were derived from the first three waves of data collection, to evaluate their influence on dementia diagnosis for the 150 participants across the waves. In each instance, the risk factor being present for a participant was coded as '1' and the risk factor being absent was coded as '0' on SPSS. This is the preferred format for SPSS of 1=Yes and 0=No (Pallant, 2020).

3.6.1 No Educational Attainment

Educational attainment was already available for participants as it was noted in the PIQ for Wave 1. This variable was taken directly from the Pre-Interview Questionnaire form which asked what the highest level of completed education each participant had achieved. The categories on the form were: some primary level education, primary level or equivalent completed, intermediate/junior/group certificate or equivalent, leaving certificate or equivalent, diploma/certificate, primary degree or postgraduate/higher degree.

These categories were collapsed and recoded initially as no education, having primary education and having secondary or higher education (coded 0,1,2). However, there was only one person with Down syndrome in the sample that had secondary or higher education (coded 2) so the categories were further collapsed into 'no education' (1) and 'some education' (0). To reduce missing data, Waves 2 and 3 were checked for any additional data entered in later waves regarding the educational attainment of each individual participant.

3.6.2 Hearing Loss

Questions on a participant's hearing status were covered in the Physical Health section of the CAPI interview in all 3 waves. Participants were asked about the status of their hearing, with a hearing aid if the person wore one or without a hearing aid. This self- or proxy-reported hearing status was coded into categories of Excellent, Very Good, Good, Fair, Poor or Deaf.

The hearing status categories of Excellent, Very Good or Good were collapsed into a category of No Hearing Loss (coded as 0=No) and the categories of Fair, Poor, or Deaf were collapsed into a category of Has Hearing Loss (coded as 1=Yes) for all waves. This covers hearing status as being either without hearing aid or hearing supported by a hearing aid.

3.6.3 Hypertension, Depression & Diabetes

These variables were constructed based on a reported clinical diagnosis of the condition AND/OR medications prescribed for the condition. The researcher consulted with a Consultant Psychiatrist and a Pharmacist, Trinity College, about proposed variable parameters. Both clinicians agreed with the proposed use of clinical diagnosis of the condition AND/OR medications prescribed for the condition as being the correct parameters to use in constructing these illness variables for this study. These are objective indicators based on accepted medical and psychiatric protocols for diagnosis and prescribing, so are standardised across the sample.

The medication data consist of a cleaned dataset of clinical diagnosis and medication data for all illnesses as reported from the PIQs and constructed by pharmacists in the team.

Medications were coded using the World Health Organisation (WHO) Anatomical Therapeutic Chemical Classification (ATC) System. All PIQ medication entries and ATC Codes input into the statistics software SPSS were independently reviewed and confirmed by two pharmacists. The ATC system was developed to standardise the classification of medications across the world and continues to be overseen by the World Health Organisation (World Health Organisation, 2024). The medication dataset indicated if a participant had a clinical diagnosis of any of the health conditions of Hypertension, Depression and Diabetes and /or was on medication for these health conditions. The coding for all was 1 for having the health condition and 0 for not having it.

3.6.4 Alcohol

In the first and second waves of the data, participants were asked about their frequency of alcohol intake. Those who answered that they drank alcohol on 3 or more days a week or more frequently were viewed as having frequent alcohol consumption, coded as 1, risk factor being present. Questions on alcohol frequency were not included in Wave 3. Given the very low prevalence of frequent alcohol consumption reported across Waves 1 and 2 in the sample, a decision was made to code Wave 3 frequent alcohol consumption status as the same as reported Wave 2 status.

3.6.5 Obesity

Height and Weight Questions for each participant were asked in PIQ, these were then calculated by IDS-TILDA data co-ordinators for BMI. BMI was also measured directly as part of Health Fair data from Wave 2. There was a variable already present in all three waves for BMI for participants.

In Wave 1 the obesity variable was reviewed with all those with BMI ≥ 30 coded as obese plus any that were 29.5+, rounding up to 30. Those at 29.4 or lower BMI were coded as not being obese. The same initial coding strategy using BMI was undertaken for the obesity variable in Waves 2 and 3; however, there was a large amount of missing data for this variable in these two waves. Waist circumference, another relevant variable measured in the health fair, was a new variable in Waves 2 and 3. Waist circumference was used as a proxy for BMI for Waves 2 and 3 where BMI data was not available, to reduce missing data. In the IDS-TILDA data, people were coded at various levels of disease risk for their weight circumference (1= normal, 2= increased risk, 3= substantially at risk). All those coded as 3 or higher for waist circumference (‘substantially at risk’ for adverse health effects) were coded as obese (1) and those coded at 2 or lower (normal or at risk) for waist circumference were coded as not obese (0).

A chi-squared analysis was run to explore how well the BMI and Waist Circumference scores aligned. In Wave 2, the Chi-Squared Test for Independence (with Pearson Chi-Squared Value) indicated a significant association between obesity status as categorised by BMI score and level of risk as indicated by Waist Circumference Measurement, X^2 (2, n=406) = 136.887, p=<.001, Cramer's V = .581, indicating a large effect size. No cases classified as having a Normal Waist Circumference were classified as Obese from their BMI Scores.

In Wave 3, the Chi-Squared Test for Independence (with Pearson Chi-Squared Value) indicated a significant association between obesity status as categorised by BMI score and level of risk as indicated by Waist Circumference Measurement, X^2 (2, n=258) = 58.740, p=<.001, Cramer's V = .477, indicating a medium (nearing to large) effect size. Only 1 person was classified as being obese from their BMI scores whilst also being measured as having a waist circumference within the normal range. Therefore, the use of Waist Circumference in Waves 2 and 3 as a proxy for BMI appears to be justified to reduce missing data.

3.6.6 Smoking

Smoking status was recorded in Waves 1 and 2 of the data but was not gathered in Wave 3. Given the very low prevalence of smoking status in the sample, a decision was made to code Wave 3 smoking status as the same as reported Wave 2 status. Being a smoker was coded as 1, risk factor present.

3.6.7 Social Isolation

The adapted NHATS typology (Cudjoe et al., 2020) was used to inform the construction of the social isolation variable, using the four sub-variables suggested. These four sub-variables were constructed for each participant to comprise their overall Social Isolation score for each wave. Any responses of 'Don't Know', 'Unclear', 'Refused to Answer' were re-labelled as missing responses for all sub-variables.

To create the social isolation variable for each participant, using the NHATS scoring typology, a score of 1 is given to each sub-variable present, equating to maximum 4, minimum 0 for social isolation scoring. A score of 0 is viewed as Severely Socially Isolated, a score of 1 is viewed as Socially Isolated and a score of 2+ is viewed as Socially Integrated (Cudjoe et al., 2020). This creates the initial social isolation variable for each participant, enabling aggregation then into coding for SPSS risk factor presence or absence (1 or 0). The stages in construction of the social isolation variable for each participant, leading to final SPSS coding, are now outlined in detail.

The sub-variables constructed to give a total social isolation score were:

1. ***Living arrangement*** (living with at least one other person)

The living arrangement sub-variable in each wave was constructed using responses to the question "How many people live where you live (under the same roof as you), excluding paid staff". All responses of 0 were scored as 0 and responses of 1+ people were scored as 1.

2. ***Core discussion network size*** (talking to two or more people about important personal items in the past year)

The Core Discussion network size sub-variable in each wave was initially constructed by summing the responses to how many people the person reported confiding in (1=Yes and 0=No for each confidant-type); there were fourteen categories of family and friend types (including 'Other') listed in the IDS-TILDA questions into a "SumConfide" sub-variable. A Categorical "Confide" sub-variable was then constructed with a score of 0 = 0 or 1 people confided in from the SumConfide sub-variable and a score of 1=2 or more people confided in from the SumConfide sub-variable.

However, there were a significant percentage of missing answers to this question across the waves (32% Wave 1, 56% Wave 2, 58% Wave 3). Many participants were not able to answer this question, particularly those with higher levels of need. It can therefore be inferred that this question may not be suitable for inclusion as part of the subset of variables in constructing the social isolation variable. It may not sufficiently reflect the life experience of people with ID in terms of social isolation/connectedness.

The NHATS typology for core discussion network size was re-examined. It was noted that this sub-variable "is adapted from decades of work indicating the importance of the number of people a participant talks to about important matters" (Cudjoe et al., 2020, p. 108). Re-examination of the questions in the Social Connectedness theme across the CAPI waves yielded another possible question suitable for construction of this sub-variable: How often do you meet up with a family member or friend? The frequencies recorded for this question range from never through to yearly, monthly and weekly frequencies up to three or more times a week.

It was decided that meeting up in person at least once per month with a significant person (family member or friend) may be a reasonable substitute for the SumConfide variable. Meeting up in person is more conducive to personal conversation than over the phone or text/email/letter and meeting a person reasonably regularly implies a close relationship where personal issues may be discussed/disclosed and support sought. The CAPI questions in Wave 1 asked about frequency

of meeting with family member(s) and/or with friends. The CAPI questions in Waves 2 and 3 provided more detail with several questions asking about frequency of meeting with spouse / partner / mother / father / brother / sister / aunt/uncle / niece/nephew / cousin / other / friends, enabling a more detailed picture of the frequency of meeting with significant others to be constructed.

Therefore, a new SocialConnect sub-category variable was constructed for each wave. In Wave 1, this was done by summing reported meeting up with family and/or friends at least once per month to either meet the threshold of meeting at least two people once per month (coded as 1) or not meet the threshold (coded as 0). In Waves 2 and 3, the number of significant people the person meets with at least once per month was countable and anyone reaching the threshold of meeting at least two people once per month met the criteria for core discussion network size (coded as 1).

3. ***Religious attendance*** (participating in organised religious services in the past month)

Monthly Religious attendance was constructed in each wave by collapsing the frequency categories in answer to the question "How often do you go to Religious Services"; there were several frequency responses to this question, ranging from 'never' to 'daily'. The categories were collapsed into 0=Less than Monthly and 1=Monthly or More Often to form the Religious Attendance sub-variable for each wave.

4. ***Social participation*** (participating in community clubs or organisations in the past month).

The Sum of answers to several questions "Are you an active participant of political party/trade union, tenants' group, charitable associations, education/arts/music groups, retirement club, Special Olympics, arch network, advocacy, other, social clubs?" and "How often do you undertake voluntary work?" were calculated as a Sum Social Participation (SP) sub-variable. The frequency responses to voluntary work were collapsed into a categorical frequency variable (0=less than once per month & 1=once per month or more often). Being an active participant of various groups was taken as meaning being a regular participant (at least once per month) in the groups(s) with a score of 1 given for each of the types of groups the person reported being an active participant in. All scores were summed to provide a Sum Social Participation score. This Sum SP sub-variable was then constructed as a categorical SP sub-variable with a score of 1 for active participation in one or more community activities or a score of 0 for no participation in community activities for each participant.

Construction of Social Isolation Variable for each Participant for each Wave. These four categorical sub-variables (each with scores of 1 & 0) were summed to form a Sum Social Isolation (SI) variable for each participant for each wave. This Sum SI variable was then constructed as a categorical SI variable with a Sum SI score of 0 being scored as O for "Severely Socially Isolated", a Sum SI score of 1 being scored as 1 for "Socially Isolated" and a Sum SI Score of 2 or more being scored as 2 for "Socially Integrated" for each participant, as per NHATS scoring procedure for adapted SI typology.

This procedure gives a categorical Social Isolation Variable for each wave, with each participant being categorised as Severely Socially Isolated, Socially Isolated or Socially Integrated for each wave. These categories were then collapsed and recoded into 2 categories of Social Isolation Present (coded 1 from previous coding 1 or 0) and Social Isolation not present (coded 0 from previous coding 2) for risk factor coding.

3.6.8 Physical Inactivity

The World Health Organization (2019a) notes that there is more evidence for aerobic exercise rather than resistance training in terms of the effect on reducing cognitive decline and they recommend that adults aged 65 years plus should undertake at least **150 minutes of moderate-intensity physical activity** throughout the week, with each activity to be of at least 10 minutes' duration.

Wave 1. Wave 1 information on physical activity relied on self-report/informant report data of how often the person engaged in mild, moderate or vigorous activity. Mildly energetic physical activity was defined as lasting 10 to 20 minutes causing minimal or no sweating, or mild increase in breathing or heart rate, for example, bowls, walking, golf, light exercises, vacuuming, laundry or home repairs. Moderate physical activity was defined as activity lasting at least 10 to 20 minutes and causing only light sweating or a moderate increase in breathing or heart rate, for example, gardening, cleaning the car, walking at a moderate pace, dancing, floor or stretching exercises, swimming or cycling. Vigorous physical activity was defined as activity lasting at least 10 to 20 minutes, causing heavy sweating or a large increase in breathing or heart rate, for example, running or jogging, exercise bike, vigorous swimming, cycling, aerobics or gym workout, tennis, heavy housework or gardening like digging with a spade or shovel. Participants could answer in frequencies of 'more than once a week', 'once a week', 'once to three times a month', 'never or hardly ever' to each type of activity level.

For Wave 1, based on the information available, a physical activity variable was constructed based on report of engaging in at least moderate exercise **more than once** per week for each participant with coding of Yes (1) or No (0). There is a recognition of potential over-estimation of being active based on this data but nothing more detailed is available in Wave 1. When physical activity is measured as a binary variable (yes/no), without access to the level of intensity of the activity in more detail, associations between levels of physical activity and healthy ageing outcomes are lower compared to more nuanced/detailed measures of physical activity (Daskalopoulou et al., 2017).

Wave 2. The International Physical Activity Questionnaire (IPAQ) was used to assess Physical Activity in Wave 2, with scoring based on 2005 IPAQ scoring recommendations (IPAQ Research Committee, 2005) with 3 categories of Physical Activity (Low, Moderate & High). These were then collapsed into a dichotomous variable Low = not engaging in Moderate Physical Activity (coded 0) & Moderate/High = engaging in at least Moderate Physical Activity (coded 1).

Wave 3. The International Physical Activity Questionnaire (IPAQ) was used to assess Physical Activity with 3 categories of Physical Activity, Inactive (coded 1), Minimally Active (coded 2) & HEPA Active (coded 3), based on the 2004 IPAQ scoring recommendations (Craig et al., 2004). There is also another category included of No Activity (coded as 0).

On reviewing the parameters for scoring for each of these categories in both Waves, Low=Inactive, Moderate=Minimally Active & High=HEPA Active. Decision made to recode Wave 3 categories to Low, Moderate and High and to collapse 0 (No Activity) and 1 (Inactive) into 1 category of Low.

Overall Physical Inactivity Variable. For Wave 1, the Physically Inactive Risk Factor Variable was constructed by recoding those who do engage in at least Moderate Activity once per week from 1 to 0 (Physically Active) and those who don't engage in at least Moderate Activity once per week from 0 to 1 (Physically Inactive).

Both IPAQ scoring guidelines emphasise that, as per Tudor-Locke et al. (2011), activity needs to be over and above basal activity levels to be health-promoting, so the Low, Moderate and High categories were collapsed into the categories of 1=Health Promoting PA (Moderate and High Physical Activity) and 0=Not Sufficiently Health Promoting PA (Low Physical Activity). Then these categories were recoded from Not Sufficiently Health Promoting PA (coded 0) to Physically Inactive (1) and recoded from Health Promoting PA (coded 1) to Physically Active (coded 0) for all to form the risk factor variable of Physical Inactivity for each participant for Waves 2 and 3.

3.7 Building the Lagged Regression Model

Risk of diagnosis of dementia by Wave 4 (dependant variable) can be assessed longitudinally across IDS-TILDA data waves 1-3 for each participant in relation to their biopsychosocial risk factors (predictors). The advantages of using longitudinal data to monitor a disease progression include increased statistical power (in comparison to cross-sectional data) and the ability to explore the variability patterns in both groups and individual participants over the waves (Garcia & Marder, 2017).

The dependent categorical variable of Dementia Diagnosis was coded as being present as 1 and not being present as 0 in SPSS database for each participant (up to Wave 4). The wave of reporting of dementia diagnosis was also recorded for each participant. The age of dementia diagnosis was recorded for each participant, where provided. Each risk factor (categorical, independent variable) was coded as being present (1) or not being present (0) for each participant in SPSS database for each Wave 1, 2 and 3.

The lag point chosen for each participant (N=150) was the previous wave's datapoints (3 years previous) before either:

1. Recorded Wave of Dementia diagnosis
2. No Dementia diagnosis at Wave 4
3. Last wave participation prior to attrition with no Dementia diagnosis recorded

Table 3.2 overleaf gives an overview of these lag points.

Table 3.2

Overview of lag points chosen

Dementia Diagnosis (*by Wave 4)*	Wave of Diagnosis	Lag Datapoints Chosen	Longitudinal or Cross-Sectional
Yes	4	Wave 3	Longitudinal
	3	Wave 2	Longitudinal
	2	Wave 1	Longitudinal
	1	Wave 1	Cross-Sectional
No	N/A	Wave 3	Longitudinal
Attrition *(with no diagnosis)*	**Last Wave prior to Attrition**	**Lag Datapoints Chosen**	**Longitudinal or Cross-Sectional**
Yes	Wave 3	Wave 2	Longitudinal
	Wave 2	Wave 1	Longitudinal
	Wave 1	Wave 1	Cross-Sectional

Those who came into the IDS-TILDA study with a pre-existing dementia diagnosis in Wave 1 did not have 3 years previous reported lag datapoints available. Their independent variable data, is, of necessity, cross-sectional in nature. There were N=14 people with a pre-existing diagnosis of dementia reported in Wave 1 in the sample. Despite this, they were included in the analysis as the sample size would have suffered commensurately if they were left out and they offer additional information points on the biopsychosocial ageing experience of this cohort.

3.8 Initial Demographic Analysis

3.8.1 Chi-Squared Test for Independence

This test is used when exploring the significance of the relationship between two categorical variables, having two or more categories, testing the observed against the expected frequencies (Pallant, 2020). This is a non-parametric test, meaning that normal distribution is not assumed. The assumptions that must be met to use this test are random sampling and independent observations. Expected value of cells needs to be 5 or greater in at least 80% of the cells in the table and cells in the table are mutually exclusive.

Cross-tabulations using Chi-squared Test for Independence were performed on the lagged regression model dataset to establish if lagged risk factor prevalence varied by gender, level of ID or educational attainment, all of whom remained unchanged throughout the period of data collection from Waves 1 – 4. Only significant or approaching significant associations will be reported.

Effect sizes for each Test are reported using the phi coefficient for 2X2 tables and Cramer's V for tables larger than 2X2. Null hypothesis significance testing has some drawbacks, given its sensitivity to sample size and the arbitrary .05 p value; therefore, effect size is also useful to consider when reporting on results, as recommended by the Wilkinson Task Force on reporting of statistics in psychology (Wilkinson, 1999). Effect sizes estimate the 'magnitude of effect between variables [and] …are resistant to sample size influence' (Ferguson, 2009, p. 532). Generally, these criteria for estimating effect size are used: .1+ for small effect, .3+ for medium effect and .5+ for large effect (Cohen, 1992). See Table 3.3 overleaf. Effect size supplements interpretation of the statistical significance of a finding and enables comparison of the magnitude of change in health status between different significant predictor variables (Hevey & McGee, 1998).

Table 3.3

Effect sizes

	Coefficient, *r*	
Strength of Association	***Positive***	***Negative***
Small	.1 to .3	-0.1 to -0.3
Medium	.3 to .5	-0.3 to -0.5
Large	.5 to 1.0	-0.5 to -1.0

Note: Guidance for estimating effect size in statistical analysis. Adapted from: "What does Effect Size tell you?" by McLeod (2023), https://www.simplypsychology.org/effect-size.html.

3.9 Regression Analysis

Regression analysis enables the testing of the effectiveness of independent variables' ability to predict dependent variable outcomes, with predictor variables being continuous or categorical or a mix of both (Pallant, 2020). Linear (multiple) regression is used in cases where the dependent variable is continuous and logistic regression is used in cases where the dependent variable is categorical. Logistic regression is useful in epidemiological research as it enables odds ratios to be derived i.e. an estimate of relative risk based on the association between categorical variables (Irala et al., 1997).

The assumptions of regression include that there is independence of observations in dependent variable outcomes and that there is a lack of significant multicollinearity between independent variables (Ranganathan et al., 2017). Sample size impacts on the power of the analysis e.g. large number of predictors with smaller sample sizes reduces power.

3.10 Lagged Logistic Regression Analysis

This analysis aimed to assess the longitudinal impact of biopsychosocial risk factors on dementia diagnosis in a representative sample (N=150) of Irish people ageing with Down syndrome.

3.10.1 Testing Assumptions: Assessing Outliers

Outliers in the dataset were considered as they may affect regression results. Standardised residual (Z) scores for the independent variables were created using linear regression for the lagged dataset, screening for values exceeding 3.29 standard deviations above or below the mean, indicating outliers. This analysis of standard residuals showed that the data contained no outliers (Std. Residual Min = -1.665, Std. Residual Max = 2.560).

3.10.2 Testing Assumptions: Assessing Multicollinearity

Multicollinearity were also considered in regression models. If the independent variables are highly inter-correlated, they will fit the model well, even if, individually, few of these variables have a significant influence on the predictor variable (Kumari, 2008). Multicollinearity can also lead to increased standard errors and less likelihood of correct assessment of the important variables in the model (Shrestha, 2020). It is one of the assumptions of performing a regression analysis that the independent variables are not highly inter-correlated (Pallant, 2020). Therefore, the extent of multicollinearity in any social sciences dataset must be measured (Kumari, 2008; Shrestha, 2020).

Spearman's Rho, the non-parametric version of Pearson's r was used on SPSS to check bivariate correlations between the independent variables in the lagged dataset. If a correlation coefficient nearing 0.8 is seen, this may indicate collinearity (Shrestha, 2020). The highest level of bivariate correlation found was between Level of Intellectual Disability and No Education (ρ=.574, p<.001, n=93), with no other correlation between independent variables exceeding 0.5.

A linear regression analysis with a check for multicollinearity diagnostics was run, using SPSS, on the lagged dataset to explore variance inflation factor (VIF) and tolerance value (inverse of VIF). The VIF measures the influence of intercorrelation of independent variables on the variance of the estimated regression coefficient (Shrestha, 2020). Low VIF scores indicate low correlation between the independent variables, with increasing VIF score (approaching 10) indicating increasing multicollinearity likelihood (Shrestha, 2020). Generally, if the VIF value is greater than 10 in any set of independent variables, there is significant multicollinearity (Kumari, 2008). Very low tolerance values (less than 0.1, approaching 0) indicate high multicollinearity,

whilst tolerance values approaching 1 indicate less multicollinearity concerns (Oke et al., 2019; Pallant, 2020; Shrestha, 2020).

VIF values remained low and tolerance values remained high, indicating no concerns of multicollinearity for the variables entering the logistic regression analysis. See Appendix D for summary overview of multicollinearity diagnostics for the lagged dataset.

3.10.3 Testing Assumptions: Independent Residuals

An assumption of regression is that there is no correlation between residuals, meaning that they are independent. If this assumption is violated, there may be an underestimation of the standard errors in the model leading to an overestimation of the statistical significance of predictor variables (Statistical Point, 2025). The Durbin-Watson Test (d) as part of linear regression output explored the presence of correlation in the regression residuals. This dataset met the assumption of independent residuals, with d = 1.860 being within the range 1.5 - 2.5, indicating no correlation between residuals (Statistical Point, 2025).

3.10.4 Testing Assumptions: Distribution

Examination of the histogram standardised regression residuals indicated that the data contained approximately normally distributed errors, as did the normal P-P plot of standardised residuals, which showed points that were close to the line throughout. The scatterplot of standardised regression residuals showed that the data met the assumptions of homogeneity of variance and linearity.

3.10.5 Testing Assumptions: Non-Zero Variances

The dataset met the assumption of non-zero variances for all variables.

3.10.6 Power Analysis Calculation

The G-Power software application, recommended for sample size and power calculations (Kang, 2011) was used to calculate the sample size required to achieve 75% power with one-tailed probability in logistic regression analysis. The most recently available version of the software (version 3.1.9.7) was used for analysis of existing sample size. This software is often reported by psychological researchers as being used to calculate power (Stanley et al., 2018).

Odds ratio was determined as 0.56, calculated from 44% of participants with dementia and 56% of participants without dementia. Based on these parameters, a sample size of 375 participants is required to yield 75% power in the logistic regression analysis. This study's sample size of 150 participants yields a reduced power of 43% for the logistic regression analysis for one-

tailed probability, based on G-Power calculations. See Appendices E and F for G Power analysis screenshots. Given the complex multifactorial nature of dementia, studies with low power can still provide meaningful preliminary evidence on potential associations between predictor variables and health outcomes, supporting the further development of analytic models. These preliminary studies can also generate effect size estimates that inform the designing of future studies with higher power. It has been argued that small effects still have value in exploring the aetiology of health conditions over time, particularly with underserved populations (Gotz et al., 2022).

3.10.7 Multiple Imputation by Chained Equations (MICE)

The use of longitudinal data also poses some methodological challenges such as missing data across waves which can decrease the power of the analysis and increase bias in results (Garcia & Marder, 2017). Previous practices for managing missing data points in longitudinal datasets have included: only using those participants that have full data sets in the analysis (complete-case analysis), replacing a participant's missing data point with the last observed one in the series (last observation carried forward analysis) and using simple imputation methods to replace missing values (e.g. with a mean value) (Garcia & Marder, 2017). However, all these methods have significant drawbacks, particularly when used in disease progression modelling and with categorical/ordinal data, including artificially lowering standard errors with narrowing confidence intervals (Garcia & Marder, 2017).

To reduce missing data in the dataset, the multiple imputation by chained equations (MICE) method was chosen. This is a generally accepted method of dealing with missing data in longitudinal datasets. It has been used in studies using data from TILDA, IDS-TILDA and the English longitudinal ageing study ELSA (Kim et al., 2022; Lynch et al., 2024; Nguyen et al., 2020; Qazvini, 2023) and has been shown to be quite accurate in its imputation of missing data, reducing bias, including in longitudinal studies (Biering et al., 2015; Muller & Woods, 2022). Multiple Imputation provides several estimated values for each missing datapoint, through a series of generated datasets, giving valid standard errors and confidence intervals for these estimates (Chevret et al., 2015). The researcher can specify the number of imputed datasets to be generated from the multiple imputation process (N=5 datasets is a common specification).

The MICE method imputes missing data, forming several imputation datasets and pooled datasets (using Rubin's rules) from Missing at Random (MAR) data. The assumption is that missing data is Missing at Random i.e. missing on observed and not unobserved values (Azur et al., 2011). Given that the CAPI interviews took place in people's homes at a time of their choosing, data was

collected in a consistent fashion across all interviews; therefore, data is likely to be missing at random, rather than being due to systematic differences between missing and observed values as is the case for Data Missing Not at Random (MNAR) (Sterne et al., 2009). Generally, if missing data is at or below 5% level, it can be treated as not affecting analysis and does not have to be specifically dealt with (Jakobsen et al., 2017; Madley-Dowd et al., 2019). Otherwise, a method for dealing with missing data is required.

MICE, also known as fully conditional specification, enables the specification of a different model for the distribution of each variable considering all the other variables (Chevret et al., 2015; Costantini et al., 2024). This means that different models can be specified for different types of dependent variable e.g. continuous or binary. Missing data levels on any variable should not be above 40% for MICE usage (Jakobsen et al., 2017; Madley-Dowd et al., 2019). See Appendix G for a visual outline of the MICE process.

An important decision is how many variables to include in the MICE imputation process as predictors for missingness: it is recommended to include as many variables as possible in the process to reduce bias of parameter estimates and to keep confidence intervals within correct range (Costantini et al., 2024). However, when there are very many independent variables, a strategy may need to be designed to reduce the number of predictor variables used in MICE (Costantini et al., 2024); however, in this case the number of independent variables are small enough for all to be used if required.

It is recommended not to include variables as predictors in the MICE process if they have greater than approximately 20% missing data (Melissa J Azur et al., 2011; Tabachnick & Fidell, 2013). All independent variables were used as predictors for imputation except No Education due to the large number (32%) of missing cases. All independent variables with missing data were imputed through MICE procedure using SPSS. Imputation constraints for the analysis are outlined in Appendix H.

The starting point of the random number generator was set at a fixed point of 950 to support reproduction of results if required. Fifty iterations of the model were requested to be run, with a resulting 5 imputed datasets (each with slightly different imputed data along with the same original existing datapoints in each case) and a pooled dataset. Five to ten imputed datasets are recommended in the literature to be requested, with five being a common specification (Melissa J Azur et al., 2011; Madley-Dowd et al., 2019). These imputed models are stored in SPSS stacked on top of each other in one database along with the original dataset. Imputed values can be

marked or unmarked using the 'Mark Imputed Data' option in the Data View window of SPSS. It is then possible to undertake a logistic lagged regression using the original dataset and the five imputed datasets. The imputed datasets give imputed prevalence rates for those variables (such as No Education and Obesity) that have a percentage of missing values.

3.10.8 Overall Performance of Individual Full Logistic Regression Models

The Original Dataset Model performed better than the Imputed Dataset models. It significantly (p = .006) outperformed the null baseline model. It exhibited an excellent goodness of fit (.722, p>.05) for the data. Imputed Model 4 is the only other model that performed better than the null model (p=.038) with a goodness of fit of .229 (p>.05) for the data. Therefore, the results for logistic regression will focus on these two models, presented in the Results section. See Tables 3.4 and 3.5.

Table 3.4

Overview of model performance

Model Number	Step	X^2	df	p
Original Dataset	1	32.206	15	**.006**
Imputed Model 1	1	22.732	15	.090
Imputed Model 2	1	18.780	15	.224
Imputed Model 3	1	24.577	15	.056
Imputed Model 4	1	25.969	15	**.038**
Imputed Model 5	1	19.482	15	.193

Table 3.5

Overview of model fit

Model Number	Step	X^2	df	p
Original Dataset	1	4.486	7	.722
Imputed Model 1	1	14.567	8	.068
Imputed Model 2	1	12.795	8	.119
Imputed Model 3	1	15.770	8	.046
Imputed Model 4	1	10.540	8	.229
Imputed Model 5	1	12.582	8	.127

3.10.9 Presentation of Logistic Regression Results

Odds Ratio (OR) and Confidence Interval (CI) will be presented for predictors. The odds ratio signifies the strength and direction of the association between the predictor variable and the dependent variable, in this case dementia diagnosis. It quantifies the ratio of the odds of the outcome occurring in one group compared to the odds of the outcome occurring in another group. The Confidence Interval offers a range of values within which the true odds ratio is likely to fall. An odds ratio greater than 1 indicates a positive association, implying higher odds of the outcome, while a ratio less than 1 signifies a negative association, suggesting lower odds. See Results section for more details.

3.10.10 Forward Stepwise Logistic Regression

Forward stepwise logistic regression was undertaken with the Original Dataset Model and Imputed Dataset Model 4 to determine the strongest predictors in each of these models. Forward stepwise regression was chosen as there are many independent variables with a smaller sample size, meaning it is more suitable to use than backward stepwise regression, as it does not have to consider the full model from the start.

However, stepwise regression has limitations in that it does not consider all possible combinations of predictor variables, and it can give biased regression coefficients (larger) and smaller p-values and confidence intervals. It was felt useful to run the forward stepwise regression in this instance to examine if a similar pattern of stronger predictors emerged when compared with the direct logistic regression analysis of predictor strength.

3.11 Linear Regression Analysis

Further analyses were run to explore the relative influence of the risk factors on age of dementia diagnosis. Linear regression analysis aimed to assess the longitudinal impact of biopsychosocial risk factors on age of dementia diagnosis in a representative sample (N=150) of Irish people ageing with Down syndrome.

A new subset of the data was created with only those diagnosed with dementia (N=66) included. Multiple Imputation Chain Equations (MICE) were used to impute missing values, resulting in an Original DementiaY Model and 5 imputed DementiaY models. No Education, due to high percentage of missing values, was once again not used as a predictor in the MICE process.

3.11.1 Power Analysis Calculation

Statistical power was explored for this analysis. A formula for calculating adequate power in multiple regression for a given sample size is proposed as N>50+8m (Tabachnick & Fidell, 2013, p. 213), where *m* is the number of independent variables. This formula comes with a caveat, however; it can over-estimate the required sample size when the number of independent variables is greater than seven, also depending on the effect size required/desired (Green, 1991).

Based on this formula, including all 13 independent variables in the analysis would require a sample size of 154 participants. The actual sample size is much smaller than this, at 66 participants. Therefore, risk factors were aggregated into three categories to reduce number of independent variables in the analysis to increase power. Those diagnosed with dementia over the 4 waves of data collection (N=66) were coded as having 0-3 lagged risk factors present (1), 4-6 lagged risk factors present (2) or 7-10 lagged risk factors present (3). Linear regression was then performed to evaluate the impact of these categories of aggregated risk factors, along with demographics, on age of dementia diagnosis. Three participants did not have an age of diagnosis recorded from the sample of 66 diagnosed with dementia.

3.11.2 Review of Normality, Residuals, Outliers and Multicollinearity

Review of kurtosis and skewness found neither had values exceeding a range between -1 to +1 so data was within acceptable limits of normal distribution. Examination of the histogram standardised regression residuals indicated that the data contained approximately normally distributed errors, as did the normal P-P plot of standardised residuals, which showed points that were close to the line throughout. The scatterplot of standardised regression residuals showed that the data met the assumptions of homogeneity of variance and linearity.

Further examination of standardised residuals indicated very few outliers across the datasets; outliers are indicated by standardised residuals of more than 3.3 or less than -3.3 (Tabachnick & Fidell, 2013, p. 125). Analysis of Cook's distance across all models in the Residuals Statistics table did not yield a value greater than 1 so it can be surmised that outliers were not having a significant influence on overall model performance (Tabachnick & Fidell, 2013). One person was recorded as having an age of diagnosis of 34, which is significantly younger than the mean age of diagnosis of dementia of 52.71 and can potentially be viewed as an outlier. However, as it was reported as part of the CAPI interview during IDS-TILDA interviews and does not appear to be having a significant impact on models' performance, it was not removed.

Viewed across the original dataset and the 5 imputed and 1 pooled model datasets, multicollinearity was not problematic as assessed by Pearson's bivariate correlation table with no correlations >.55 seen. Tolerance and Variance Inflation Factor (VIF) were also within acceptable limits in the Coefficients table (nothing below .10 for Tolerance or above 10 for VIF).

3.12 Conclusion

This Methodology chapter has given an overview of the data collection procedures and the participant sampling used in this research. It has described the methods used to derive the independent variable risk and demographic factors. It has described the method used to derive the dependent variable of dementia diagnosis. It has described the assumption testing and use of statistical analyses for the modelling. The next chapter will discuss the results of this modelling.

Chapter 4: Results

4.1 Introduction

The results chapter will outline the descriptive statistics for this sample, highlighting any significant interactions of demographics on risk factor prevalence and comparing the risk factor profile of this sample with the general ageing population. The results of logistic regression modelling regarding ability of risk factor profile to predict dementia diagnosis will be presented, along with a focus on any individually significant predictive risk factors. The results of linear regression modelling regarding cumulative number of risk factors having an influence on age of dementia diagnosis will be presented. A more detailed look at the life experience and risk factor profile of a sub-sample of participants will then be presented to support understanding of the ageing experience of people with Down syndrome.

4.2 Descriptive Statistics

4.2.1 General Demographics of the Sample Across the Waves

There were 150 people with Down syndrome in the original sample, with 65 men (43%) and 85 women (57%). Just over half of the sample (54%) were aged 40-49 at Wave 1, with 37% aged 50-59 and 9% aged 60+. There were more people with moderate intellectual disability within the sample (55%) than with mild (15%) or severe (30%) intellectual disability. There was good retention of these participants across the three data collection waves, with N=141 participating in Wave 2 and N=112 in Wave 3. Most of the attrition over the waves was due to the death of participants.

An overview of the types of living situations people reported across the IDS-TILDA waves can be seen in Table 4.1 overleaf. Despite the ageing of the sample across the data collection period, the proportions of those living independently or with family remained at 20% across all waves. Some movement is observed between community group home settings and more congregated settings across waves; most likely reflecting two opposing forces, policy to move away from congregated settings in recent years on one hand (Ryan, 2017) and the need for higher supports for some people as they age on the other, which may be met in a more congregated setting where available (Roebuck, 2021).

Table 4.1

Overview of reported residential status across IDS-TILDA waves

Data Collection Wave		n	%	Total
Wave 1	*Independent/With Family*	30	20.1	149
	Community/Group Home	63	42.3	
	More Congregated Residential Setting	56	37.6	
Wave 2	*Independent/With Family*	28	19.9	141
	Community/Group Home	68	48.2	
	More Congregated Residential Setting	45	31.9	
Wave 3	*Independent/With Family*	22	19.6	112
	Community/Group Home	51	45.5	
	More Congregated Residential Setting	39	34.8	

4.2.2 Dementia Diagnosis

There were 66 people (44%) in total reported as diagnosed with dementia by Wave 4 from the original sample of 150 people with Down syndrome in Wave 1. Several participants entered Wave 1 with an existing diagnosis of dementia (N=14).

Table 4.2

New dementia diagnosis in each IDS-TILDA wave

New Dementia Diagnosis	Total N	Percentage
Wave 1	14	9.3
Wave 2	28	18.7
Wave 3	20	13.3
Wave 4	4	2.7
Not Diagnosed	84	56

The mean age of dementia diagnosis in the sample was 52.7 years, whilst the median age was 53 years. This aligns with other research on the average age of diagnosis in this population (Iulita et al., 2022). Three participants did not have age of diagnosis reported. The youngest age at which dementia was reported as having been diagnosed was 34, prior to entry to the study, with the oldest age of reported diagnosis being 66.

Chi-squared analysis found a significant effect for gender on dementia diagnosis in the sample χ^2 (1, N=150) = 4.1, p = .043, phi = .179. Over half of women in the sample (52%) were diagnosed with dementia by Wave 4, compared to one-third of the men (34%). No significant difference in prevalence of dementia diagnosis was found by level of intellectual disability or residential setting following chi-squared analysis.

4.2.3 Risk Factor Profiling Across the Waves

Risk factor frequencies varied across the waves for this sample population. Table 4.3 below gives a summary overview of the relative frequencies of risk factors in each Wave.

Table 4.3

Risk factor frequency profile for all waves

	Wave 1 Total N=150	**Wave 2 Total N=141**	**Wave 3 Total N=112**
Risk Factor Present	**n (%)**	**n (%)**	**n (%)**
No Education	42 (28)	42 (28)	42 (28)
Hearing Loss	36 (24)	34 (22.7)	38 (25.3)
Hypertension	18 (12)	18 (12)	12 (8)
Frequent Alcohol	7 (4.7)	4 (2.7)	4 (2.7)
Obesity	57 (38)	48 (32)	42 (28)
Smoker	2 (1.3)	1 (0.7)	1 (0.7)
Depression	30 (20)	39 (26)	29 (19.3)
Social Isolation	23 (15.3)	28 (18.7)	11 (7.3)
Physical Inactivity	105 (70)	113 (75.3)	75 (50)
Diabetes	3 (2)	3 (2)	6 (4)

Not all participants reported answers for all questions. Percentages given reflect the prevalence of each risk factor in the sample relative to 'No' or 'Missing' answers for that risk factor.

Missing Data across Waves. There was a significant lack of information about participants' early educational attainment, with 32% of the sample not reporting an answer for this factor. This may be because the participants and those supporting them did not have access to historical educational records for the IDS-TILDA data collection. Some people of this age group may have been in congregated settings/institutions where educational attainment was not recorded, and they or their families may not know what level they reached. Of those reporting some educational attainment, only 1 person in the sample reported attending secondary school, with everyone else attending to primary school level.

In Wave 1, Obesity had 16.7% missing answers, and Social Isolation had 8.7% missing answers, with a low percentage of missing answers in the rest of the risk factors reported by participants. In Wave 2, Education and Obesity once again had many missing responses, at 32% and 29.3% respectively, with a low percentage of missing data in the other risk factors in this wave. All other variables in this wave had less than ten per cent of missing data. In Wave 3, there is at least 25% of missing data for each risk factor; however, there is also a participant attrition rate of 25.3% from Wave 1 contributing to some of the missing data. This does not, however, explain all the missing data in the sample, with some due to missing responses. Most variables have low levels again of missing data, over and above attrition rate, but Obesity and No Education continue with significant missing data into this wave.

4.3 The Ageing Experience of People with Down syndrome

Regression analysis enables the testing of the effectiveness of independent variables' ability to predict dependent variable outcomes, with predictor variables being continuous or categorical or a mix of both (Pallant, 2020). This study's lagged logistic regression analysis aimed to assess the longitudinal impact of biopsychosocial risk factors on dementia diagnosis in a representative sample (N=150) of Irish people ageing with Down syndrome. Prior to running the full logistic regression analysis, the lagged risk factor profile of the sample was derived and investigated as to the ageing experience of people with Down syndrome in this study sample, in comparison to those in the general population.

The risk factor prevalence derived for the lagged regression model is presented here (Table 4.4). These outline overall risk factor prevalence at the 3 years' previous lag point pertaining to each participant. There were missing data in some variables, and the percentage prevalence of each risk factor is presented relative to percentage of 'No' or 'Missing' answers for each risk factor. The total number (N) of answers recorded for each risk factor is also given for missingness reference in this table.

Table 4.4

Lagged risk factor prevalence in the sample

Risk Factor Present	N (%) Prevalence	Total N
No Education	42 (28)	102
Hearing Loss	46 (30.7)	150
Hypertension	18 (12)	150
Frequent Alcohol	7 (4.7)	149
Obesity	54 (36)	119
Smoker	2 (1.3)	149
Depression	35 (23.3)	150
Social Isolation	19 (12.7)	137
Physical Inactivity	108 (72)	150
Diabetes	3 (2)	147

4.3.1 Risk Factor Profile Comparisons

The overall pattern of risk factor prevalence found in this sample population was quite different to risk factor prevalence noted in the general population. Risk factor prevalence for the general ageing population was drawn from global epidemiological figures (Cudjoe et al., 2020; Hunt et al., 2023; Jalali et al., 2024; Livingston et al., 2017; McKee & Morley, 2021; Mongan et al., 2021; Silveira et al., 2022; Sun et al., 2022; Teo et al., 2023; Zhou et al., 2021). Table 4.5 below gives a comparison of risk factor prevalence in the general ageing population and the prevalence rate found in the Original Dataset lagged regression model from this research study. For most variables, the general population prevalence data is taken from the Irish TILDA study of older people, to which the IDS-TILDA study is matched. Where not available, the general population prevalence is taken from global epidemiological data for older people. This was felt to be the most appropriate comparison information available for the prevalence data for those ageing with Down syndrome in this study. Imputed risk factor prevalence from Imputed Model 4 is included for those risk factors in the sample for which there were significant missing data. This model was one of several models derived from MICE procedure to impute missing data. Imputed Model 4 prevalence figures are used as this model best fit the data.

Table 4.5

Risk factor prevalence comparison between populations

Risk Factor	**Prevalence***		
	Older General Pop %	***Original Dataset %***	***Imputed Model 4 %***
No Education	0	28	41
Hearing Loss	32	31	
Hypertension	52	12	
Frequent Alcohol	14	5	
Obesity	35	36	45
Smoker	11	1	
Depression	19	23	
Social Isolation	25	13	15
Physical Inactivity	43	72	
Diabetes	6	2	

**Percentages have been rounded to nearest whole number*

4.3.2 Investigation of associations between risk factors and demographics

Cross-tabulations using Chi-Squared Tests of Independence were performed to preliminarily explore for any significant associations between risk factor prevalence with the demographic variables of gender, level of intellectual disability and lagged residential setting. The lagged Interactions between demographics were also explored to broaden understanding of the lived reality for participants as they aged. Throughout, Phi coefficient values indicating effect size are given for 2X2 tables and Cramer's V are given for 3X2 tables (Pallant, 2020).

Interactions between Demographic Variables. Chi-Squared Tests of Independence were conducted to assess associations between demographic variables.

Interactions with Gender. There was no significant association found between gender and level of intellectual disability or gender and residential setting. See Table 4.6 overleaf. Cramer's V is reported indicating effect size for 3X2 (or greater) tables.

Table 4.6

Gender and other demographics

Risk Factor		Gender		χ^2	df	p	Cramer's V
		Male	*Female*				
Level of ID	Mild	11 (18.3)	10 (12.7)	2.765	2	.251	.141
	Moderate	28 (46.7)	48 (60.6)				
	Sev/Profound	21 (35)	21 (26.6)				
Residential Setting	Ind/Family	16 (24.6)	13 (15.5)	2.104	2	.349	.119
	Group Home	28 (43.1)	38 (45.2)				
	Congregated	21 (32.3)	33 (39.3)				

Level of Intellectual Disability and Residential Setting. A Chi-Squared Test of Independence indicated a highly significant association between Level of Intellectual Disability and Residential Setting, χ^2 (4, n=138) = 34.314, p<.001, Cramer's V = .353. A significantly higher proportion of those with severe/profound intellectual disability reported living in more congregated settings than those with moderate or mild intellectual disability. Only 2% (n=1) of the total sample with severe/profound intellectual disability are reported as living independently or in their family home. See table 4.7 below.

Table 4.7

Residential status and level of intellectual disability

Risk Factor		**Level of ID**			**χ^2**	**df**	**p**	**Cramer's V**
		Mild	*Moderate*	*Sev/Prof*				
		n (%)	*n (%)*	*n (%)*				
Residential Status	Ind/Family	6 (28.6)	19 (25.3)	1 (2.4)	34.314	4	**<.001**	.353
	Group	13 (61.9)	37 (49.3)	11 (26.2)				
	Congregated	2 (9.5)	19 (25.3)	30 (71.4)				

Interactions between Gender and Risk Factor Prevalences. No significant differences in risk factor prevalence for gender were found. Most cells did not have an expected count less than 5, except cells indicating Yes Smoker, Yes Frequent Alcohol and Yes Diabetes. Pearson Chi-Square values are presented in the table below, with Yates' Continuity Correction value presented for 2X2 tables. See Table 4.8.

Table 4.8

Gender and risk factor prevalence

Risk Factor		**Gender**		**χ^2**	**df**	**p**	**Phi**
		Male	*Female*				
No Education	Yes	19 (44)	23 (38.9)	.105	1	.746	-.052
Hearing Loss	Yes	20 (30.8)	26 (30.6)	.000	1	1.000	-.002
Hypertension	Yes	7 (10.8)	11 (12.9)	.023	1	.879	.033
Frequent Alcohol	Yes	5 (7.7)	2 (2.4)	1.275	1	.259	-.124
Obesity	Yes	20 (36.4)	34 (53.1)	2.711	1	.100	.168
Smoker	Yes	1 (1.5)	1 (1.2)	.000	1	1.000	-.015
Depression	Yes	14 (21.5)	21 (24.7)	.067	1	.795	.037
Social Isolation	Yes	7 (11.1)	12 (16.2)	.377	1	.539	.074
Physical Inactivity	Yes	42 (64.6)	66 (77.6)	2.490	1	.115	.144
Diabetes	Yes	2 (3.1)	1 (1.2)	.042	1	.839	-.065

Interactions between Level of Intellectual Disability and Risk Factor Prevalences. Cross-tabulations were undertaken, using Chi-Squared Tests of Independence, to assess any significant associations between risk factor prevalence and Level of Intellectual Disability. Most cells did not have an expected count less than 5, except some cells indicating Yes Hypertension, Yes Frequent Alcohol, Yes Smoker, Yes Depression, Yes Social Isolation and Yes Diabetes. Pearson Chi-Square values are presented in the table below with Cramer's V indicating effect sizes for 3X2 tables in all cases. See Table 4.9 overleaf. Factors in bold are significant and factor in italics is approaching significance.

Table 4.9

Level of intellectual disability and risk factor prevalence

Risk Factor		**Level of ID**			χ^2	**df**	**p**	**Cramer's V**
		Mild N (%)	*Moderate N (%)*	*Sev/Prof N (%)*				
No Education	Yes	1 (5.9)	14 (29.8)	24 (82.6)	31.772	2	**<.001**	.584
Hearing Loss	Yes	2 (9.5)	27 (35.5)	13 (30.9)	5.291	2	.071	.195
Hypertension	Yes	2 (9.5)	5 (6.6)	9 (21.4)	5.952	2	*.051*	.207
Frequent Alcohol	Yes	1 (4.76)	3 (4)	2 (4.76)	.048	2	.976	.019
Obesity	Yes	7 (35)	38 (59.4)	8 (30.8)	7.761	2	**.021**	.266
Smoker	Yes	1 (4.8)	1 (1.3)	0 (0)	2.238	2	.327	.127
Depression	Yes	5 (23.8)	15 (19.7)	12 (28.6)	1.200	2	.549	.093
Social Isolation	Yes	2 (9.5)	6 (8.7)	8 (22.2)	4.134	2	.127	.181
Physical Inactivity	Yes	13 (61.9)	51 (67)	37 (88)	7.441	2	**.024**	.231
Diabetes	Yes	1 (5)	0 (0)	2 (4.8)	3.714	2	.156	.165

A Chi-Squared Test of Independence indicated a highly significant association between Level of Intellectual Disability and No Education, χ^2 (2, n=93) = 31.772, p<.001, Cramer's V = .584. A Chi-Squared Test of Independence indicated the approaching of a significant association between Level of Intellectual Disability and Hypertension, χ^2 (2, n=139) = 5.952, p = .051, Cramer's V = .207. However, 2 cells had an expected count of less than 5 in this table, so this violates an assumption of the chi-squared test.

A Chi-Squared Test of Independence indicated a significant association between Level of Intellectual Disability and Obesity, χ^2 (2, n=110) = 7.761, p = .021, Cramer's V = .266. A Chi-Squared Test of Independence indicated a significant association between Level of Intellectual Disability and Physical Inactivity, χ^2 (2, n=110) = 7.441, p = .024, Cramer's V = .231. See Table 4.10 below for an overview of percentage prevalence of each risk factor by level of intellectual disability.

Table 4.10

Significant or almost significant risk factors stratified by level of intellectual disability

Level of Intellectual Disability	**No Educational Attainment %**	**Hypertension %**	**Obesity %**	**Physical Inactivity %**
Mild	6	10	35	62
Moderate	30	7	59	67
Severe/profound	83	21	31	88

Interactions between Residential Settings and Risk Factor Prevalences. Cross-tabulations were undertaken, using Chi-Squared Tests of Independence, to assess any significant associations between risk factor prevalence and Residential Setting (lagged). Most cells did not have an expected count less than 5, except some cells indicating Yes Hypertension, Yes Frequent Alcohol, Yes Smoker, Yes Social Isolation and Yes Diabetes. Pearson Chi-Square values are presented in the table below with Cramer's V indicating effect sizes for 3X2 tables in all cases. See Table 4.11 overleaf. Factors in bold are significant.

Table 4.11

Residential setting and risk factor prevalence

Risk Factor			**Residential Setting**		χ^2	**df**	**p**	**Cramer's V**
		Family/Ind N%	*Group N%*	*Congregated N%*				
No Education	Yes	8 (42.1)	14 (29.8)	20 (57.1)	6.183	2	**.045**	.247
Hearing Loss	Yes	9 (31)	19 (28.8)	18 (33.3)	.288	2	.866	.044
Hypertension	Yes	2 (6.9)	2 (3)	14 (25.9)	15.570	2	**<.001**	.323
Frequent Alcohol	Yes	3 (10.3)	2 (3.1)	2 (3.7)	2.549	2	.280	.131
Obesity	Yes	12 (42.9)	29 (50)	13 (40.6)	.855	2	.652	.085
Smoker	Yes	0 (0)	1 (1.5)	1 (1.9)	.516	2	.773	.059
Depression	Yes	2 (6.9)	13 (19.7)	20 (37)	10.485	2	**.005**	.265
Social Isolation	Yes	4 (14.3)	7 (11.7)	8 (16.3)	.495	2	.781	.060
Physical Inactivity	Yes	14 (48.3)	46 (69.7)	47 (87)	14.266	2	**<.001**	.309
Diabetes	Yes	0 (0)	2 (3)	1 (1.9)	.904	2	.636	.079

A Chi-Squared Test of Independence indicated a highly significant association between a more congregated Residential Setting and No Education, χ^2 (2, n=14) = 6.183, p<.045, Cramer's V = .247. A Chi-Squared Test of Independence indicated a highly significant association between Residential Setting and Hypertension, χ^2 (2, n=149) = 15.570, p<.001, Cramer's V = .323. The vast majority of those reporting a diagnosis of Hypertension were living in a more congregated setting. One cell had an expected count of less than 5 in this analysis.

A Chi-Squared Test of Independence indicated another significant association between Residential Setting and Depression, χ^2 (2, n=149) = 10.485, p=.005, Cramer's V = .265. A higher proportion of those living in more congregated settings had a diagnosis of depression, with over one-third having a diagnosis of clinical depression. A Chi-Squared Test of Independence indicated a highly significant association between Residential Setting and Physical Inactivity, χ^2 (2, n=149) = 14.266, p <.001, Cramer's V = .309. Those living in community group homes or more congregated settings were more likely to be physically inactive than those living independently or with family.

4.3.3 Overview of Demographic and Risk Factor Profiles

Initial Chi-Squared Tests of Independence were undertaken to investigate any associations between demographic variables or between demographic variables and lagged risk factor prevalences.

Those with severe/profound intellectual disability were more likely to live in congregated settings and to have no educational attainment reported. There was more than double the prevalence of hypertension in those with severe/profound intellectual disability than those with mild intellectual disability. Participants living in congregated residential settings were more likely to have hypertension, depression, to be physically inactive and to have no education.

There was a high level of physical inactivity in general across the sample, with over three quarters of participants within the severe/profound range of intellectual disability being reported as physically inactive. Those within the moderate range of intellectual disability were significantly more likely to be obese than those within the mild or severe/profound range of intellectual disability.

4.4 Influence of Risk Factors on Subsequent Dementia Diagnosis

4.4.1 Original Dataset Model

A binary lagged logistic regression was performed on the original dataset model to assess the impact of a set of predictor variables on the odds of dementia diagnosis. The lagged dataset points for this risk factor model were derived for each participant from either 1. the previous wave datapoints prior to a dementia diagnosis OR 2. the previous wave datapoints prior to last wave completed before dropping out of study with no diagnosis OR Wave 4 datapoints if no dementia diagnosis throughout and all waves completed. There was a consistent period of 3 years between each wave of data collection.

The original dataset model contained thirteen independent variables: Gender, Level of Intellectual Disability, Residential Status, Hearing Loss, No Education, Hypertension, Frequent Alcohol Consumption, Obesity, Smoker, Depression, Social Isolation, Physical Inactivity and Diabetes. The full model containing all predictors was statistically significant, χ^2 (15, N=150) = 32.206, p=.006, indicating that the model can distinguish between those participants who are diagnosed with dementia and those who are not. The Hosmer and Lemeshow Test also indicated goodness-of-fit support for the model, with a non-significant result χ^2 (7, N=150) = 4.486, p=.722. The original dataset model correctly classified 77.3% of cases, with a positive predictive value overall of 73.9% (sensitivity of the model) and a negative predictive value of 79% (specificity of the model). This is an improvement on the null model which correctly classified 60.6% of cases.

Only 2 of the independent variables made a uniquely statistically significant contribution to the model (risk of dementia diagnosis). Compared with living independently/ with family (the reference category), **living in a more congregated setting** had a significantly higher risk of dementia diagnosis (p=.006), with an odds ratio of 224.9 (CI (95%) = 4.7-10743.6). Those living in a community group home did not differ significantly in their risk of dementia diagnosis from those living independently/with family (p=.094). The other significant predictor was **physical inactivity** (p=.010), with an odds ratio of 15.17 (CI (95%) = 1.9-120.6). An overview of the contribution of each predictor to the model is given below, with odds ratios, probability and confidence intervals (Table 4.12 overleaf).

The confidence intervals for the odds ratios of both predictors were very wide; this can arise from variables with small frequencies across categories interacting in the model, which may reduce confidence in interpretations (Irala et al., 1997). It is recommended to assess the

goodness-of-fit of the model as another way of validating it when this issue arises; this has been done in this case (Irala et al., 1997). The Original Dataset model exhibited excellent goodness of fit (.722, p>.05).

Table 4.12

Full logistic regression model of predictors of dementia diagnosis (Original dataset model)

Risk Factor		**OR (ExpB)**	**p**	**CI**
Gender		1.309	.722	.297-5.758
Level ID	*Mild*		.181	
	Moderate	1.752	.540	.292-10.517
	Severe/Prof	.103	.188	.004-3.028
Residential Status	*Ind/Family*		.023	
	Group	6.407	.094	.731-56.168
	Congregated	224.916	**.006**	4.709-10743.61
No Education		.802	.832	.105-6.128
Hearing Loss		2.342	.389	.338-16.213
Hypertension		.296	.304	.029-3.012
Frequent Alcohol		.661	.825	.017-25.873
Obesity		3.093	.186	.581-16.457
Smoker		.496	.796	.002-101.517
Depression		.267	.171	.040-1.770
Social Isolation		2.434	.444	.249-23.786
Physical Inactivity		15.170	**.010**	1.908-120.625
Diabetes		.000	1.000	.000

Factors in bold are significant

4.4.2 Imputed Dataset Model 4

A binary lagged logistic regression was performed on imputed dataset model 4 to assess the impact of the set of predictor variables on the odds of dementia diagnosis. The lagged dataset points for this risk factor model were derived for each participant from either 1. the previous wave datapoints prior to a dementia diagnosis OR 2. the previous wave datapoints prior to last wave completed prior to dropping out of study with no diagnosis OR Wave 4 datapoints if no dementia diagnosis throughout and all waves completed. There was a consistent period of 3 years between each wave of data collection.

This model contained thirteen independent variables: Gender, Level Intellectual Disability, Residential Status, Hearing Loss, Hypertension, Frequent Alcohol, Obesity, Smoker, Depression, Social Isolation, Physical Inactivity and Diabetes, with imputed datapoints included where there was missing data. The full model containing all predictors was statistically significant, X^2 (15, N=150) = 25.969, p=.038, indicating that the model can distinguish between those participants who have a dementia diagnosis and those who do not. The Hosmer and Lemeshow Test also indicated goodness-of-fit support for the model, with a non-significant result χ^2 (8, N=150) = 10.540, p=.229. The model correctly classifies 67.3% of cases, with a positive predictive value overall of 63.9% (sensitivity of the model) and a negative predictive value of 69.7% (specificity of the model). This represented a substantial improvement on the null model which correctly classifies 56% of cases.

Only 2 of the independent variables made a uniquely statistically significant contribution to the model (risk of dementia diagnosis). Compared with living independently/ with family (the reference category), **living in a more congregated setting** was a significant predictor of dementia diagnosis (p=.037), with an odds ratio of 4.04 (CI (95%) = 1.089-14.991). Those living in a community group home did not differ significantly in their risk of dementia diagnosis from those living independently/with family (p=.184). The other significant predictor was **social isolation** (p=.048), with an odds ratio of 3.15 (CI (95%) = 1.009 – 9.835). **Physical Inactivity** was nearing significance as a predictor (p=.077) in this model. See Table 4.13 overleaf.

Table 4.13

Full logistic regression model of predictors of dementia diagnosis (Imputed dataset model 4)

Risk Factor		**OR (ExpB)**	**p**	**CI**
Gender		1.734	.160	.805-3.732
Level ID	*Mild*		.235	
	Moderate	.562	.296	.192-1.649
	Severe/Prof	.292	.089	.071-1.207
Residential Status	*Ind/Family*		.109	
	Group	2.143	.184	.697-6.586
	Congregated	4.040	**.037**	1.089-14.991
No Education		1.428	.448	.568-3.590
Hearing Loss		.747	.479	.334-1.672
Hypertension		.617	.423	.189-2.012
Frequent Alcohol		2.317	.395	.334-16.082
Obesity		1.119	.779	.510-2.456
Smoker		.224	.369	.009-5.859
Depression		1.525	.338	.642-3.622
Social Isolation		3.150	**.048**	1.009-9.835
Physical Inactivity		2.243	*.077*	.917-5.483
Diabetes		.645	.712	.063-6.596

Factors in bold are significant and factor in italics is nearing significance

4.4.3 Forward Stepwise Logistic Regression

Forward stepwise logistic regression was undertaken with the Original Dataset Model and Imputed Dataset Model 4 to determine the strongest predictors in each of these models. This analysis was undertaken to examine if a similar pattern of stronger predictors emerged when compared with the direct logistic regression analysis of predictor strength.

In the Original Dataset Model, the predictor of Physical Inactivity emerged as the most significant predictor of whether a person would be reported as having Dementia 3 years later. The analysis yielded an odds ratio (OR) of 7.667 for Physical Inactivity, with a 95% Confidence Interval (CI) of 1.981-29.67, p=.003.

In Imputed Dataset Model 4, the two predictors emerging as significant predictors of whether a person would be reported as having Dementia 3 years later were Social Isolation and Physical Inactivity. The analysis (2nd step) yielded an odds ratio of 3.445 for Social Isolation, with a 95% Confidence Interval of 1.352-9.164, p=.013 and an odds ratio of 2.452 for Physical Inactivity, with a 95% Confidence Interval of 1.118-5.378, p=.025. See Table 4.14 below.

Table 4.14

Significant predictors (reduced model) using forward stepwise logistic regression

Original Dataset		**OR (expB)**	**p**	**CI**
	Significant Predictors			
Step 1	Physical Inactivity	7.667	.003	1.981-29.674
Imputed Dataset Model 4				
	Significant Predictors			
Step 1	Social Isolation	3.520	.010	1.352-9.164
Step 2	Social Isolation	3.445	.013	1.302-9.120
	Physical Inactivity	2.452	.025	1.118-56.378

4.4.4 Overview of Modelling Results

The Original Dataset Model exhibited excellent goodness of fit, indicating that it fit the data well, in comparison to the null model. It exhibited a substantial improvement, against the null model, in the predictive value of who would be classified with dementia 3 years later. Some independent variables appeared to make a uniquely statistically significant contribution to the model, namely, Living in a more Congregated Setting and Physical Inactivity. However, there was a wide Confidence Interval for the odds ratios for each of these variables and so these results need to be interpreted with extreme caution; it may indicate that they are not statistically significant overall.

The Imputed Dataset Model 4 exhibited a reasonable goodness of fit for the data in comparison to the null model. It exhibited a substantial improvement in predictive value over the null model. Some independent variables appeared to make a uniquely statistically significant contribution to the model, namely Living in a more Congregated Setting and Social Isolation. There was a narrower Confidence Interval for these odds ratios which leads to more confidence in these findings as potentially being significant predictors in the model.

Forward stepwise logistic regression analysis of both models yielded reasonably aligned results with logistic regression analysis, with Physical Inactivity and Social Isolation being identified as significant predictors, Physical Inactivity for the Original Dataset Model and both factors for Imputed Dataset Model 4. Confidence intervals for odds ratios in Imputed Dataset Model 4 were narrower than Original Dataset Model, leading to more confidence in the significance of these results.

Logistic regression identifies associations rather than causation, therefore any interpretation of the above requires caution. It can be said that there appears to be some association between the risk factors as a whole and the odds of being diagnosed with dementia in the subsequent 3 years in this sample, with three risk factors emerging as perhaps having a stronger association with subsequent dementia diagnosis, namely Living in a more Congregated Setting, Physical Inactivity and Social Isolation. However, given the relatively small sample size in relation to the large number of independent variables, only very tentative interpretations of association can be made.

4.5 Influence of Risk Factors on Age of Dementia Diagnosis

Further analyses were run to explore the relative influence of the risk factors on age of dementia diagnosis. Risk factors were aggregated into three aggregate categories to reduce the number of independent variables in the analysis, thereby increasing power (0-3, 4-6 and 7-10 risk factors).

4.5.1 Descriptive Statistics

Descriptive statistics are outlined in Table 4.15 overleaf.

Table 4.15

Descriptive statistics for the original and imputed model datasets

Model Number		Mean	Std Deviation	N
Original Dataset	*Age of Diagnosis*	52.71	5.655	63
	Gender	1.67	.475	66
	Level ID	2.20	.664	59
	Residence	2.32	.687	65
	Number Risk Factors	1.15	.361	66
Imputed Model 1	*Age of Diagnosis*	52.71	5.655	63
	Gender	1.67	.475	66
	Level ID	2.17	.692	66
	Residence	2.32	.683	66
	Number Risk Factors	1.24	.432	66
Imputed Model 2	*Age of Diagnosis*	52.71	5.655	63
	Gender	1.67	.475	66
	Level ID	2.15	.707	66
	Residence	2.30	.701	66
	Number Risk Factors	1.24	.466	66
Imputed Model 3	*Age of Diagnosis*	52.71	5.655	63
	Gender	1.67	.475	66
	Level ID	2.15	.685	66
	Residence	2.33	.687	66
	Number Risk Factors	1.27	.482	66
Imputed Model 4	*Age of Diagnosis*	52.71	5.655	63
	Gender	1.67	.475	66
	Level ID	2.11	.726	66
	Residence	2.33	.687	66
	Number Risk Factors	1.30	.495	66
Imputed Model 5	*Age of Diagnosis*	52.71	5.655	63
	Gender	1.67	.475	66
	Level ID	2.20	.706	66
	Residence	2.32	.683	66
	Number Risk Factors	1.27	.482	66
Pooled Estimates	*Age of Diagnosis*	52.71		63
	Gender	1.67		66
	Level ID	2.15		66
	Residence	2.32		66
	Number Risk Factors	1.27		66

4.5.2 Ability of Models to Predict Age of Dementia Diagnosis in the Sample

Table 4.16 below shows that the adjusted R squares evaluating model performance across the original dataset model and imputed models were relatively small, indicating only a small contribution of predictors to age of dementia diagnosis. The adjusted R square for Imputed Model 5 is .128, explaining almost 13% of variance in the model. Adjusted R squares are reported, rather than R squares, which may over-estimate model variance in cases with small sample sizes (Pallant, 2020).

The use of categorical independent variables to predict a continuous dependent variable can lead to a lower R square value in the model due to variance in any of the independent variables being restricted to 1, 2 or 3 (quantity of aggregated risk factors present) in this case.

Table 4.16

Overall performance of models in predicting age of dementia diagnosis

Model Number	R	R Square	Adj. R Square	Std Error
Original Dataset	.312	.098	.027	5.579
Impute Model 1	.288	.083	.020	5.599
Impute Model 2	.310	.096	.034	5.559
Impute Model 3	.369	.136	.076	5.435
Impute Model 4	.257	.066	.002	5.650
Impute Model 5	.429	.184	.128	5.282

Overall model fit as measured by ANOVA analysis shows a significant fit for one of the imputed datasets: Imputed Model 5, F (4,62) =3.270, p=.017. This means that this regression model fits the data better than the null model and indicates that the predictor variables (Quantity of Risk Factors, Gender, Level ID and Residential Status) significantly improved the fit of these models. See Table 4.17 below.

Table 4.17

Overall model fit

Model Number		**Sum of Squares**	**df**	**F**	**p**
Original Dataset	*Regression*	171.647	4	1.379	.254
	Residual	1587.339	51		
	Total	1758.986	55		
Impute Model 1	*Regression*	164.323	4	1.310	.277
	Residual	1818.534	58		
	Total	1982.857	62		
Impute Model 2	*Regression*	190.348	4	1.540	.203
	Residual	1792.509	58		
	Total	1982.857	62		
Impute Model 3	*Regression*	269.502	4	2.281	.071
	Residual	1713.355	58		
	Total	1982.857	62		
Impute Model 4	*Regression*	131.436	4	1.029	.400
	Residual	1851.421	58		
	Total	1982.857	62		
Impute Model 5	*Regression*	364.896	4	3.270	**.017**
	Residual	1617.961	58		
	Total	1982.857	62		

4.5.3 Contribution of Individual Predictors to Model Performances

Results for the models with best performance and fit were reviewed for the contribution of their individual predictors. Results for all models are given in the table below, including a pooled model from all imputed datasets. Part correlation coefficients are reported. Squaring the value of the part correlation coefficient gives an indication of the total amount of variance in age of dementia diagnosis uniquely explained by that predictor variable (Pallant, 2020).

In Imputed Model 5, the number of accumulated risk factors was a significant predictor in the model t(*df*)=3.289, p=.002. The number of accumulated risk factors had a part correlation coefficient of .390, squaring this gives .152, indicating a unique contribution of 15% in this model to total variance in age of diagnosis. Gender, level of intellectual disability or residential status did not significantly contribute to model variance in predicting age of dementia diagnosis. See Table 4.18 overleaf.

Table 4.18

Relative contribution of individual predictors to model performances

Model Number		β	t	p	Part Correlation	Collinearity	
						Tolerance	*VIF*
Original Dataset	*Gender*	.139	1.041	.303	.138	.989	1.011
	Level ID	.000	.002	.999	.000	.786	1.272
	Residence	.055	.375	.709	.050	.813	1.230
	Risk Factors	.261	1.911	.062	.254	.948	1.055
Model Number 1	*Gender*	.141	1.114	.270	.140	.991	1.009
	Level ID	-.049	-.368	.714	-.046	.896	1.116
	Residence	.080	.604	.548	.076	.893	1.119
	Risk Factors	.229	1.802	.077	.227	.981	1.019
Model Number 2	*Gender*	.178	1.400	.167	.175	.967	1.034
	Level ID	.030	.221	.826	.028	.831	1.203
	Residence	.021	.151	.881	.019	.796	1.256
	Risk Factors	.259	1.989	.051	.248	.922	1.085
Model Number 3	*Gender*	.149	1.216	.229	.148	.987	1.013
	Level ID	.014	.106	.916	.013	.792	1.263
	Residence	.021	.159	.874	.019	.820	1.220
	Risk Factors	.328	2.600	.012	.317	.937	1.067
Model Number 4	*Gender*	.169	1.313	.194	.167	.972	1.028
	Level ID	-.050	-.346	.731	-.044	.781	1.280
	Residence	.042	.296	.768	.038	.797	1.254
	Risk Factors	.206	1.529	.132	.194	.883	1.133
Model Number 5	*Gender*	.138	1.159	.251	.138	.987	1.013
	Level ID	-.117	-.894	.375	-.106	.823	1.215
	Residence	.112	.908	.367	.108	.921	1.086
	Risk Factors	.416	3.289	.002	.390	.881	1.136
Pooled	*Gender*		1.227	.220	.154		
	Level ID		-.225	.832	-.031		
	Residence		.393	.695	.052		
	Risk Factors		1.837	.074	.277		

4.5.4 Overview of Risk Factor Influence on Age of Dementia Diagnosis

It appears that there may be some association between number of risk factors accumulated by an individual and the age at which they are subsequently diagnosed with dementia. However, the overall model only explains a relatively small part of the variance in age of dementia diagnosis and other unexplored factors may be more influential. Small sample sizes and use of categorical independent variables reduced the power of linear regression analysis to assess variance in age of diagnosis.

4.6 Individual Lives, Individual Ageing Journeys

It is important to acknowledge that each participant within IDS-TILDA Waves has their own individual experience of positive (or less positive) ageing. It was decided to explore this in more detail, using the information gained from derivation of Lancet risk factors to inform a biopsychosocial 'snapshot' of participants' life experiences of ageing as a person with Down syndrome. The derived Lancet risk factors for this research cover mental and physical health, lifestyle behaviours and social aspects of each person's experience, all crucial dimensions of positive ageing (Fernández-Ballesteros et al., 2019). More subjective dimensions such as loneliness, resilience, optimism are not included in this exploration and it is acknowledged that these are also important aspects of positive ageing (Kleineidam et al., 2018).

Five people were chosen to explore life experience of dementia diagnosis in differing decades – one person aged 43, one person aged 53 (median age of diagnosis in sample) and one person aged 62 (no-one was diagnosed at age 63), along with the youngest (age 34) and oldest (age 66) reported diagnoses of dementia in the sample. Three people without a diagnosis of dementia across the waves were also examined for comparison purposes.

These case studies have been included to give a more granular overview of the actual ageing experience of several participants within the sample, at different decades of age, both with and without a dementia diagnosis. It gives an opportunity to review participants' changes in risk factors across the 3 waves and provides a more detailed overview of their ageing experience than is possible from the necessarily aggregated data used in the statistical analysis. The findings from the case studies align with the statistical findings, in that risk factors are tending to cluster into a few brain health domains, adding more detail to the overall statistical findings.

4.6.1 Youngest and Oldest Reported Diagnosis of Dementia

Case Study 1 (CS1)

CS1 came into Wave 1 being recorded as having a pre-existing diagnosis of dementia, with age of diagnosis recorded as 34. This was a man with severe/profound intellectual disability who participated in Waves 1-3 of data gathering. He is recorded as living in a more congregated residential setting across all three waves. This person was reported as having no educational attainment.

This individual had several risk factors present, particularly from Wave 2. He reported a pre-existing diagnosis of depression, concurrent with the diagnosis of dementia. It is very unusual to have a diagnosis of dementia from such a young age, even with Down syndrome. It is also notable that this person continued to participate in Waves 2 and 3 of IDS-TILDA, indicating some stability of functioning and longevity, which again is not highly indicative of an early onset dementia diagnosis in this population.

Symptoms of depression are often very similar to symptoms of early-stage dementia in this population. It can be speculated that this may be an incorrect dementia diagnosis, particularly as standardised assessment instruments were uncommon in Irish support services at the time IDS-TILDA research began in Wave 1. It also highlights the previously discussed difficulties in assessing people within the severe/profound range of intellectual disability for dementia. However, it is reported as a clinical diagnosis of dementia in the data so must be recorded as such in this research. See Table 4.19 overleaf.

Table 4.19

CS1 risk factor profile across waves

	Hearing Loss	Hypertension	Frequent Alcohol	Obesity	Smoker	Depression	Social Isolation	Physical Inactivity	Diabetes
Wave1	no	no	no	missing	no	yes	no	yes	no
Wave2	no	yes	no	missing	no	yes	yes	yes	no
Wave3	no	yes	no	missing	no	yes	yes	no	no

Case Study 2 (CS2)

CS2 participated in Waves 1 -3 and was reported as having a dementia diagnosis in Wave 3, with age of diagnosis recorded as 66. This was a man with severe/profound intellectual disability. He is recorded as living in a community group home setting across all three waves. This person was reported as having no educational attainment. See Table 4.20 below.

Table 4.20

CS2 risk factor profile across waves

	Hearing Loss	Hypertension	Frequent Alcohol	Obesity	Smoker	Depression	Social Isolation	Physical Inactivity	Diabetes
Wave1	yes	no	no	missing	no	no	yes	yes	yes
Wave2	yes	no	yes	missing	no	no	yes	yes	yes
Wave3	yes	no	yes	missing	no	no	yes	yes	yes

This gentleman had many risk factors across the waves, with a diagnosis in Wave 3. Despite living in a community setting, he is reported as being socially isolated in all three waves. He also presents with hearing loss, which may contribute to less engagement in community.

4.6.2 Diagnosis of Dementia

Case Study 3 (CS3)

CS3 came into Wave 1 recorded as having a pre-existing diagnosis of dementia, with age of diagnosis recorded as 43. This was a woman with moderate intellectual disability, who participated in Waves 1 and 2 of data gathering. She is recorded as living in a community group home setting in Wave 1 and then in a family home setting in Wave 2. This person was reported as having no educational attainment. See Table 4.21 below.

Table 4.21

CS3 risk factor profile across waves

	Hearing Loss	Hypertension	Frequent Alcohol	Obesity	Smoker	Depression	Social Isolation	Physical Inactivity	Diabetes
Wave1	no	no	no	yes	no	no	no	yes	no
Wave2	no	no	no	missing	no	yes	no	yes	no

This lady moved from a community group home to a family setting, which is an unusual direction of movement in residential terms for this population. It can be speculated that perhaps she moved home to her family for more support as she declined with dementia; she did not participate in Wave 3, perhaps due to further decline or death. Depression diagnosis in Wave 2 may indicate declining wellbeing overall in this case, aligning with depression co-occurring with dementia in this population (Dekker et al., 2015).

Case Study 4 (CS4)

Case Study 4 participated in Waves 1-3 and was reported as having a dementia diagnosis in Wave 3, with age of diagnosis recorded as 53. This was a woman with moderate intellectual disability living in a community group home setting across all Waves. Educational attainment was not reported for this participant.

Table 4.22

CS4 risk factor profile across waves

	Hearing Loss	Hypertension	Frequent Alcohol	Obesity	Smoker	Depression	Social Isolation	Physical Inactivity	Diabetes
Wave1	no	no	no	yes	no	no	yes	yes	no
Wave2	no	no	no	yes	no	no	no	yes	no
Wave3	no	no	no	yes	no	yes	no	no	no

It can be noted that this lady also developed depression concurrent with dementia diagnosis, as often occurs in this population (Ballard et al., 2016; Dekker et al., 2015). Being reported as being physically active for wave 3, along with receiving a dementia diagnosis, may indicate that efforts were made to support this person to become more active to promote her health. She is reported as obese across all waves.

Case Study 5 (CS5)

Case Study 5 participated in the first two waves of data gathering and was reported as having a dementia diagnosis in Wave 2, with age of diagnosis recorded as 62. This was a woman with moderate intellectual disability living in a community group home setting in Wave 1 and moving to a more traditional residential/congregated setting in Wave 2. Educational attainment was not reported for this participant. See Table 4.23 below.

Table 4.23

CS5 risk factor profile across waves

	Hearing Loss	Hypertension	Frequent Alcohol	Obesity	Smoker	Depression	Social Isolation	Physical Inactivity	Diabetes
Wave1	no	no	no	missing	no	no	yes	yes	no
Wave2	no	yes	no	missing	no	no	yes	yes	no

This lady moved to more congregated living supports in Wave 2, perhaps due to diagnosis of dementia and higher support needs. It can be noted that her social isolation and physical inactivity is reported to be unchanged with the move to the new residential setting.

4.6.3 No Dementia Diagnosis

For comparison, three other participants who were not diagnosed with dementia by Wave 4 were also examined for risk factor prevalence. These were chosen from their ages in Wave 1, representing different decades of entry into the study.

Case Study 6 (CS6)

Case Study 6 was age 43 on entry into Wave 1 of the study. This person participated in Waves 1 – 3 of data gathering. This was a woman with moderate intellectual disability living independently or in a family setting across all three waves. She was reported as having some educational attainment.

Table 4.24

CS6 risk factor profile across waves

	Hearing Loss	Hypertension	Frequent Alcohol	Obesity	Smoker	Depression	Social Isolation	Physical Inactivity	Diabetes
Wave1	no	no	no	no	no	no	yes	yes	no
Wave2	no	no	no	missing	no	no	no	yes	no
Wave3	no	no	no	missing	no	no	no	yes	no

This lady was reported as physically inactive across all waves, reflecting the high prevalence of this risk factor across the sample. Overall, she presents with a lower number of risk factors, and it is notable that she is living in a more independent/family living situation for all waves.

Case Study 7 (CS7)

CS7 was age 53 on entry into Wave 1 of the study. This person participated in Waves 1 -3 of data gathering. This was a man with severe/profound intellectual disability who lived in a community group home setting across all waves of data gathering. He was reported as having no educational attainment.

Table 4.25

CS7 risk factor profile across waves

	Hearing Loss	Hypertension	Frequent Alcohol	Obesity	Smoker	Depression	Social Isolation	Physical Inactivity	Diabetes
Wave1	no	no	no	yes	no	no	yes	yes	no
Wave2	no	no	no	yes	no	no	no	yes	no
Wave3	no	no	no	yes	no	yes	no	no	no

This gentleman presented with several risk factors across the waves. He developed depression as he aged, reported in Wave 3.

Case Study 8 (CS8)

CS8 was age 62 on entry into Wave 1 of the study. This person participated in Waves 1 – 3 of data gathering. This was a woman with moderate intellectual disability who lived in a community group home setting across all waves of data gathering. Educational attainment level was not reported for this participant.

Table 4.26

CS8 risk factor profile across waves

	Hearing Loss	Hypertension	Frequent Alcohol	Obesity	Smoker	Depression	Social Isolation	Physical Inactivity	Diabetes
Wave1	yes	no	no	yes	no	no	yes	no	no
Wave2	yes	no	no	yes	no	no	yes	yes	no
Wave3	yes	no	no	yes	no	no	no	yes	no

This lady had several risk factors present without a diagnosis of dementia recorded by Wave 4.

4.6.4 Life experience of Ageing in this Sub-Sample

Experience of ageing tended to cluster within higher prevalences of a few risk factors, with high prevalences of obesity, depression, social isolation and physical inactivity being found across the waves for participants. All participants were reported as physically inactive in at least one of their waves of participation with half of participants being reported as physically inactive for all waves of their participation. Three out of the eight participants here developed depression in Wave 3, over one third of this sub-sample (37.5%). Another person was reported as having depression across all waves, meaning a depression prevalence of 50% in this random sub-sample by Wave 3. Half of the participants in this sub-sample had missing obesity data. Where obesity data is recorded (4 out of these 8 participants), it is present in every case. See summary Table 4.27 overleaf.

Table 4.27

Prevalence of risk factors per biopsychosocial ageing domain

BPS Domain	**Risk Factor**	**%Present per Participant (in at least 1 wave)**
Physical Health	*Hearing Loss*	25
	Hypertension	25
	Diabetes	13
	Obesity	50*
Mental Health	*Depression*	50
Social Engagement	*Social Isolation*	88
Lifestyle Behaviours	*Frequent Alcohol*	13
	Smoker	0
	Physical Inactivity	100

**Plus 38% missing data*

High rates of social isolation were reported as being present in at least one wave for participants in this sub-sample, in contrast to lower overall lagged regression model prevalence of social isolation. Seven out of the eight participants had social isolation reported as being present for them in at least one reporting Wave. Levels of social isolation overall decreased in this sub-sample by Wave 3, with 50% of participants no longer reporting social isolation as being present – reflecting the trend of lower social isolation rates in the overall participant sample by the third wave of data collection. Lower prevalence rates of the other risk factors of hypertension, hearing loss, smoking, diabetes and alcohol consumption were reported, in contrast to the general population and in line with the overall participant sample findings.

This sub-sample gives a more granular overview of the presentation of participants across waves. It can be noted that the residential setting of most participants remained relatively stable, even if a diagnosis of dementia was made. Presence of risk factors is quite clustered into a few variables (obesity, depression, social isolation, physical inactivity) with several of the Lancet model risk factors having low prevalence in this sub-sample. In some aspects of positive ageing, these people appear to be doing well, whilst there remain significant challenges in other aspects of positive ageing such as mental health, social engagement and weight management/physical activity.

4.7 Overall Summary of Results

Mean age of dementia diagnosis in this sample population is 52.7 years (median 53 years), in line with other research with this population (Iulita et al., 2022). There was a significant effect for gender with this population, with more than half the women in the sample diagnosed with dementia, in comparison to one-third of the men. Emerging research into gender differences in this population is finding a higher burden of tau pathology and small vessel cerebrovascular disease in women with Down syndrome in comparison to their male peers (Andrews et al., 2025). Level of intellectual disability did not appear to significantly influence the risk of dementia diagnosis in this sample.

A different risk prevalence profile was found for this sample, in comparison to peers in the general ageing population, with higher levels of No Education, Obesity, Depression and physical inactivity in this sample. A more detailed look at individual risk profiling found a tendency for a clustering of risk factors into a few variables (obesity, depression, social isolation, physical inactivity) with other risk factors having a low prevalence. This highlights a potentially

different ageing experience for people ageing with Down syndrome and the need to design positive ageing supports and interventions specifically geared towards their needs.

Demographic variables had some influence on risk factor prevalence also, with a significant effect of level of intellectual disability on no education, obesity and physical inactivity, with hypertension approaching significance. Those with severe/profound intellectual disability emerged with a significantly increased prevalence of the risk factors of no education, hypertension and physical inactivity. Those with moderate intellectual disability had the highest levels of obesity. Residential setting also influenced risk factor prevalence with those living in more congregated settings having significantly higher prevalence of no education, hypertension, depression and physical inactivity. Those with severe/profound disability in the sample were significantly more likely to live within more congregated settings; they were at risk of a significantly different ageing experience based on these results.

Regression modelling showed two models (original dataset and imputed model 4) were a good predictive fit for diagnosis of dementia. Living in a more congregated setting, physical inactivity and social isolation emerged as individual significantly predictive risk factors across these two models. Regression modelling appeared to show some association between number of risk factors present for an individual and age of dementia diagnosis. However, given relatively small sample size for regression modelling, these are tentative associations that may indicate domains of future research for dementia risk in this population.

Chapter 5: Discussion

5.1 Introduction

This chapter will give an integrative overview of ways in which the results from this research can make a positive difference in the lives of those ageing with Down syndrome. It will highlight how the results align with other relevant research findings and explain the impact on this sample's ageing experience arising from the findings, including how this may diverge from the ageing experience of those in the general population. Recommendations for further research, policy, practice and education will be made along with an outline of how these findings can be disseminated to support positive ageing for people with Down syndrome.

5.2 Positive Ageing for People with Down syndrome

What does positive ageing look like for a person with Down syndrome? It's not the absence of disease or optimal physical and cognitive functioning (Rowe & Kahn, 1997), given the significantly elevated prevalence of DSAD and other chronic conditions as this population ages (Fonseca et al., 2019; Fortea et al., 2021; Videla et al., 2022). There is a cumulative effect of these health impacts alongside their lifelong intellectual disability. This may mean that those ageing with Down syndrome do not have the internal coping or external social support resources to selectively optimise their functioning for positive ageing (Baltes & Baltes, 1990; Carstensen, 1992; Kahana & Kahana, 2003)

A "new narrative of ageing" emphasises the broad scope and synergy of various biopsychosocial aspects of ageing required to enhance the experience of positive ageing (Diehl et al., 2020, p. 582). There is now a recognition that the social and emotional aspects of ageing are as important as the physical aspects, including for people ageing with Down syndrome (Arnett et al., 2020; Depp et al., 2010; Gangadharan et al., 2009). Many people with Down syndrome report a subjectively positive attitude towards their ageing, despite the many challenges they may face (Burke et al., 2014; Gangadharan et al., 2009).

Positive psychology's approach to ageing has much applicability for those ageing with Down syndrome, refocusing on strengths and meaning as one ages, away from losses and deficits (de Vries & McGlinchey, 2023; Heller & van Heumen, 2021). People have autonomy over the direction of their life as they age, making decisions about what represents a positive ageing process for them (Heller & van Heumen, 2021). This is a powerful lens in which to support

positive ageing for people with Down syndrome, given their historical (and still current?) lack of choice about their own lives (Franits, 2005). A nuanced positive psychology approach to positive ageing incorporates a broad range of domains, including maintaining physical and cognitive functioning but also adapting resiliently to the experience of ageing and remaining actively engaged in your own life (Annele et al., 2019; Fernández-Ballesteros et al., 2019). These newer approaches have the flexibility to be relevant to the life experience of those ageing with Down syndrome or other lifelong disability (Kleineidam et al., 2019).

The research in this thesis has undertaken a detailed exploration into the lived reality of those ageing with Down syndrome in recent times in Ireland, using the rich longitudinal biopsychosocial data repository that is the IDS-TILDA dataset. The research explores this group's biopsychosocial factors of positive ageing, using the Lancet model of brain health (Livingston et al., 2020) as a framework, given their significantly increased DSAD risk and the recognised importance of maintaining cognitive health as part of positive ageing (Fernández-Ballesteros et al., 2019; Fortea et al., 2021).

5.3 Brain Health and Positive Ageing

There is now robust evidence internationally regarding the importance of biopsychosocial factors in maintaining brain health and reducing dementia risk across the lifespan (Livingston et al., 2024; Livingston et al., 2020; Livingston et al., 2017; World Health Organization, 2022a, 2022b). The applicability of these models of brain health have not been tested in some minority populations, including those with Down syndrome, despite their significantly increased dementia risk as they age and resulting ceiling placed on their life expectancy (Iulita et al., 2022). There appears to be some heterogeneity within the population of people ageing with Down syndrome regarding their "risk and resilience" to DSAD, affecting their experience of positive ageing in this regard (Boyle et al., 2025; Krinsky-McHale, 2008).

The question arises as to what extent the biopsychosocial risk factors outlined in the Lancet dementia model (Livingston et al., 2020) are relevant to maintaining cognitive health or postponing cognitive decline in this population with almost total Alzheimer's penetrance with age. Another question regards the relative prevalence of the risk factors in this model for those ageing with disability as compared to the general population. These may differ given their often-diverging life circumstances with lack of self-determination, increased carer supports and potentially lower social inclusion opportunities (Franits, 2005; Ijezie et al., 2023). This research aimed to explore these important issues in relation to the positive ageing of people with Down

syndrome. Relative risk profiles established for this population can provide useful guidance on where to focus support/intervention efforts to enhance positive ageing in this population.

5.4 Research Aims

This research aimed to explore the influence of various biopsychosocial factors on the risk of developing dementia in a sample of people ageing with Down syndrome. It used ten risk factors from the Lancet dementia risk model (2020) and demographic factors as independent variables. Lagged logistical regression analysis was the method used to investigate the longitudinal effect of these BPS factors on risk of dementia diagnosis three years later. The relative prevalence of various risk factors found in this population enables a comparison to those of ageing peers in the general population, giving an overview of similarities and differences in the ageing experience.

5.5 The Ageing Experience: Demographics and Dementia Risk

5.5.1 Demographics and Biopsychosocial Factors

No gender difference in risk factor profiles was found. This is surprising, as in the general population and in previous research with Down syndrome, differences in gender prevalence have been found in hypertension, frequent alcohol use, obesity, physical inactivity (Glantz et al., 2020; Lin & Li, 2021; Westrop et al., 2019; Zhou et al., 2021).

Some differences in the pattern of risk factor profiles across levels of intellectual disability were found. A significant association between higher level of disability and lower levels of education was found within the sample, aligning with experiences in obstacles to progression in education worldwide for this cohort (Alquraini & Gut, 2012; Olson et al., 2016). Despite low overall levels of hypertension in this population, those within the severe/profound range of intellectual disability had significantly higher levels of hypertension (21.4% of this sub-group) than those with mild or moderate intellectual disability. They also had significantly higher levels of physical inactivity (88% of this sub-group) than those within other intellectual disability ranges. It can be inferred from this finding that the very low levels of physical activity reported in this group could be driving higher levels of hypertension as they aged, despite the protective physiological effect of their genetic syndrome.

Those within the moderate range of intellectual disability were more likely to be obese (59.3% of sub-group compared to approximately one-third of the other sub-groups). Percentage levels of obesity in participants in the mild and severe/profound range of intellectual disability

were roughly equivalent (35% and 30.7%), despite those within the severe/profound range being the most physically inactive. Those within the mild range of intellectual disability were the most physically active of the sample, which may have conferred some protection against obesity. They may also have been more able to understand and implement advice around healthy eating. Those within the severe/profound range of intellectual disability are less able to prepare meals, make meal choices or buy treats for themselves and are more reliant on caregivers to provide meals. Therefore, these participants may be supported to eat within a healthy calorific range by family or staff members conscious of weight management, potentially conferring a protective effect against obesity. A relatively high level of missing data for obesity within the sample leads to less confidence in the generalisability of these findings, with potential for further research in this area.

Residential Settings. People ageing with Down syndrome in this sample have different life circumstances than the general population, in that they are more likely not to live independently or with family members. This research found that most participants across the waves lived either in community group homes or more congregated settings (80% in each wave) rather than with family or independently (20% in each wave). Given age ranges from 45 years of age within the sample, this is quite a different life circumstance than their peers in the general community, who usually need higher living supports/congregate supports only in their older age. Approximately 50% of those aged 80+ in the general community are in a nursing home (Skudlik et al., 2023), which is a significantly lower percentage at a much older age than those in this sample with Down syndrome living in state-provided residences.

Participants with a higher level of intellectual disability were even more likely to live in congregated settings than those with moderate or mild intellectual disability, with only 2% with severe/profound intellectual disability reported as living with their family. This trend has also been reported in reviews of housing options for this population (Roebuck, 2021). Those living in congregated settings were significantly more likely to have hypertension, be depressed, have lower levels of education and higher levels of physical inactivity, than those living with family, independently or in community group homes. Movement between community group homes and more congregated settings observed across waves reflects the dynamic interplay between a policy of movement into community and the frequent need for specialised medical supports with ageing (Roebuck, 2021; Ryan, 2017).

These are important findings highlighting a significant deviation from the general population's living circumstances at a much younger age for this population, with attendant potential loss of self-determination and community integration opportunities for these people ageing with Down syndrome. When people lose the ability to self-direct their own life and lifestyle behaviours, the potential for making independent positive ageing choices may decrease, leading to a decreased quality of life for this population as they age. This is not in keeping with positive ageing models' focus on assets and resources and lies more within a deficits-based model of lack of self-determination and choice as one ages, reducing one's perception of ageing being a positive experience (Cosco et al., 2013). It also may reduce the individual's ability to maintain or enhance emotional and social health opportunities, integral aspects of maintaining cognitive function and brain health (Livingston et al., 2020).

Ageing with severe/profound intellectual disability. These findings indicate a concerning divergence in the ageing experience for those with a higher level of support need compared to those with mild to moderate intellectual disability. Those ageing with severe/profound intellectual disability have higher levels of physical inactivity, hypertension and lower levels of education than their peers. They are more likely to live in congregated settings, with less opportunity to engage in meaningful daily activities and social interactions within their community. They may also have less opportunity to positively age, given higher rates of adverse biopsychosocial circumstances in these congregated settings (higher depression and lower physical activity). The increased risk of living in a congregated setting may be compounding adverse ageing circumstances they are already more likely to experience.

5.5.2 Demographics and Dementia Risk

Almost half of the participants from this study sample taken from Wave 1 of IDS-TILDA research had developed dementia by Wave 4 (44%, N=66 out of 150). There is a mean age of diagnosis of 52.7 years, an age aligned with other research findings on dementia in this population (Fortea et al., 2021; Iulita et al., 2022). One participant within the severe/profound intellectual disability range presented with a very young age (34) of reported dementia diagnosis; this may indicate a misdiagnosis, highlighting the acknowledged difficulty in assessment and diagnosis of people within this ability range (Wissing et al., 2022a; Wissing et al., 2022b). Overall, this sample population was aligned with the body of research findings showing a high incidence of dementia as they aged.

There was a significantly higher percentage of females than males with dementia within this sample. This study finding may warrant further investigation across further IDS-TILDA waves, to see if the higher risk for females is replicated. Mixed findings on gender differences for dementia in this population have been found, with a recent meta-analysis finding no significant gender difference, despite the theory that earlier menopause in this population leads to lower circulating levels of oestrogen, with subsequent neurodegenerative effects (Andrews et al., 2022; Iulita et al., 2023). However, emerging evidence is pointing to a higher tau and small vessel cerebrovascular disease burden in women with Down syndrome, recommending a focus on gender differences in DSAD (Andrews et al., 2025). Findings of a significant gender difference in this study may add to emerging research in this area. There was no effect of level of intellectual disability found on dementia diagnosis within this sample, aligned with other findings for this population (Boyle et al., 2025; Hartley et al., 2023), despite the acknowledged difficulties in assessing DSAD in those with more severe/profound disability (Wissing et al., 2022c).

Living in a congregated setting emerged as one of the significant predictors of later dementia diagnosis in this sample. It can be speculated, if participants began to lose functioning during a prodromal period leading to dementia diagnosis, this may precipitate a move to a higher support setting prior to a confirmed diagnosis of dementia. A difference in type of residential setting by dementia diagnosis is not found within this sample, however. Higher levels of illness, sedentary behaviour, challenging behaviours, loss of skills and social isolation have been found as the life experience for those living in congregated settings (McConkey et al., 2016; Roebuck, 2021). Congregated living is acknowledged as posing barriers to positive ageing; it has been found that lower quality of life in congregated settings can impact on cognitive health and functioning for those in the general population, due to lessened opportunities for social and community interactions (Chang et al., 2017). A systematic review of social connectedness on health outcomes in general community congregated settings found a significant lack of social engagement influencing higher levels of depression and lower levels of physical and cognitive functioning (Lim et al., 2023). These general community findings are echoed in the findings of this research for people ageing with Down syndrome.

Living in a congregated setting compounds risk, with both a higher risk for modifiable risk factors being present and for developing dementia. Living in a congregated setting is associated with higher levels of hypertension, depression and physical inactivity in the general population, with subsequent impact on dementia risk (Livingston et al., 2024; Livingston et al., 2020). Higher levels of depression have been found in the general ageing population living in nursing homes, a similar congregate setting (Jalali et al., 2024; Moreno-Agostino et al., 2021). Physical inactivity levels have been found to be significantly higher also in older adults in the general population living in residential care settings as opposed to community settings (Douma et al., 2017). Hypertension rates of up to 90% prevalence have been reported for residents in nursing homes (Vu et al., 2020). It appears that these dementia risk factors are associated with higher prevalence rates in congregated settings than for those living in community settings. The general population are exposed to these higher risks from an older age when entering a nursing home, typically often only from 80+ years of age (Skudlik et al., 2023). Those ageing with Down syndrome may be exposed to these higher risks to their brain health from young or middle adulthood, if living in a congregated setting.

These findings regarding the demographic of residential settings highlight a significant divergence in life experience between the general ageing population and those ageing with Down syndrome. People with Down syndrome are at much higher risk of living within more congregated settings and from a younger age than their ageing peers in the general population. This may expose them to higher dementia risk over a longer period in their lives. Living in a congregated setting from an earlier age is a population-specific potentially significant risk factor not explored in dementia risk modelling from midlife for those in the general population. It has been recommended that type of residence be included in dementia risk studies with people with Down syndrome (Pounds et al., 2025). It appears that the experience of people ageing with Down syndrome living in congregated settings is worthy of further research and exploration in terms of their opportunities for positive ageing, including maintenance of cognitive functioning.

5.6 The Ageing Experience: Biopsychosocial Factors and Dementia Risk

A different risk factor profile for positive ageing emerged in this sample of participants with Down syndrome than in the general population. This is to some extent to be expected, given the differing genetic profile and potential differing life experiences of people ageing with Down syndrome to those in the general ageing population. Exploration of individual case studies in more detail also highlighted a clustering of risk factors presenting as barriers to positive

ageing in this sample: depression, social isolation (which decreased over the waves), physical inactivity and obesity.

5.6.1 Overall Dementia Risk Modelling

The two most significant Lancet Commission risk factors in this study were Social Isolation and Physical Inactivity. It is important to note that No Education was derived from childhood educational attainment for this study sample, in line with the Lancet Commission modelling of early life educational attainment level being a significant dementia risk factor. The remaining Lancet Commission risk factors are placed either as a midlife or later life risk factor in the generic population model. It was not feasible to derive the remaining variables for this study from midlife or later life due to people with Down syndrome experiencing accelerated ageing and there being no accepted age range for mid-life vs later life in this cohort.

5.6.2 Social Isolation

Social isolation emerges as a significant predictor of later dementia diagnosis within this study. Social inclusion is as vital to the health and well-being of people with intellectual disability as it is for those in the general population (Harrison et al., 2021; McCausland et al., 2021). The movement towards actively facilitating social inclusion for people with intellectual disability in their communities has been ongoing for the past 50 years (Bigby et al., 2009). Social isolation levels decreased in this sample across the waves, potentially reflecting a growing policy and practice acknowledgement of importance of living in community and meaningful community engagement.

Any potential synergistic effect of loneliness and social isolation on later dementia diagnosis within the sample was not examined. Loneliness may be an important element in the ageing experience of this population but was not within the scope of the Lancet model risk factors; it has not been found to independently increase dementia risk (Penninkilampi et al., 2018; Shen et al., 2022). Loneliness may be an important element of the life experience of those ageing with Down syndrome and potentially could be included in future research to explore any potential synergistic effect with social isolation on brain health.

The precise meaning of social inclusion/isolation for people with intellectual disability, remains a topic of some debate in the literature. There is no widely accepted or agreed-upon definition of social inclusion for this population in the literature, with differences in scope of social networks, type of settings for social participation to happen in (segregated vs community) and the depth of the social connection required (Simplican et al., 2015). The concept of social inclusion can be used interchangeably with related concepts in the literature, including social capital and community participation, both of which are complex concepts lacking accepted definitions also (Simplican et al., 2015). In summary, meaningful social inclusion for this cohort may not necessarily be measured by existing social isolation/social network assessment tools.

The findings regarding social isolation in this sample reflect this conceptual and measurement difficulty. Whilst, intuitively, one might feel that people ageing with intellectual disability may be very socially isolated, due to their presenting vulnerabilities and support needs, in fact, the opposite is the case. There are much lower levels of objective social isolation, as measured by the NHATs typology, in this sample population than in the general population (sample 13% vs general 25%). However, closer examination of the construct of social isolation as an **objective** indicator of social connections clarifies why this may be the case. Very few people in this cohort will be 'severely socially isolated' as most people live with someone else in their home, so nearly everyone scores at least one mark (severely socially isolated is categorised as 0 marks). The vast majority, if not all, of this cohort will also have staff support on a regular basis so will not be socially isolated in the traditional sense of the term. Many people live in family or community group home settings where the emphasis is on regular engagements in the community, again lowering the risk of social isolation. Whilst participants may subjectively feel a sense of loneliness or might choose to live with different people or engage in different community activities, this is not the same construct as social isolation. This construct is clearly defined in the Lancet dementia risk model as being an objectively measured construct of frequency of social interactions, rather than the qualitative perception of them (Livingston et al., 2024; Livingston et al., 2020).

These findings suggest that the life experience of people with Down syndrome regarding social isolation may be different from those ageing in the general population; they may be at lower risk overall of being ***objectively*** socially isolated. A person with Down syndrome may feel lonely or alone without experiencing objective social isolation. The social connections the person ageing with Down syndrome has experienced over the course of their life may not be by choice (e.g. imposed housemates, moving to different town/community, staff rostering

changes), impacting their subjective experience of social engagement and interactions. It is important to note these subtle differences in the life experience of social isolation throughout the life of a person with Down syndrome, including the lack of choice and agency in many cases in contrast to their peers.

People with Down syndrome may have a “passive presence” within the community, rather than an active and engaged participation in community life with other community members (Bigby & Wiesel, 2019, p. 2). Radical democratic theory posits that a diversity of community interactions ranging across a spectrum of risk, based on personal choice and opportunity, is a vision of true wide-ranging social inclusion for people with Down syndrome (Clifford Simplican & Leader, 2015). Contact theory posits that social inclusion for this cohort is only fostered under certain conditions: meaningful personal interactions of sufficient frequency and duration, interactions that promote equal status and co-operation and are facilitated by supporters (Craig & Bigby, 2015). John O’Brien’s Five Accomplishments model clearly highlights the importance of having an active meaningful community presence and participation as being central to the experience of a good life (Ee et al., 2022; O'Brien, 1992). Lack of meaningful social engagement may be present for people ageing with Down syndrome despite objectively frequent social and community interactions.

The most significant limitation in the derivation of the Social Isolation variable is that the measurement tool used is not developed specifically or validated for this population. The version of measurement chosen for this research does more closely match the life experience of older people with Down syndrome in not focusing on a marriage question (Cudjoe et al., 2020). There is significant debate in the literature around the measurement of the concept of social isolation within the general ageing population, indicating the difficulties in operationalising this construct for other ageing population groups, including those with Down syndrome (Ejiri et al., 2021; Newall & Menec, 2019).

Many people ageing with Down syndrome live in supported community homes or more congregated settings and the existing social isolation assessment tools fail to adequately assess the specific social ecosystem pertaining in these settings (Boamah et al., 2021). Is the experience of ageing in a congregated setting a different tenor of experience of social isolation that we currently can’t measure or is it within the realm of experiencing loneliness? Is being surrounded by people but not having significant meaningful interactions with them loneliness or social isolation? Perhaps a frequency of social interactions is assumed in such settings but is not actually present. Meaningful community presence and participation is central to a good quality

of life for people with Down syndrome (Bigby & Wiesel, 2019; Harrison et al., 2021; O'Brien, 1992; van Asselt-Goverts et al., 2015). The current measurement of social isolation does not consider if they have active or passive presence in community: being present in community does not automatically enhance meaningful social inclusion (Bigby, 2008).

The literature is clear: social isolation is an objective indicator of lack of social interactions and networks; this is the accepted risk factor for dementia, not loneliness (Livingston et al., 2024; Livingston et al., 2020; Livingston et al., 2017). Various pathophysiological pathways for the effect of social isolation on the brain have been proposed but the association is not still clearly understood (Shen et al., 2022). Are we really interested in this context in measuring a more subjective underlying concept of meaningful connections that are missing in the experience of people in more congregated settings: both those ageing with Down syndrome and older people in the general population? This is one of the central questions arising from this thesis. We need to develop validated social isolation instruments, based on strong theoretical foundations, that more accurately measure/reflect the life experience of those in congregated residential settings. Social engagement experiences may start to converge in later life, with both ageing populations living in more congregated settings, e.g. nursing homes, that may not be by choice. The difficulty of accurately measuring social isolation in congregated settings has been highlighted in the general ageing literature, with the recognition that being surrounded by other people in such settings may not equate to meaningful social interaction opportunities (Boamah et al., 2021). The phrase 'lonely in a crowd' comes to mind to describe this experience. A synergistic effect with loneliness may also be operational in such settings, raising the risk for cognitive decline and dementia even further (Holt-Lunstad & Steptoe, 2022; Lennartsson et al., 2021).

It is interesting to note that Social Isolation as a risk factor was one of the strongest predictors of later dementia diagnosis within the modelling, despite having a relatively low prevalence as a risk factor in the lagged regression models. This indicates that it may be having a relatively strong predictive effect in the overall model and certainly warrants further investigation.

There is an urgent requirement for reliable and validated assessment tools for social isolation to be developed for use with this population, to explore these research questions, particularly for use within congregated settings. These more nuanced measures of social isolation within congregated social ecosystems might also be usefully applied to the ageing experience of the general population in nursing homes. Whilst it appears that people ageing with Down syndrome may be at lower risk of objective social isolation than their peers in the general population, this is a difficult construct to accurately assess in this population, given a higher percentage living in congregated settings from an earlier age. New assessment instruments need to be developed for this population to more accurately capture their life experience of meaningful social interaction and connection.

5.6.3 Physical Inactivity

Physical inactivity emerged as a potential predictor of later dementia risk in this sample. There is very robust evidence to support physical inactivity as a strong determinant of brain health for everyone throughout the lifespan, with numerous physiological protective mechanisms activated in the body through regular exercise (Tari et al., 2025). Positive changes in brain volume and increased cognitive functioning have been observed with an increase in physical activity in people with Down syndrome (Fleming et al., 2022; Pape et al., 2021; Peven et al., 2022).

It is concerning that over two thirds (72%) of the sample in the lagged regression model were recorded as physically inactive with almost all of those with severe/profound intellectual disability recorded as physically inactive, given the strength of this predictor. With the very robust evidence of the benefits of regular physical activity for overall health and brain health, it appears that this may be an important area of intervention to promote brain health for those ageing with Down syndrome. Physical activity has many systemic benefits, contributing to a more active and positive older age (Daskalopoulou et al., 2017). The high levels of physical inactivity in this sample represent a significant concern in supporting positive ageing, including brain health, in this population.

Actual levels of physical inactivity may be even higher than modelled due to lack of detailed measurement of activity in Wave 1 potentially leading to an underestimation of this factor in that wave. When physical activity is measured as a binary variable (yes/no), not analysing the level of intensity of the activity in more detail, associations between levels of physical activity and healthy ageing outcomes are lower compared to more nuanced/detailed

measures of physical activity (Daskalopoulou et al., 2017). In Wave 1, physical activity variable was constructed as a report of engaging in moderate physical activity more than once per week or less than once per week, in comparison to the other waves where more detailed information on intensity and frequency of physical activity was collated into IPAQ categories.

Use of objective measurements of physical activity levels, such as accelerometers, are less subject to reporting and recall bias than self- or proxy-reported questionnaires (Daskalopoulou et al., 2017; Falck et al., 2016). There can be heterogeneity between definitions and understandings of physical activity (Daskalopoulou et al., 2017; Falck et al., 2016). The IPAQ tool used in this research, however, has been found to have good criterion validity and is "a useful tool" for evaluating physical activity with older adults (age 65+), compared with accelerometer data (Tomioka et al., 2011, p. 459).

5.6.4 No Education

Cognitive reserve and maintenance of cognitive reserve is recognised as an integral part of ageing well (Annele et al., 2019; Depp et al., 2010; Fernández-Ballesteros et al., 2019). Educational attainment is often used as a proxy for cognitive reserve within population studies, with higher levels of education associated with a younger brain age and a lower lifetime risk, up to 7% reduction, of cognitive decline and dementia (Anatürk et al., 2021; Larsson et al., 2017; Livingston et al., 2020). Every one-year increase in education has been shown to reduce dementia prevalence rates by 17% (Clouston et al., 2020).

No Education did not emerge as a significant factor for later dementia risk in this sample. Extremely low levels of educational attainment have been reported in this sample, with a significant amount of missing data for this factor, indicating the historical lack of importance / emphasis placed on education as an achievable attainment for people with Down syndrome. This is deeply concerning, reflecting the disenfranchisement of older people with Down syndrome from access to recognised education progression pathways in early life. There may then be a potential significant impact across their lifespan on their brain health and a concomitant reduction in their experience of positive ageing.

Overall, progression to secondary level education in this sample was very low, with only one participant out of 150 in the sample recorded as having secondary level education. As might be expected, those within the higher ranges of intellectual disability were less likely to have gained any educational attainment, in line with previous research findings (Alquraini & Gut, 2012; Olson et al., 2016). It is to be hoped that younger participants in later waves of IDS-TILDA

are reporting more educational attainment and at higher levels within the Irish education system. However, recent research has shown continuing low levels of progression to university by people with a disability (Casey et al., 2020). Existing avenues of lifelong learning for people with Down syndrome vary in quality and accreditation status, reflecting a lack of consistent and high standard educational offerings for this population. This limits their ability to engage in high quality lifelong learning to support cognitive reserve as they age.

Lifelong learning is promoted as a protective factor in maintaining brain health and cognitive functioning for older adults and an important factor in supporting positive ageing (Chen et al., 2015; Wenzel et al., 2024). However, the evidence continues mixed on this point with other research finding that lifelong learning contributes less to maintaining cognitive reserve than a high level of educational attainment to young adulthood (Kremen et al., 2019). The Lancet brain health model continues to emphasise the central importance of educational attainment in early life rather than a focus on later life learning in reducing dementia risk across the lifespan (Livingston et al., 2024; Livingston et al., 2020; Livingston et al., 2017).

It can be speculated that, for those with low educational attainment in early life, engaging in (good quality) lifelong learning may have a disproportionate effect on their brain health, compared to those with a high level of education to young adulthood. A limitation of this research study is that it does not consider the quality and quantity of lifelong learning participants with Down syndrome have engaged in during their adulthood. This was not a measurable variable, due to the great variation in types of lifelong learning opportunities people engaged in, from within-centre classes to community classes to more structured FETAC and other accredited courses. Given the movement towards more access to structured educational opportunities for this population, it is to be hoped that the contribution of lifelong learning opportunities may be more measurable in the future as a potential contributor to brain health across the lifespan. Some research has suggested a positive impact of employment and education on cognitive reserve in adults with Down syndrome (Piro-Gambetti et al., 2024; Temple et al., 2001).

5.6.5 Hearing Loss

Hearing loss almost doubles the risk of developing dementia (Livingston et al., 2020; Livingston et al., 2017). It is generally accepted that people with Down syndrome are at higher risk of hearing loss than those in the general population (Willems et al., 2021) and have lower compliance with wearing prescribed hearing aids (Coppens-Hofman et al., 2011). This will have a significant impact on their quality of life, social interactions and brain health.

However, despite this proven higher penetrance of hearing loss, hearing deficit rate reported in this sample was roughly equivalent to hearing deficit rate in the general population. This may be explained through significant under-estimation of hearing loss in people ageing with Down syndrome found when relying on proxy and self-report, as opposed to audiological testing (McCarron, 2023). Under-reporting of hearing loss in the sample may have led to an under-estimation of the relative influence of actual hearing loss levels in this modelling for risk of dementia. There is often an under-recognition by the person and/or their supporters of hearing loss, combined with low levels of compliance to wearing hearing aids if prescribed (Coppens-Hofman et al., 2011; Willems et al., 2021). This would appear to create significant risks of hearing loss in this population, not reflected in this study's modelling. Use of objective hearing testing as part of data gathering (as was undertaken in later waves of IDS-TILDA research) generates more accurate hearing loss data in sample populations.

5.6.6 Hypertension

The low levels of hypertension in this sample are in line with other research and the genetically protective effect of having Down syndrome for this risk factor (Roy-Vallejo et al., 2020). Higher levels of hypertension in those within the severe/profound range of intellectual disability and in those living in more congregated settings were found, which could be explored for replication in larger samples. Very high levels of hypertension have also been found in those living in nursing homes in the general population, which may be a function of ageing and increased comorbidities (Vu et al., 2020). Those living with Down syndrome in congregated settings are more likely to have higher support needs and more comorbidities (including hypertension), potentially from a younger age than their peers in the general population (Roebuck, 2021). There may also be an interactional effect with higher levels of physical inactivity; those living in congregated settings and those with severe/profound intellectual disability had very high levels of physical inactivity.

It is important to note that in this sample, those diagnosed with hypertension were on medication to reduce blood pressure levels. Clinically diagnosed hypertension is controlled in this sample, therefore, it may not be a measurable risk factor, given previous research findings in the general population that hypertensive medication lowers risk of dementia (Abell et al., 2018). Hypertension did not emerge as a predictive risk factor, aligning with the findings of other research in this area, with appropriate medication for hypertension removing it as a significant risk factor for later dementia diagnosis (Ding et al., 2020).

Only those with a clinical diagnosis and / or prescribed medication for hypertension were categorised as having hypertension in this sample. This may mean that some of those with undiagnosed hypertension were wrongly categorised as not having the condition. Untreated hypertension is a significant risk factor over time for dementia and may not have been fully captured in this model (Livingston et al., 2024; Livingston et al., 2020).

5.6.7 Alcohol and Smoking

Very low levels of frequent alcohol intake and smoking were found in this sample population, in line with other research findings (Chapman & Wu, 2012; McCarron, 2023; Robertson et al., 2020). In the general population, these are major modifiable dementia risk factors, with smoking contributing an estimated 5% of later life risk of dementia (Livingston et al., 2020). These are not significant factors driving dementia risk in this population and this was shown in this research also.

Although those ageing with Down syndrome have a very high risk of Alzheimer's disease (Fortea et al., 2021), the very low levels of smoking and frequent alcohol use do not appear to significantly influence the risk of dementia in this population. An ethical question arises in relation to rates of smoking and alcohol use, relating to the lifestyle choices people with Down syndrome are free to make, in comparison to those in the general population. Historically, people with Down syndrome did not have the autonomy to experiment with lifestyle behaviours such as smoking or frequent alcohol use, due to oversight/control from carers.

Recent Irish legislation, the Assisted Decision-Making Act, emphasises the right of people with intellectual disability to make their own choices, once deemed competent to do so, even if these choices may have adverse consequences for the person (Donnelly et al., 2021). Evidence of higher levels of cigarette and alcohol consumption has been found in those living independently with Down syndrome and other intellectual disability (Swerts et al., 2017).

A study of older Irish people's smoking and alcohol consumption found that those with a positive attitude to their ageing process were more likely to choose to engage in healthy lifestyle behaviours, with reduced smoking and alcohol consumption (Villiers-Tuthill et al., 2016). Attitudes towards the ageing process are highly individual amongst all of us, including people with Down syndrome. Some people ageing with Down syndrome may choose to engage in less healthy lifestyle behaviours, due to habit or to cope with the ageing process. If the spirit of the Assisted Decision-Making Act is truly supported, in the future more people ageing with Down syndrome may choose to engage in smoking or drinking behaviours, with a subsequent increasing impact on their brain health and positive ageing. This is potentially an unintended consequence of this legislation, but an important advance in one sense in the self-determination of people with Down syndrome, choosing how they cope with the ageing process.

5.6.8 Obesity

Obesity affects brain health in several ways, including impairment of metabolic functioning and increased systemic inflammation (Moreau et al., 2021; Ruze et al., 2023). It can also have a significant adverse effect on positive ageing, greatly increasing the risk of several chronic health conditions and depression (Endalifer & Diress, 2020; Lin & Li, 2021).

Rates of obesity are up to 35% of the global ageing population, with women being more at risk of the condition (Lin & Li, 2021). Roughly equivalent prevalence for obesity was found in this sample, at 36%, with no gender differences found. There was approximately one-fifth of the sample missing data for obesity calculation, leading to a need to impute the missing data in MICE models. The imputed dataset estimated a much higher rate of obesity in the sample (45%), based on their overall profiles, implying a potential underestimation of the influence of obesity in the original dataset modelling. Worldwide epidemiological studies estimate significantly increased risk of obesity in people with Down syndrome, again with women being more at risk (Dierssen et al., 2020; Moreau et al., 2021). However, obesity was not found to be a risk factor predictor in this research, using either original dataset or imputed dataset modelling.

There were also two methods used to derive obesity from the dataset, to maximise data available: BMI and waist circumference. Although guidelines indicate that using both methods are acceptable in measuring obesity (World Health Organization, 2011), and testing showed no significant differences between obesity categorisation between the two methods, it is preferable to use one consistent measurement method to maximise data consistency.

5.6.9 Depression

Higher rates of depression have a significant adverse impact on brain health and have been found to have an adverse impact on self-rated positive ageing comparable to poor physical health (Jeste et al., 2013). Prevalence of clinically diagnosed depression in this sample is higher at 23% than that in the general ageing population at 19%. Measurement and clinical diagnosis of depression remains fraught with difficulties in this population, particularly for those with higher levels of need and less verbal ability, with low levels of confidence in making diagnoses by health professionals (A. Axmon et al., 2018; Hinde & Mason, 2020; Hsieh et al., 2020). Prevalence estimation of depression in people with intellectual disability and Down syndrome varies widely in the literature, reflecting difficulties with communication of symptoms, atypical presentations and diagnostic overshadowing (A. Axmon et al., 2018; Scheirs et al., 2022; Walton & Kerr, 2016). No significantly increased rates of diagnosed depression have been found in studies with people with Down syndrome, in comparison to the wider population with intellectual disability (Walker et al., 2011).

There is a high rate of co-occurrence of depression with dementia in both the general population and those ageing with Down syndrome (Cooper et al., 2020; Hakim, 2022). The high prevalence (almost 50%) of dementia in this sample population, leads to speculation if the actual prevalence of depression is higher than reported in this sample. There are also acknowledged physiological risk factors for depression in people with Down syndrome: smaller total brain volume, smaller hippocampus, reduced serotonin levels and increased levels of hypothyroidism (Thom et al., 2021; Walker et al., 2011).

Depression did not emerge as a significant risk factor in this modelling; however, this may have been influenced by the methodological issues outlined above. More research needs to be undertaken to establish the actual prevalence of clinical depression within the ageing population with Down syndrome in Ireland; this may include the need to develop new assessment protocols and tools for more accurate proxy and self-report of depression symptoms in this population.

In the general population, previous literature indicates that older adults may be more likely to have depressive symptomatology than to meet the threshold for diagnosis of clinical depression (Jeste et al., 1999). This may also be the case with adults ageing with Down syndrome, indicating that more may be experiencing depressive symptoms at some level as they age than are formally diagnosed with depressive disorder. Whilst IDS-TILDA measures

depressive symptomatology using the Glasgow Depression Scale, it was felt, in consultation with other experienced clinicians, that this 'snapshot' would not be accurate enough clinically to inform the derivation of the Depression variable. This aligns with the recommendation that depressive symptomatology at one time-point is not enough to inform evaluation of later dementia risk (Kaup et al., 2016). Low and moderate levels of depressive symptomatology have not been found to raise later dementia risk; only high and increasing levels of depressive symptoms, leading to increased likelihood of formal clinical depression diagnosis, are found to independently increase later dementia risk (Kaup et al., 2016).

Aligned with the general population, those ageing with Down syndrome diagnosed with clinical depression are likely to be prescribed anti-depressants, potentially reducing the risk effect of this factor for later dementia diagnosis. This population, however, may be under-diagnosed and under-treated for depression (Thom et al., 2021), indicating that the actual effect of depression in the modelling may not have been fully captured. Not all those in the sample who meet the clinical threshold of having depression may have a diagnosis or be receiving anti-depressants to manage the condition.

5.6.10 Diabetes

Diabetes can have a substantial adverse impact on quality of life as one ages and on risk of cognitive decline and dementia (Maltese et al., 2024). Lower prevalence of clinically diagnosed diabetes at 2% is found in this sample population than is noted in the epidemiological literature for those with Down syndrome, at approximately 10% (Chicoine et al., 2021). This may reflect some under-diagnosis or under-reporting of the condition or may simply be an accurate reflection of the prevalence in this sample.

Lower rates of all types of diabetes in people with Down syndrome than the general population have been found in a large-scale epidemiological study (Baksh et al., 2023). This is surprising when one considers that people with Down syndrome are more likely to be obese and increased visceral fat is linked to increased systemic inflammation and development of diabetes (Moreau et al., 2021). The findings from this sample echo this lower rate of prevalence of diabetes in people ageing with Down syndrome. Diabetes is not found to be a dementia risk factor in this sample.

5.7 Limitations of this Research

Limitations around these findings include the recognised fact of underdiagnosis and late diagnosis of dementia in this population (Benejam et al., 2020; British Psychological Society, 2015; Videla et al., 2022; Wissing et al., 2022c). Dementia diagnosis in this sample was taken from medical records based on doctor's diagnosis, which may have underestimated prevalence of dementia in this population.

This data for this thesis is limited to a relatively small sample of people ageing with Down syndrome in Ireland and so may not be fully representative of the wider population ageing with Down syndrome. Small sample sizes also limit the generalisability and power of this research. Alternative statistical modelling techniques, such as mixed effects regression (MER) modelling, might have yielded more from the data (Garcia & Marder, 2017). Generalised linear mixed models (GLMM) are an example of MER and require an ability to design the analysis with R programme coding. A future research design, using GLMM, could be used to examine the cumulative effect of the participants' status for each risk factor in each wave (present/absent) on their later dementia risk.

Derivation of independent variables was based on a longitudinal nationally representative observational dataset of people ageing with intellectual disability. It is not a clinical dataset and some data was missing, as is quite common in health-related longitudinal datasets (Ibrahim & Molenberghs, 2009). Wider confidence intervals indicate a large range of values present for the population, lessening the accuracy of estimates. These indicate that the ageing experience may be diverging significantly within this cohort, reflected in differences in those living in more congregated settings and with higher levels of support need. These findings indicate the importance of nuance in the approach to healthy ageing interventions in people ageing with Down syndrome; calibrated to their specific life circumstances and presentation of need.

Complex health conditions such as dementia and cancer are acknowledged to be multifactorial in origin, with many influences, both known and unknown, playing a part in the development of the condition over the lifespan. It has been argued that it is important not to overlook the value of small effects findings in terms of their influence on health conditions over time (Götz et al., 2022). Similarly, studies with low power can still provide meaningful preliminary evidence on potential associations between predictor variables and health outcomes, supporting the further development of analytic models. These preliminary studies

can also generate effect size estimates that inform the designing of future studies with higher power. The present modelling offers an initial examination of the hypothesised relationships within this population, contributing to the scant body of literature in this area and providing preliminary empirical parameters for future corroborating studies. It is hoped that this study offers reproducibility and replicability to inform future more highly powered research with this population (Wicherts et al., 2016). This research is presented as exploratory, addressing an under-explored area of research in the fields of positive ageing and dementia risk profiling for people with Down syndrome. The findings may inspire further research testing larger sample sizes using population-based epidemiological modelling techniques, the gold standard in the field (Matranga et al., 2021).

5.8 Integrative Overview of Findings

Every person ageing with Down syndrome is an individual, experiencing a personal journey into older age. Each person has a right to supports for positive ageing, including cognitive health, respecting their choices about what's important to them to age well (Heller & van Heumen, 2021). As a population group, however, people ageing with Down syndrome may have a different life experience of ageing, having coped with a lifelong disability and frequent lack of empowerment and choice in their lives (Franits, 2005). They have a significantly higher risk of developing many health disorders as they age, including DSAD (Fortea et al., 2021; McCarron, McCallion, et al., 2017; McCarron et al., 2013).

This research aimed to explore the influence of various biopsychosocial factors on the risk of developing dementia in a sample of people ageing with Down syndrome. Some significant associations were found in this study: living in a congregated setting, physical inactivity and social isolation all emerged as potential drivers of risk of later dementia diagnosis risk in this population. These study findings suggest future potentially useful avenues of research and need to be tested and replicated in a larger sample to have greater confidence in these as being significant risk factors.

The significant genetically driven probability for this population of developing Alzheimer's disease, at a 90% lifetime risk (Jenkins et al., 2025), implies that any biopsychosocial interventions to reduce risk of dementia may only postpone the onset of this disease rather than reducing relative risk overall. Comparisons have been drawn in the literature to other genetically driven conditions, such as the BRCA gene for breast and ovarian cancers (Dubois et al., 2024), in terms of the inevitability of the development of Alzheimer's disease in people

ageing with Down syndrome. This comparison also carries the implied futility of lifestyle interventions in the absence of any curative medical treatment or medication (such as surgery for those carrying the BRCA gene). However, research has found variation in age of onset of DSAD within this population (Boyle et al., 2025), implying that there are other influences at work affecting the individual timing of the full clinical expression of Alzheimer's Disease. This offers an opportunity to further explore dementia risk factors across the lifespan for this cohort, particularly given the differing risk profile found in this study for this population compared to the general population. Intervention focus needs to be on the modifiable risk factors particularly pertinent to this population, given their differing ageing circumstances and risk profiles. These dementia risk factors also cover a broad range of biopsychosocial domains that are important for positive ageing in this population.

These study findings can support the fuller conceptualisation of ageing and wellbeing from a biopsychosocial perspective for this population. People ageing with Down syndrome have the right to be supported to age in as healthy a way as possible, regardless of their risk of neurodegeneration in later life. The Lancet brain health model offers an excellent set of clinical guidelines with a focus on biopsychosocial factors, to support the positive ageing of people with Down syndrome, starting from early adulthood, given the accelerated ageing process they experience. Supporting brain health from young adulthood is now becoming a focus of research; the Next Generation Brain Health Team are currently exploring modifiable risk factors for dementia in young adulthood with a view to clinical recommendations (Farina et al., 2024).

It is important to study dementia risk and progression in this population to inform a greater understanding of the development of AD in all people (Fortea et al., 2021; Hamadelseed et al., 2022; Pape et al., 2021). Whilst this is, of course, a laudable aim and will also benefit those ageing with Down syndrome, I feel that we can do more to concentrate on supporting people with Down syndrome to achieve a meaningful life despite their genetic inheritance. The focus must be on supporting this group to achieve health promoting behaviours from a young age and throughout the lifespan to maximise daily functioning and quality of life. People with Down syndrome can be supported from a young age to increase health span and compress morbidity towards the end of life. Although their genetic inheritance means the odds are stacked against them in terms of dementia risk, we can do much to support people with Down syndrome to live a good life right through to the end of their life.

5.9 Contribution to Knowledge

This thesis uniquely contributes to the knowledge base on the lived ageing experience of a sample of people with Down syndrome through an examination of the influence of a range of biopsychosocial risk factors on Alzheimer's Disease onset. I have tested the Lancet brain health model for this minority population for the first time, exploring the relative influence of the risk factors in the model on later dementia risk in this population. I have used the risk factor profiles derived for this population to learn more about the opportunities and barriers to positive ageing for people with Down syndrome, in comparison to their ageing peers in general community. This has been informed by the literature and models of positive ageing.

5.10 Overall Summary and Recommendations

The finding in this research of a varying clinical prevalence profile of the Lancet risk factors in comparison to those in the general population offers a biopsychosocial roadmap for focusing on the particular risk factors that are very prevalent in this population and developing interventions to address these. Supports for positive ageing in this population can be developed in consultation with people with Down syndrome themselves. The most important measure of the effectiveness of positive ageing interventions often comes from individuals themselves, in rating what is individually important to them for this construct (Jeste et al., 2013).

Given the proven early onset of clinical biomarkers for Alzheimer's disease in people with Down syndrome, it is imperative that they be supported from leaving school to achieve their chosen life goals. This population does not have time on its side. More attention needs to be paid from policy, funding and service delivery perspectives on the narrow window of time this group have, to achieve life goals before their functioning starts to decline in their mid-forties. Transition planning at varying life stages needs to become more urgent and more broadly focused, incorporating the Lancet model as an aid to achieving a good quality of life. A focus on increased health span promotion and compression of morbidity, even with the acknowledged ceiling on lifespan, is crucial.

5.10.1 Recommendations for Further Research

- Further exploration of the relative risk factor prevalence profiles within subsets of this population, by demographics, may be useful, given the findings of significantly varied prevalence of some risk factors across demographics in this research.
- Conceptualisation of social isolation for this population, based on their life experiences. Development of a validated reliable psychological assessment tool to measure social

isolation in people ageing with Down syndrome, that considers the nuances of living in congregated settings or in more community-based settings from younger ages.

- Investigate the synergistic effects of loneliness and social isolation on dementia risk in this population.
- Explore the Lancet brain heath model with later waves of IDS-TILDA using more powerful generalised linear mixed modelling techniques, to see if the findings of this research can be replicated. Include vision and cholesterol as two other important risk factors within the modelling.

5.10.2 Recommendations for Practice

- Use of the Lancet brain health model to develop a set of clinical practice guidelines in brain health promotion through the lifespan for people with Down syndrome. These can also inform positive ageing interventions, developed in collaboration with older people themselves.
- Guidelines for ethically supporting people with Down syndrome to promote their brain health from an early age need to be developed. Disclosure of significantly increased dementia risk and the importance of brain health promotion throughout the lifespan needs to be handled in a sensitive manner, raising awareness whilst not unduly alarming or distressing. An acknowledgement of the fact that brain health promotion may not decrease dementia risk overall but may postpone onset and/or increase quality of life as one ages needs to be incorporated into the guidelines.

5.10.3 Recommendations for Policy

- Policy guidelines on brain health promotion for this population need to be developed, to inform clinical practice and service delivery. These need to incorporate a lifespan approach with an emphasis on inclusion of a focus on brain health in transition planning at various life stages.
- Policy guidelines on supporting positive ageing in a more biopsychosocial holistic manner for this population are urgently needed to inform service delivery and clinical practice.

5.10.4 Recommendations for Education

- It is important that staff supporting people in intellectual disability services are aware of the Lancet Commission Model's recommendations to support brain health throughout the lifespan. Adequate educational pathways for staff in terms of upskilling their ability to effectively support someone as they age need to be developed and become widely available / embedded into service provision models.
- Promoting equity of access to training is also important. It is recommended that experiential and inclusive brain health training modules be developed that provide an opportunity for people supported, family members and staff to work together to become more familiar with the Lancet Commission Model's risk factors and how to promote their brain health across the life span. Brain health supports are relevant for all, regardless of age or ability and an inclusive approach to education promotes equity of access to this important health information.

5.11 Dissemination and Future Plans

I have started to draft a paper on the main research findings which I plan to submit to the Journal of Intellectual Disability Research for peer review. I also plan to write a paper focusing on the construct of social isolation as relates to people with Down syndrome (particularly those in congregated settings). This will include a discussion on the nuanced expression of social isolation in this population, its interaction with loneliness and the findings from this research of social isolation being a significant risk factor for dementia in this population.

I have presented my PhD results to senior management within my own organisation Corlann (formerly Brothers of Charity Services, West Region). I have started discussion around the development of a brain health support post as part of our Psychology Department. This would give scope to promote and embed brain health supports across the lifespan within our organisation for people supported and would provide leadership and expertise in the organisation for this. As Chair of the Social Prescribing programme in County Roscommon, I continue to advocate for the provision of a Specialist Social Prescriber post that will focus on addressing social isolation in people ageing with Down syndrome and intellectual disability of other aetiology.

I have given general community talks on the importance of brain health through the Healthy Libraries programme in Counties Longford and Roscommon in the last few years. I am a member of many high-level community interagency groups in County Roscommon where I hope to promote the importance of supporting brain health for all members of the population, including those ageing with Down syndrome. I have been invited to speak about brain health and my PhD findings to the Roscommon County Council CEO and Age Friendly Alliance county group in February 2026. Through engagement with the wider community and important county stakeholders in this way, my hope is that there will be a recognition that support for brain health promotion needs to be embedded across all policies and practices within the county, across various Council Departments. This will be of benefit to all those ageing in the county, including people supported with Down syndrome and intellectual disability of other aetiology.

Chapter 6: Conclusion

"I want you to know that I am a man with Down syndrome and my life is worth living."

John Franklin Stephens (2018)

Advocate/Athlete/Actor with Down syndrome

In conclusion, this research has explored the relative applicability of the Lancet Commission dementia risk model to a sample population of people ageing with Down syndrome. People ageing with Down syndrome are at significantly higher risk of developing Alzheimer's disease in their lifetime due to their genetic inheritance. Given their differing life, ageing and health experiences, this population may present with a differing risk factor prevalence profile and these factors may have different significance weightings than in the general population dementia risk model. These research findings will support positive ageing recommendations for people ageing with Down syndrome.

A differing risk factor profile was found for this sample population, with increased prevalence of No Education, Obesity, Physical Inactivity and Depression and decreased prevalence of Hypertension, Social Isolation, Frequent Alcohol, Smoking and Diabetes. Similar prevalence of Hearing Loss was found as in the general population. People ageing with Down syndrome may have a differing life experience of ageing, with many at risk of living in service-provided settings rather than at home with family from a much younger age than in the general population. Preliminary associations can be drawn from this study, indicating that physical inactivity, social isolation and living in a congregated setting, may have particular importance for dementia risk in this population.

Whilst the genetic risk for DSAD is almost universal for people ageing with Down syndrome, this research indicates that some acknowledged dementia risk factors may be important to target for intervention across the lifespan. Whilst such interventions may not reduce the risk of developing dementia, it may delay the onset of dementia and / or support more positive ageing overall for this cohort. This is a population deserving careful consideration of their ageing experiences and how these may diverge from the experience of the general population, leaving them at risk of adverse ageing circumstances, as well as their increased dementia risk. Future more highly powered research is required to replicate and expand on these findings, with the aim of building a more specific dementia risk model based on this population's specific ageing experiences.

In summary, this research advances the knowledge in the field through exploring the life experience of a sample of people ageing with Down syndrome, with a specific focus on the relative influence of a range of biopsychosocial determinants of Alzheimer's disease. The broader implications of these findings for enhancing the quality of life of people with Down syndrome across the lifespan have been discussed, with a range of research, practice and policy recommendations arising from the research findings. Further research is required to test replicability of these findings and to further explore how to best support optimal biopsychosocial ageing with this population, increasing health span and compressing morbidity to later in life.

The genetic inheritance of nearly full penetrance of Alzheimer's disease with age may seem to provide a very bleak vista for older people with Down syndrome and their families. However, at the conclusion of my research I see a future with hope, hope for a new vision of positive ageing supports that, whilst taking account of the reality of DSAD risk, refuses to lose sight of the humanity and rights of people with Down syndrome as they age. This vision uses what we know about the biopsychosocial factors involved in positive ageing to support people with Down syndrome to achieve a dignified and valued older age, regardless of their dementia status. As John Franklin Stephens so powerfully reminds us about living with Down syndrome: "My life is worth living".

Reference List

Abell, J. G., Kivimäki, M., Dugravot, A., Tabak, A. G., Fayosse, A., Shipley, M., Sabia, S., & Singh-Manoux, A. (2018). Association between systolic blood pressure and dementia in the Whitehall II cohort study: Role of age, duration, and threshold used to define hypertension. *European Heart Journal*, *39*(33), 3119-3125. https://doi.org/10.1093/eurheartj/ehy288

Abshire, M., Dinglas, V. D., Cajita, M. I. A., Eakin, M. N., Needham, D. M., & Himmelfarb, C. D. (2017). Participant retention practices in longitudinal clinical research studies with high retention rates. *BMC Medical Research Methodology*, *17*(30), 1-10. https://doi.org/10.1186/s12874-017-0310-z

Almeida, O., Hankey, G., Yeap, B., Golledge, J., & Flicker, L. (2017). Depression as a modifiable factor to decrease the risk of dementia. *Translational Psychiatry*, *7*(5), e1117-e1117. https://doi.org/10.1038/tp.2017.90

Alquraini, T., & Gut, D. (2012). Critical components of successful inclusion of students with severe disabilities: Literature review. *International Journal of Special Education*, *27*(1), 42-59. https://eric.ed.gov/?id=EJ979712

Alshahrani, M., Sabatini, S., Mohan, D., Brain, J., Pakpahan, E., Tang, E. Y., Robinson, L., Siervo, M., Naheed, A., & Stephan, B. C. M. (2024). Dementia risk prediction modelling in low- and middle-income countries: Current state of evidence. *Frontiers in Epidemiology*, *4*, 1397754. https://doi.org/10.3389/fepid.2024.1397754

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders: DSM-5 (5th Edition)* (Vol. 5). American Psychiatric Association. https://doi.org/10.1108/RR-10-2013-0256

Anatürk, M., Kaufmann, T., Cole, J. H., Suri, S., Griffanti, L., Zsoldos, E., Filippini, N., Singh-Manoux, A., Kivimäki, M., & Westlye, L. T. (2021). Prediction of brain age and cognitive age: Quantifying brain and cognitive maintenance in aging. *Human Brain Mapping*, *42*(6), 1626-1640. https://doi.org/10.1002/hbm.25316

Andrews, E. J., Martini, A. C., & Head, E. (2022). Exploring the role of sex differences in Alzheimer's disease pathogenesis in Down syndrome. *Frontiers in Neuroscience*, *16*, 954999. https://doi.org/10.3389/fnins.2022.954999

Andrews, E. J., Ngo, P. T., Pascual, J. R., Gonzalez, F., Phelan, M., Wright, S. T., Harp, J., Schmitt, F., Lai, F., & Lao, P. J. (2025). Age and sex are associated with Alzheimer's disease neuropathology in Down syndrome. *Alzheimer's & Dementia*, *21*(7), e70408. https://doi.org/10.1002/alz.70408

Annele, U., Satu, K. J., & Timo, E. S. (2019). Definitions of successful ageing: A brief review of a multidimensional concept. *Acta Bio Medica: Atenei Parmensis*, *90*(2), 359. https://doi.org/10.23750/abm.v90i2.8376

Antonarakis, S. E., Skotko, B. G., Rafii, M. S., Strydom, A., Pape, S. E., Bianchi, D. W., Sherman, S. L., & Reeves, R. H. (2020). Down syndrome. *Nature Reviews Disease Primers*, *6*(1), 9-43. https://doi.org/10.1038/s41572-019-0143-7

Appollonio, I., Leone, M., Isella, V., Piamarta, F., Consoli, T., Villa, M., Forapani, E., Russo, A., & Nichelli, P. (2005). The Frontal Assessment Battery (FAB): Normative values in an Italian population sample. *Neurological Sciences*, *26*(2), 108-116. https://link.springer.com/article/10.1007/s10072-005-0443-4

Armstrong, N. M., An, Y., Doshi, J., Erus, G., Ferrucci, L., Davatzikos, C., Deal, J. A., Lin, F. R., & Resnick, S. M. (2019). Association of midlife hearing impairment with late-life temporal lobe volume loss. *JAMA Otolaryngology–Head & Neck Surgery*, *145*(9), 794. https://doi.org/10.1001/jamaoto.2019.1610

Arnett, J. J., Robinson, O., & Lachman, M. E. (2020). Rethinking adult development: Introduction to the special issue. *American Psychologist*, *75*(4), 425-430. https://doi.org/10.1037/amp0000633

Arnold, S. E., Arvanitakis, Z., Macauley-Rambach, S. L., Koenig, A. M., Wang, H.-Y., Ahima, R. S., Craft, S., Gandy, S., Buettner, C., & Stoeckel, L. E. (2018). Brain insulin resistance in type 2 diabetes and Alzheimer disease: Concepts and conundrums. *Nature Reviews Neurology*, *14*(3), 168-181. https://doi.org/10.1038/nrneurol.2017.185

Ashcroft, R., & Van Katwyk, T. (2016). An examination of the biomedical paradigm: A view of social work. *Social Work in Public Health*, *31*(3), 140-152. https://doi.org/10.1080/19371918.2015.1087918

Aslam, A. A., Baksh, R. A., Pape, S. E., Strydom, A., Gulliford, M. C., & Chan, L. F. (2022). Diabetes and obesity in Down syndrome across the lifespan: A retrospective cohort study using UK electronic health records. *Diabetes Care*, *45*(12), 2892-2899. https://doi.org/10.2337/dc22-0482

Aston, D. (2019). *Higher education opportunities for students with intellectual disabilities in the Republic of Ireland - A national response*. Inclusive National Higher Education Forum. https://doi.org/10.13140/RG.2.2.29887.66721

Austad, S. N., Wood, M. A., Villeda, S. A., Voss, J. L., Sahay, A., & Albert, M. (2019). Innovative approaches in cognitive aging. *Neurobiology of Aging*, *83*, 150-154. https://doi.org/10.1016/j.neurobiolaging.2019.04.013

Auty, E., & Scior, K. (2008). Psychologists' clinical practices in assessing dementia in individuals with Down syndrome. *Journal of Policy & Practice in Intellectual Disabilities*, *5*(4), 259-268. https://doi.org/10.1111/j.1741-1130.2008.00187.x

Axmon, A., Björne, P., Nylander, L., & Ahlström, G. (2018). Psychiatric diagnoses in older people with intellectual disability in comparison with the general population: A register study. *Epidemiology & Psychiatric Sciences*, *27*(5), 479-491. https://doi.org/10.1017/S2045796017000051

Axmon, A., Björne, P., Nylander, L., & Ahlström, G. (2018). Psychiatric diagnoses in relation to severity of intellectual disability and challenging behaviors: A register study among older people. *Aging & Mental Health*, *22*(10), 1344-1350. https://doi.org/10.1080/13607863.2017.1348483

Azur, M. J., Stuart, E. A., Frangakis, C., & Leaf, P. J. (2011). Multiple imputation by chained equations: What is it and how does it work? *International Journal of Methods in Psychiatric Research*, *20*(1), 40-49. https://doi.org/10.1002/mpr.329

Bacon, F., & Montagu, B. (1857). *The Works of Francis Bacon* (Vol. 1). Parry & McMillan.

Baksh, R. A., Pape, S. E., Chan, L. F., Aslam, A. A., Gulliford, M. C., & Strydom, A. (2023). Multiple morbidity across the lifespan in people with Down syndrome or intellectual disabilities: A population-based cohort study using electronic health records. *The Lancet Public Health*, *8*(6), e453-e462. https://doi.org/https://doi.org/10.1016/

Baldwin, A., Birks, M., Mills, J., & Budden, L. (2014). Putting the philosophy into PhD. *Working Papers in the Health Sciences*, *1-10*, 1-4. https://www.researchgate.net/profile/Adele-Baldwin/publication/273694286_Putting_philosophy_into_PhD/links/550f51370cf2752610a00d2d/Putting-philosophy-into-PhD.pdf

Ballard, C., Mobley, W., Hardy, J., Williams, G., & Corbett, A. (2016). Dementia in Down's syndrome. *The Lancet Neurology*, *15*(6), 622-636. https://doi.org/10.1016/S1474-4422(16)00063-6

Baltes, P. B., & Baltes, M. M. (1990). Psychological perspectives on successful aging: The model of selective optimization with compensation. *Successful Aging: Perspectives from the Behavioral Sciences*, *1*(1), 1-34. https://doi.org/10.1017/CBO9780511665684.003

Bar-Tur, L. (2021). Fostering well-being in the elderly: Translating theories on positive aging to practical approaches. *Frontiers in Medicine*, *8*, 200. https://doi.org/10.3389/fmed.2021.517226

Barbalho, S. M., de Alvares Goulart, R., Bechara, M., Audi, M., LM, G. C., & Buchain, D. (2020). Myokines: A descriptive review. *The Journal of Sports Medicine and Physical Fitness*, *60*, 1583-1590. https://doi.org/10.23736/S0022-4707.20.10884-3

Barnard, M., Swanepoel, M., Ellapen, T. J., Paul, Y., & Hammill, H. V. (2019). The health benefits of exercise therapy for patients with Down syndrome: A systematic review. *African Journal of Disability 8*(1), 1-9. https://doi.org/10.4102/ajod.v8i0.576

Barnes, D. E., & Yaffe, K. (2011). The projected effect of risk factor reduction on Alzheimer's disease prevalence. *The Lancet Neurology*, *10*(9), 819-828. https://doi.org/10.1016/S1474-4422(11)70072-2

Barnes, T. L., Howie, E. K., McDermott, S., & Mann, J. R. (2013). Physical activity in a large sample of adults with intellectual disabilities. *Journal of Physical Activity and Health*, *10*(7), 1048-1056. https://doi.org/10.1123/jpah.10.7.1048

Barroeta, I., Videla, L., Carmona-Iragui, M., Fortea, J., & Rafii, M. S. (2025). Current advances and unmet needs in Alzheimer's disease trials for individuals with Down syndrome: Navigating new therapeutic frontiers. *Alzheimer's & Dementia*, *21*(6), e70258. https://doi-org.elib.tcd.ie/10.1002/alz.70258

Barulli, D., & Stern, Y. (2013). Efficiency, capacity, compensation, maintenance, plasticity: Emerging concepts in cognitive reserve. *Trends in Cognitive Sciences*, *17*(10), 502-509. https://doi.org/10.1016/j.tics.2013.08.012

Baumeister, R. F., & Leary, M. R. (1997). Writing narrative literature reviews. *Review of General Psychology*, *1*(3), 311-320. https://doi.org/10.1037/1089-2680.1.3.311

Baumgart, M., Snyder, H. M., Carrillo, M. C., Fazio, S., Kim, H., & Johns, H. (2015). Summary of the evidence on modifiable risk factors for cognitive decline and dementia: A population-based perspective. *Alzheimer's & Dementia*, *11*(6), 718-726. https://doi.org/10.1016/j.jalz.2015.05.016

Beller, J., & Wagner, A. (2018a). Disentangling loneliness: Differential effects of subjective loneliness, network quality, network size, and living alone on physical, mental, and cognitive health. *Journal of Aging and Health*, *30*(4), 521-539. https://doi.org/10.1177/0898264316685843

Beller, J., & Wagner, A. (2018b). Loneliness, social isolation, their synergistic interaction, and mortality. *Health Psychology*, *37*(9), 808-813. https://doi.org/10.1037/hea0000605

Benejam, B., Videla, L., Vilaplana, E., Barroeta, I., Carmona-Iragui, M., Altuna, M., Valldeneu, S., Fernandez, S., Giménez, S., & Iulita, F. (2020). Diagnosis of prodromal and Alzheimer's disease dementia in adults with Down syndrome using neuropsychological tests. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*, *12*(1), e12047. https://doi.org/10.1002/dad2.12047

Bent, S., McShea, L., & Brennan, S. (2015). The importance of hearing: A review of the literature on hearing loss for older people with learning disabilities. *British Journal of Learning Disabilities*, *43*(4), 277-284. https://doi.org/10.1111/bld.12148

Berkman, L. F., & Syme, S. L. (1979). Social networks, host resistance, and mortality: A nine-year follow-up study of Alameda County residents. *American Journal of Epidemiology*, *109*(2), 186-204. https://doi.org/10.1093/oxfordjournals.aje.a112674

Bettcher, B. M., Gross, A. L., Gavett, B. E., Widaman, K. F., Fletcher, E., Dowling, N. M., Buckley, R. F., Arenaza-Urquijo, E. M., Zahodne, L. B., Hohman, T. J., Vonk, J. M. J., Rentz, D. M., & Mungas, D. (2019). Dynamic change of cognitive reserve: Associations with changes in brain, cognition, and diagnosis. *Neurobiology of Aging*, *83*, 95-104. https://doi.org/10.1016/j.neurobiolaging.2019.08.016

Biering, K., Hjollund, N. H., & Frydenberg, M. (2015). Using multiple imputation to deal with missing data and attrition in longitudinal studies with repeated measures of patient-reported outcomes. *Clinical Epidemiology*, *7*, 91-106. https://doi.org/10.2147/CLEP.S72247

Bigby, C. (2008). Known well by no-one: Trends in the informal social networks of middle-aged and older people with intellectual disability five years after moving to the community. *Journal of Intellectual and Developmental Disability*, *33*(2), 148-157. https://doi.org/10.1080/13668250802094141

Bigby, C., Clement, T., Mansell, J., & Beadle-Brown, J. (2009). 'It's pretty hard with our ones, they can't talk, the more able bodied can participate': Staff attitudes about the applicability of disability policies to people with severe and profound intellectual disabilities. *Journal of Intellectual Disability Research*, *53*(4), 363-376. https://doi.org/10.1111/j.1365-2788.2009.01154.x

Bigby, C., & Wiesel, I. (2019). Using the concept of encounter to further the social inclusion of people with intellectual disabilities: What has been learned? *Research and Practice in Intellectual and Developmental Disabilities*, *6*(1), 39-51. https://doi.org/10.1080/23297018.2018.1528174

Bittles, A., & Glasson, E. (2004). Clinical, social, and ethical implications of changing life expectancy in Down syndrome. *Developmental Medicine and Child Neurology*, *46*(4), 282-286. https://doi.org/10.1017/S0012162204000441

Bittles, A. H., Bower, C., Hussain, R., & Glasson, E. J. (2007). The four ages of Down syndrome. *European Journal of public health*, *17*(2), 221-225. https://doi.org/10.1093/eurpub/ckl103

Boamah, S. A., Weldrick, R., Lee, T.-S. J., & Taylor, N. (2021). Social isolation among older adults in long-term care: A scoping review. *Journal of Aging and Health*, *33*(7-8), 618-632. https://doi.org/10.1177/08982643211004174

Bowling, A. (1993). The concepts of successful and positive ageing. *Family Practice*, *10*(4), 449-453. https://doi.org/10.1093/fampra/10.4.449

Boyle, P. A., Wilson, R. S., Yu, L., Barr, A. M., Honer, W. G., Schneider, J. A., & Bennett, D. A. (2013). Much of late life cognitive decline is not due to common neurodegenerative pathologies. *Annals of Neurology*, *74*(3), 478-489. https://doi.org/10.1002/ana.23964

Boyle, R., Koops, E. A., Ances, B., Andrews, E. J., Arenaza-Urquijo, E. M., Benjanin, A., Brickman, A. M., Buckley, R. F., Clas, G. S., & Costello, E. (2025). Resistance and resilience to Alzheimer's disease in Down syndrome. *Alzheimer's & Dementia*, *21*(4), e70151. https://doi.org/10.1002/alz.70151

Bozeman, S. R., Hoaglin, D. C., Burton, T. M., Pashos, C. L., Ben-Joseph, R. H., & Hollenbeak, C. S. (2012). Predicting waist circumference from body mass index. *BMC Medical Research Methodology*, *12*(1), 115. https://doi.org/10.1186/1471-2288-12-115

Branford, D., & Shankar, R. (2022). Antidepressant prescribing for adult people with an intellectual disability living in England. *The British Journal of Psychiatry*, *221*(2), 488-493. https://doi.org/doi:10.1192/bjp.2022.34

British Psychological Society. (2015). *Dementia and people with intellectual disabilities: Guidance on the assessment, diagnosis, interventions and support of people with intellectual disabilities who develop dementia*. British Psychological Society. Retrieved January 21, 2021 from https://www.bps.org.uk/guideline/dementia-and-people-intellectual-disabilities-0

Bruni, A. C., Bernardi, L., & Gabelli, C. (2020). From beta amyloid to altered proteostasis in Alzheimer's disease. *Ageing Research Reviews*, *64*, 101126. https://doi.org/10.1016/j.arr.2020.101126

Bucholc, M., McClean, P. L., Bauermeister, S., Todd, S., Ding, X., Ye, Q., Wang, D., Huang, W., & Maguire, L. P. (2021). Association of the use of hearing aids with the conversion from mild cognitive impairment to dementia and progression of dementia: A longitudinal retrospective study. *Alzheimer's & Dementia: Translational Research & Clinical Interventions*, *7*(1), e12122. https://doi.org/10.1002/trc2.12122

Budd Haeberlein, S., Aisen, P., Barkhof, F., Chalkias, S., Chen, T., Cohen, S., Dent, G., Hansson, O., Harrison, K., & Von Hehn, C. (2022). Two randomized phase 3 studies of aducanumab in early Alzheimer's disease. *The Journal of Prevention of Alzheimer's Disease*, *9*(2), 197-210. https://doi.org/10.14283/jpad.2022.30

Bull, F. C., Al-Ansari, S. S., Biddle, S., Borodulin, K., Buman, M. P., Cardon, G., Carty, C., Chaput, J.-P., Chastin, S., & Chou, R. (2020). World Health Organization 2020 guidelines on physical activity and sedentary behaviour. *British Journal of Sports Medicine*, *54*(24), 1451-1462. https://doi.org/10.1136/bjsports-2020-102955

Bull, M. J. (2020). Down syndrome. *New England Journal of Medicine*, *382*(24), 2344-2352. https://doi.org/10.1056/NEJMra1706537

Burke, E., McCarron, M., Carroll, R., McGlinchey, E., & McCallion, P. (2014). What it's like to grow older: The aging perceptions of people with an intellectual disability in Ireland. *Intellectual and Developmental Disabilities*, *52*(3), 205-219. https://doi.org/10.1352/1934-9556-52.3.205

Burke, E., O'Dwyer, M., McGlinchey, E., Foran, S., Phadraig, C. M., Carroll, R., McCallion, P., & McCarron, M. (2019). Overview of the important physical health concerns. In V. P. Prasher & M. P. Janicki (Eds.), *Physical health of adults with intellectual and developmental disabilities* (pp. 27-52). Springer. https://doi.org/10.1007/978-3-319-90083-4_3

Burke, S. N., Mormino, E. C., Rogalski, E. J., Kawas, C. H., Willis, R. J., & Park, D. C. (2019). What are the later life contributions to reserve, resilience, and compensation? *Neurobiology of Aging*, *83*, 140-144. https://doi.org/10.1016/j.neurobiolaging.2019.03.023

Burt, D. B., Primeaux-Hart, S., Loveland, K. A., Cleveland, L. A., Lewis, K. R., Lesser, J., & Pearson, P. L. (2005). Comparing dementia diagnostic methods used with people with intellectual disabilities. *Journal of Policy and Practice in Intellectual Disabilities*, *2*(2), 94-115. https://doi.org/10.1111/j.1741-1130.2005.00022.x

Byrne, J. A. (2016). Improving the peer review of narrative literature reviews. *Research Integrity and Peer Review*, *1*(1), 12-16. https://doi.org/10.1186/s41073-016-0019-2

Cabeza, R., Albert, M., Belleville, S., Craik, F. I. M., Duarte, A., Grady, C. L., Lindenberger, U., Nyberg, L., Park, D. C., Reuter-Lorenz, P. A., Rugg, M. D., Steffener, J., & Rajah, M. N. (2018). Maintenance, reserve and compensation: The cognitive neuroscience of healthy ageing. *Nature Reviews Neuroscience*, *19*(11), 701-710. https://doi.org/10.1038/s41583-018-0068-2

Canli, T., Wen, R., Wang, X., Mikhailik, A., Yu, L., Fleischman, D., Wilson, R. S., & Bennett, D. A. (2017). Differential transcriptome expression in human nucleus accumbens as a function of loneliness. *Molecular Psychiatry*, *22*(7), 1069-1078. https://doi.org/10.1038/mp.2016.186

Carlsson, C. M. (2010). Type 2 diabetes mellitus, dyslipidemia, and Alzheimer's disease. *Journal of Alzheimer's Disease*, *20*(3), 711-722. https://doi.org/10.3233/JAD-2010-100012

Carstensen, L. L. (1992). Social and emotional patterns in adulthood: Support for socioemotional selectivity theory. *Psychology and Aging*, *7*(3), 331-338. https://psycnet.apa.org/doi/10.1037/0882-7974.7.3.331

Carta, M. G., Cossu, G., Pintus, E., Zaccheddu, R., Callia, O., Conti, G., Pintus, M., Aviles Gonzalez, C. I., Massidda, M. V., Mura, G., Sardu, C., Contu, P., Minerba, L., Demontis, R., Pau, M., Finco, G., Cocco, E., Penna, M. P., Orr, G., . . . Preti, A. (2021). Moderate exercise improves cognitive function in healthy elderly people: Results of a randomized controlled trial. *Clinical Practice & Epidemiology in Mental Health*, *17*(1), 75-80. https://doi.org/10.2174/1745017902117010075

Carvill, S. (2001). Sensory impairments, intellectual disability and psychiatry. *Journal of Intellectual Disability Research*, *45*(6), 467-483. https://doi.org/10.1046/j.1365-2788.2001.00366.x

Casey, C., O'Sullivan, M., Fanagan, S., & Doyle, A. (2020). *National Ability Supports System (NASS) 2019*. Health Research Board. Retrieved 21st April 2021 from https://www.hrb.ie/wp-content/uploads/2024/06/NASS_Bulletin_2019.pdf.

Caspersen, C. J., Powell, K. E., & Christenson, G. M. (1985). Physical activity, exercise, and physical fitness: Definitions and distinctions for health-related research. *Public Health Reports*, *100*(2), 126. https://pmc.ncbi.nlm.nih.gov/articles/PMC1424733/

Cattan, M., White, M., Bond, J., & Learmouth, A. (2019). Preventing social isolation and loneliness among older people: A systematic review of health promotion interventions. *Ageing and Society*, *25*(1), 41-67. https://doi.org/10.1017/S0144686X04002594

Cattaneo, G., Bartrés-Faz, D., Morris, T. P., Sánchez, J. S., Macià, D., Tormos, J. M., & Pascual-Leone, A. (2020). The Barcelona brain health initiative: Cohort description and first follow-up. *PloS One*, *15*(2), e0228754. https://doi.org/10.1371/journal.pone.0228754

Cavanaugh, J., & Krauss Whitboume, S. (1999). Theories of aging in the biological, behavioral, and social sciences. In J. Cavanagh (Ed.), *Gerontology: An interdisciplinary perspective* (pp. 1-32). Oxford University Press.

Central Statistics Office. (2020). *Census of Population 2016 Profile 9- Health, Disability and Carers*. Central Statistics Office. Retrieved 19th November 2020 from https://www.cso.ie/en/releasesandpublications/ep/p-cp9hdc/p8hdc/p9tod/

Chan, D., Shafto, M., Kievit, R., Matthews, F., Spink, M., Valenzuela, M., & Henson, R. N. (2018). Lifestyle activities in mid-life contribute to cognitive reserve in late-life, independent of education, occupation, and late-life activities. *Neurobiology of Aging*, *70*, 180-183. https://doi.org/10.1016/j.neurobiolaging.2018.06.012

Chang, C.-F., Yang, R.-J., Chang, S.-F., Chou, Y. H., & Huang, E.-W. (2017). The effects of quality of life and ability to perform activities of daily living on mild cognitive impairment in older people living in publicly managed congregate housing. *Journal of Nursing Research*, *25*(3), 187-197. https://doi.org/10.1097/JNR.0000000000000149

Chapman, S. L. C., & Wu, L.-T. (2012). Substance abuse among individuals with intellectual disabilities. *Research in Developmental Disabilities*, *33*(4), 1147-1156. https://doi.org/10.1016/j.ridd.2012.02.009

Chatterjee, S., Peters, S. A., Woodward, M., Mejia Arango, S., Batty, G. D., Beckett, N., Beiser, A., Borenstein, A. R., Crane, P. K., & Haan, M. (2016). Type 2 diabetes as a risk factor for dementia in women compared with men: A pooled analysis of 2.3 million people comprising more than 100,000 cases of dementia. *Diabetes Care*, *39*(2), 300-307. https://doi.org/10.2337/dc15-1588

Chen, C. J., Ringenbach, S. D. R., Crews, D., Kulinna, P. H., & Amazeen, E. L. (2015). The association between a single bout of moderate physical activity and executive function in young adults with Down syndrome: A preliminary study. *Journal of Intellectual Disability Research*, *59*(7), 589-598. https://doi.org/10.1111/jir.12163

Chen, C. C., & Ringenbach, S. (2016). Dose–response relationship between intensity of exercise and cognitive performance in individuals with Down syndrome: A preliminary study. *Journal of Intellectual Disability Research*, *60*(6), 606-614. https://doi.org/10.1111/jir.12258

Chen, M., Lee, C., Staley, M., Wang, H., & Dugan, E. (2015). The association of lifelong learning and cognitive function: Findings from the health and retirement study. *The Gerontologist*, *55*, 480-480. https://doi.org/10.1093/geront/gov201.08

Chen, Y., Demnitz, N., Yamamoto, S., Yaffe, K., Lawlor, B., & Leroi, I. (2022). Defining brain health: A concept analysis. *International Journal of Geriatric Psychiatry*, *37*(1). https://doi.org/10.1002/gps.5564

Chevret, S., Seaman, S., & Resche-Rigon, M. (2015). Multiple imputation: A mature approach to dealing with missing data. *Intensive Care Medicine*, *41*(2), 348-350. https://doi.org/10.1007/s00134-014-3624-x

Chicoine, B., Rivelli, A., Fitzpatrick, V., Chicoine, L., Jia, G., & Rzhetsky, A. (2021). Prevalence of common disease conditions in a large cohort of individuals with Down syndrome in the United States. *Journal of Patient-Centered Research and Reviews*, *8*(2), 86. https://doi.org/10.17294/2330-0698.1824

Chow, Y. Y., Verdonschot, M., McEvoy, C. T., & Peeters, G. (2022). Associations between depression and cognition, mild cognitive impairment and dementia in persons with diabetes mellitus: A systematic review and meta-analysis. *Diabetes Research and Clinical Practice*, *185*, 109227. https://doi.org/10.1016/j.diabres.2022.109227

Clifford Simplican, S., & Leader, G. (2015). Counting inclusion with Chantal Mouffe: A radical democratic approach to intellectual disability research. *Disability & Society*, *30*(5), 717-730. https://doi.org/10.1080/09687599.2015.1021763

Clouston, S. A., Smith, D. M., Mukherjee, S., Zhang, Y., Hou, W., Link, B. G., & Richards, M. (2020). Education and cognitive decline: An integrative analysis of global longitudinal studies of cognitive aging. *The Journals of Gerontology: Series B*, *75*(7), e151-e160. https://doi.org/10.1093/geronb/gbz053

Cohen, J. (1992). Statistical power analysis. *Current directions in psychological science*, *1*(3), 98-101. https://doi.org/10.1111/1467-8721.ep10768783

Cole, J. H., Annus, T., Wilson, L. R., Remtulla, R., Hong, Y. T., Fryer, T. D., Acosta-Cabronero, J., Cardenas-Blanco, A., Smith, R., & Menon, D. K. (2017). Brain-predicted age in Down syndrome is associated with beta amyloid deposition and cognitive decline. *Neurobiology of Aging*, *56*, 41-49. https://spiral.imperial.ac.uk:8443/bitstream/10044/1/47993/7/1-s2.0-S0197458017301240-main.pdf

Cole, J. H., Marioni, R. E., Harris, S. E., & Deary, I. J. (2019). Brain age and other bodily 'ages': Implications for neuropsychiatry. *Molecular Psychiatry*, *24*(2), 266-281. https://doi.org/10.1038/s41380-018-0098-1

Cole, S. W., Capitanio, J. P., Chun, K., Arevalo, J. M., Ma, J., & Cacioppo, J. T. (2015). Myeloid differentiation architecture of leukocyte transcriptome dynamics in perceived social isolation. *Proceedings of the National Academy of Sciences*, *112*(49), 15142-15147. https://doi.org/10.1073/pnas.1514249112

Collins, E., & Watt, R. (2021). Using and understanding power in psychological research: A survey study. *Collabra: Psychology*, *7*(1), 28250. https://doi.org/10.1525/collabra.28250

Cominetti, M. R., Pott-Junior, H., Cominetti, C., Zúñiga, R. G., & Romero-Ortuno, R. (2022). Type 2 diabetes mellitus predicts cognitive decline: Evidence from the Irish longitudinal study on ageing (TILDA). *Diabetes Epidemiology and Management*, *7*, 100087. https://doi.org/10.1016/j.deman.2022.100087

Consorti, A., Di Marco, I., & Sansevero, G. (2021). Physical exercise modulates brain physiology through a network of long-and short-range cellular interactions. *Frontiers in Molecular Neuroscience*, *14,* 710303. https://doi.org/10.3389/fnmol.2021.710303

Cooper, C. M., Chin Fatt, C. R., Liu, P., Grannemann, B. D., Carmody, T., Almeida, J. R., Deckersbach, T., Fava, M., Kurian, B. T., & Malchow, A. L. (2020). Discovery and replication of cerebral blood flow differences in major depressive disorder. *Molecular Psychiatry*, *25*(7), 1500-1510. https://doi.org/10.1038/s41380-019-0464-7

Cooper, S.-A., & Collacott, R. A. (1994). Clinical features and diagnostic criteria of depression in Down's syndrome. *The British Journal of Psychiatry*, *165*(3), 399-403. https://doi.org/10.1192/bjp.165.3.399

Coppens-Hofman, M. C., Maassen, B. A., van Schrojenstein Lantman-de, H. M., & Valk, A. F. (2011). Hearing disorders and auditory speech processing difficulties in adults with Down syndrome: A review of the literature. *Journal of Hearing Science*, *1*(3), 11-17. https://hdl.handle.net/2066/127340

Coppus, A. M., Evenhuis, H. M., Verberne, G.-J., Visser, F. E., Eikelenboom, P., Van Gool, W. A., Janssens, A., & Van Duijn, C. M. (2010). Early age at menopause is associated with increased risk of dementia and mortality in women with Down syndrome. *Journal of Alzheimer's Disease*, *19*(2), 545-550. https://doi.org/10.3233/JAD-2010-1247

Cosco, T. D., Prina, A. M., Perales, J., Stephan, B. C., & Brayne, C. (2013). Lay perspectives of successful ageing: A systematic review and meta-ethnography. *British Medical Journal*, *3*(6), e002710. https://doi.org/10.1136/bmjopen-2013-002710

Costantini, E., Lang, K. M., Sijtsma, K., & Reeskens, T. (2024). Solving the many-variables problem in MICE with principal component regression. *Behavior Research Methods*, *56*(3), 1715-1737. https://doi.org/10.3758/s13428-023-02117-1

Courtin, E., & Knapp, M. (2017). Social isolation, loneliness and health in old age: A scoping review. *Health & Social Care in the Community*, *25*(3), 799-812. https://doi.org/10.1111/hsc.12311

Covelli, V., Raggi, A., Meucci, P., Paganelli, C., & Leonardi, M. (2016). Ageing of people with Down's syndrome: A systematic literature review from 2000 to 2014. *International Journal of Rehabilitation Research*, *39*(1), 20-28. https://doi.org/10.1097/MRR.0000000000000147

Cox, S. R., Lyall, D. M., Ritchie, S. J., Bastin, M. E., Harris, M. A., Buchanan, C. R., Fawns-Ritchie, C., Barbu, M. C., De Nooij, L., & Reus, L. M. (2019). Associations between vascular risk factors and brain MRI indices in UK Biobank. *European Heart Journal*, *40*(28), 2290-2300. https://doi.org/10.1093/eurheartj/ehz100

Coyle, C. E., & Dugan, E. (2012). Social isolation, loneliness and health among older adults. *Journal of Aging and Health*, *24*(8), 1346-1363. https://doi.org/10.1177/0898264312460275

Craig, C., Marshall, A., Sjostrom, M., Bauman, A., Booth, M., Ainsworth, B., Pratt, M., Ekelund, U., Yngve, A., & Sallis, J. (2003). Guidelines for data processing and analysis of the IPAQ-short and long forms. *Medicine & Science in Sport and Exercise*, *35*(8), 1381-1395. https://doi.org/10.1249/01.MSS.0000078924.61453.FB

Craig, D., & Bigby, C. (2015). "She's been involved in everything as far as I can see": Supporting the active participation of people with intellectual disability in community groups. *Journal of Intellectual and Developmental Disability*, *40*(1), 12-25. https://doi.org/10.3109/13668250.2014.977235

Crocker, J. C., Ricci-Cabello, I., Parker, A., Hirst, J. A., Chant, A., Petit-Zeman, S., Evans, D., & Rees, S. (2018). Impact of patient and public involvement on enrolment and retention in clinical trials: Systematic review and meta-analysis. *British Medical Journal*, *363*, k4738. https://doi.org/10.1136/bmj.k4738

Cudjoe, T. K., Roth, D. L., Szanton, S. L., Wolff, J. L., Boyd, C. M., & Thorpe Jr, R. J. (2020). The epidemiology of social isolation: National health and aging trends study. *The Journals of Gerontology: Series B*, *75*(1), 107-113. https://doi.org/10.1093/geronb/gby037

Cuypers, M., Leijssen, M., Bakker-Van Gijssel, E. J., Pouls, K. P. M., Mastebroek, M. M., Naaldenberg, J., & Leusink, G. L. (2021). Patterns in the prevalence of diabetes and incidence of diabetic complications in people with and without an intellectual disability in Dutch primary care: Insights from a population-based data-linkage study. *Primary Care Diabetes*, *15*(2), 372-377. https://doi:10.1016/j.pcd.2020.11.012

Dafsari, F. S., & Jessen, F. (2020). Depression—An underrecognized target for prevention of dementia in Alzheimer's disease. *Translational Psychiatry*, *10*(1), 160. https://doi.org/10.1038/s41398-020-0839-1

Dairo, Y. M., Collett, J., Dawes, H., & Oskrochi, G. R. (2016). Physical activity levels in adults with intellectual disabilities: A systematic review. *Preventive Medicine Reports*, *4*, 209-219. https://doi.org/10.1016/j.pmedr.2016.06.008

Daskalopoulou, C., Stubbs, B., Kralj, C., Koukounari, A., Prince, M., & Prina, A. M. (2017). Physical activity and healthy ageing: A systematic review and meta-analysis of longitudinal cohort studies. *Ageing Research Reviews*, *38*, 6-17. https://doi.org/10.1016/j.arr.2017.06.003

De França Bram, J. M., Talib, L. L., Joaquim, H. P. G., Carvalho, C. L., Gattaz, W. F., & Forlenza, O. V. (2019). Alzheimer's disease-related biomarkers in aging adults with Down syndrome: Systematic review. *Current Psychiatry Research and Reviews*, *15*(1), 49-57. https://doi.org/10.2174/1573400515666190122152855

De Graaf, G., Buckley, F., & Skotko, B. G. (2017). Estimation of the number of people with Down syndrome in the United States. *Genetics in Medicine*, *19*(4), 439-447. https://doi.org/10.1038/gim.2016.127

de Oliveira, L. C., & de Paula Faria, D. (2022). Pharmacological approaches to the treatment of dementia in Down syndrome: A systematic review of randomized clinical studies. *Molecules*, *27*(10), 3244. https://doi.org/10.3390/molecules27103244

de Vries, J., & McGlinchey, E. (2023). Attachment, cognitive dissonance and reciprocation in intellectual disability care provision. In F. Sheerin & C. Doyle (Eds.), *Intellectual disabilities: Health and social care across the lifespan* (pp. 39-52). Springer.

Deary, I. J. (2012). Looking for system integrity in cognitive epidemiology. *Gerontology*, *58*(6), 545-553. https://doi.org/10.1159/000341157

Deary, I. J., Corley, J., Gow, A. J., Harris, S. E., Houlihan, L. M., Marioni, R. E., Penke, L., Rafnsson, S. B., & Starr, J. M. (2009). Age-associated cognitive decline. *British Medical Bulletin*, *92*(1), 135-152. https://doi.org/10.1093/bmb/ldp033

Deery, H. A., Di Paolo, R., Moran, C., Egan, G. F., & Jamadar, S. D. (2023). The older adult brain is less modular, more integrated, and less efficient at rest: A systematic review of large-scale resting-state functional brain networks in aging. *Psychophysiology*, *60*(1), e14159. https://doi.org/10.1111/psyp.14159

Dekker, A. D., Strydom, A., Coppus, A. M., Nizetic, D., Vermeiren, Y., Naudé, P. J., Van Dam, D., Potier, M.-C., Fortea, J., & De Deyn, P. P. (2015). Behavioural and psychological symptoms of dementia in Down syndrome: Early indicators of clinical Alzheimer's disease? *Cortex*, *73*, 36-61. https://doi.org/10.1016/j.cortex.2015.07.032

Dekker, A. D., Ulgiati, A. M., Groen, H., Boxelaar, V. A., Sacco, S., Falquero, S., Carfi, A., Di Paola, A., Benejam, B., & Valldeneu, S. (2021). The behavioral and psychological symptoms of dementia in down syndrome scale (BPSD-DS II): Optimization and further validation. *Journal of Alzheimer's Disease*, *81*(4), 1505-1527. https://doi.org/10.3233/JAD-201427

Depaoli, S., Rus, H. M., Clifton, J. P., Van De Schoot, R., & Tiemensma, J. (2017). An introduction to Bayesian statistics in health psychology. *Health Psychology Review*, *11*(3), 248-264. https://doi.org/10.1080/17437199.2017.1343676

Department of Health and Aged Care Australia. (2025). *Body Mass Index and Waist Circumference*. Government of Australia. Retrieved 07th March 2025 from https://www.health.gov.au/topics/overweight-and-obesity/bmi-and-waist

Depp, C., Vahia, I. V., & Jeste, D. (2010). Successful aging: Focus on cognitive and emotional health. *Annual Review of Clinical Psychology*, *6*(1), 527-550. https://doi.org/10.1146/annurev.clinpsy.121208.131449

Depp, C. A., & Jeste, D. V. (2006). Definitions and predictors of successful aging: A comprehensive review of larger quantitative studies. *The American Journal of Geriatric Psychiatry*, *14*(1), 6-20. https://doi.org/10.1097/01.JGP.0000192501.03069.bc

Di Liegro, C. M., Schiera, G., Proia, P., & Di Liegro, I. (2019). Physical activity and brain health. *Genes 10*(9), 720. https://doi.org/10.3390/genes10090720

Diehl, M., Smyer, M. A., & Mehrotra, C. M. (2020). Optimizing aging: A call for a new narrative. *American Psychologist*, *75*(4), 577-589. https://doi.org/10.1037/amp0000598

Dierssen, M., Fructuoso, M., Martínez de Lagrán, M., Perluigi, M., & Barone, E. (2020). Down syndrome is a metabolic disease: Altered insulin signaling mediates peripheral and brain dysfunctions. *Frontiers in Neuroscience*, *14*, 670. https://doi.org/10.3389/fnins.2020.00670

Ding, J., Davis-Plourde, K. L., Sedaghat, S., Tully, P. J., Wang, W., Phillips, C., Pase, M. P., Himali, J. J., Windham, B. G., & Griswold, M. (2020). Antihypertensive medications and risk for incident dementia and Alzheimer's disease: A meta-analysis of individual participant data from prospective cohort studies. *The Lancet Neurology*, *19*(1), 61-70. https://doi.org/10.1016/S1474-4422(19)30393-X

DiProspero, N. D., Keator, D. B., Phelan, M., van Erp, T. G., Doran, E., Powell, D. K., Van Pelt, K. L., Schmitt, F. A., Head, E., & Lott, I. T. (2022). Selective impairment of long-range default mode network functional connectivity as a biomarker for preclinical Alzheimer's disease in people with Down syndrome. *Journal of Alzheimer's Disease*, *85*(1), 153-165. https://doi.org/10.3233/JAD-210572

Dodd, P., Craig, S., Kelly, F., & Guerin, S. (2010). An audit of the Irish national intellectual disability database. *Research in Developmental Disabilities*, *31*(2), 446-451. https://doi.org/10.1016/j.ridd.2009.10.011

Domènech-Abella, J., Mundó, J., Haro, J. M., & Rubio-Valera, M. (2019). Anxiety, depression, loneliness and social network in the elderly: Longitudinal associations from The Irish Longitudinal Study on Ageing (TILDA). *Journal of Affective Disorders*, *246*, 82-88. https://doi.org/10.1016/j.jad.2018.12.043

Donnelly, S., Donnelly, M., & Gleeson, C. (2021). The Assisted Decision-making Capacity Act, 2015: Reflections for the profession of social work. In: M. Donnelly & C. Gleeson (Eds.), *Towards a New Frontier for Human Rights: The Assisted Decision-Making (Capacity) Act 2015 Personal and Professional Reflections* (pp. 154-159). Health Service Executive.

Donoghue, O., O'Connell, M., & Kenny, R. (2016). *Walking to wellbeing: Physical activity, social participation and psychological health in Irish adults aged 50 years and older*. The Irish longitudinal study on ageing (TILDA). https://www.doi.org/10.38018/TildaRe.2016-00

Donovan, N. J., & Blazer, D. (2020). Social isolation and loneliness in older adults: Review and commentary of a National Academies report. *The American Journal of Geriatric Psychiatry*, *28*(12), 1233-1244. https://doi.org/10.1016/j.jagp.2020.08.005

Douma, J. G., Volkers, K. M., Engels, G., Sonneveld, M. H., Goossens, R. H., & Scherder, E. J. (2017). Setting-related influences on physical inactivity of older adults in residential care settings: A review. *BMC Geriatrics*, *17*, 1-10. https://doi.org/10.1186/s12877-017-0487-3

Down, J. L. H. (1867). Observations on an ethnic classification of idiots. *Journal of Mental Science*, *13*(61), 121-123. https://doi.org:10.1192/bjp.13.61.121

Downs, M., Clare, L., & Anderson, E. (2008). Dementia as a biopsychosocial condition: Implications for practice and research. In B. Woods & L. Clare (Eds.), *Handbook of the clinical psychology of ageing* (pp. 145-159). John Wiley & Sons.

Drachman, D. A. (2014). The amyloid hypothesis, time to move on: Amyloid is the downstream result, not cause, of Alzheimer's disease. *Alzheimer's & Dementia*, *10*(3), 372-380. https://doi.org/10.1016/j.jalz.2013.11.003

Dubois, B., Villain, N., Schneider, L., Fox, N., Campbell, N., Galasko, D., Kivipelto, M., Jessen, F., Hanseeuw, B., & Boada, M. (2024). Alzheimer disease as a clinical-biological construct - An international working group recommendation. *JAMA Neurology*, *81*(12), 1304-1311. https://doi.org/10.1001/jamaneurol.2024.3770

Duvdevany, I., & Arar, E. (2004). Leisure activities, friendships, and quality of life of persons with intellectual disability: Foster homes vs community residential settings. *International Journal of Rehabilitation Research*, *27*(4), 289-296. https://doi.org/10.1097/00004356-200412000-00006

Duzel, E., Van Praag, H., & Sendtner, M. (2016). Can physical exercise in old age improve memory and hippocampal function? *Brain*, *139*(3), 662-673. https://doi.org/10.1093/brain/awv407

Edwards, E. S., & Sackett, S. C. (2016). Psychosocial variables related to why women are less active than men and related health implications. *Clinical Medicine Insights: Women's Health*, *9*, e34668. https://doi.org/10.4137/CMWH.S34668

Ee, J., Stenfert Kroese, B., & Rose, J. (2022). Specialist mental health services for people with intellectual disabilities in Singapore - What do stakeholders think of them and how do they relate to service accomplishments? *Journal of Mental Health Research in Intellectual Disabilities*, *15*(2), 130-150. https://doi.org/10.1080/19315864.2022.2029647

Ejiri, M., Kawai, H., Ishii, K., Oka, K., & Obuchi, S. (2021). Predictors of older adults' objectively measured social isolation: A systematic review of observational studies. *Archives of Gerontology and Geriatrics*, 104357. https://doi.org/10.1016/j.archger.2021.104357

Ejskjaer, K., Uldbjerg, N., & Goldstein, H. (2006). Menstrual profile and early menopause in women with Down syndrome aged 26–40 years. *Journal of Intellectual and Developmental Disability*, *31*(3), 166-171. https://doi.org/10.1080/13668250600879222

Elbejjani, M., Auer, R., Jacobs Jr, D. R., Haight, T., Davatzikos, C., Goff Jr, D. C., Bryan, R. N., & Launer, L. J. (2019). Cigarette smoking and gray matter brain volumes in middle age adults: The CARDIA Brain MRI sub-study. *Translational Psychiatry*, *9*(1), 78. https://doi.org/10.1038/s41398-019-0401-1

Elovainio, M., Lahti, J., Pirinen, M., Pulkki-Råback, L., Malmberg, A., Lipsanen, J., Virtanen, M., Kivimäki, M., & Hakulinen, C. (2022). Association of social isolation, loneliness and genetic risk with incidence of dementia: UK Biobank Cohort Study. *British Medical Journal*, *12*(2), e053936. https://doi.org/10.1136/bmjopen-2021-053936

Endalifer, M. L., & Diress, G. (2020). Epidemiology, predisposing factors, biomarkers, and prevention mechanism of obesity: A systematic review. *Journal of Obesity*, *2020*(1), 6134362. https://doi.org/10.1155/2020/6134362

Evans, I. E., Martyr, A., Collins, R., Brayne, C., & Clare, L. (2019). Social isolation and cognitive function in later life: A systematic review and meta-analysis. *Journal of Alzheimer's disease*, *70*(s1), S119-S144. https://doi.org/10.3233/JAD-180501

Falck, R. S., McDonald, S. M., Beets, M. W., Brazendale, K., & Liu-Ambrose, T. (2016). Measurement of physical activity in older adult interventions: A systematic review. *British Journal of Sports Medicine*, *50*(8), 464-470. https://doi.org/10.1136/bjsports-2014-094413

Falgàs, N., Maure-Blesa, L., Ances, B., Flores-Aguilar, L., Hartley, S., Hassenstab, J., Iulita, M. F., Janicki, M., Koenig, K., Lao, P., Levin, J., McDade, E., Meijer, L., Rafii, M. S., Snyder, H. M., Sánchez-Valle, R., Fortea, J., Arriola Infante, J., Balasa, M., . . . Zaman, S. (2025). Genetically determined Alzheimer's disease research advances: The Down syndrome & autosomal dominant Alzheimer's disease 2024 conference. *Alzheimer's & Dementia*, *21*(7), e70309. https://doi-org.elib.tcd.ie/10.1002/alz.70309

Farina, F. R., Bridgeman, K., Gregory, S., Crivelli, L., Foote, I. F., Jutila, O.-E. I., Kucikova, L., Mariano, L. I., Nguyen, K.-H., & Thayanandan, T. (2024). Next generation brain health: Transforming global research and public health to promote prevention of dementia and reduce its risk in young adult populations. *The Lancet Healthy Longevity*, *5*(12), 100665. https://doi.org/10.1016/j.lanhl.2024.100665

Feast, L., & Melles, G. (2010, June 28 – July 1). Epistemological positions in design research: A brief review of the literature. [Oral Presentation]. 2nd International Conference on Design Education, Swinburne University of Technology, Melbourne. https://www.researchgate.net/publication/236619107_Epistemological_Positions_in_Design_Research_A_Brief_Review_of_the_Literature

Feinkohl, I., Price, J. F., Strachan, M. W. J., & Frier, B. M. (2015). The impact of diabetes on cognitive decline: Potential vascular, metabolic, and psychosocial risk factors. *Alzheimer's Research & Therapy*, *7*(1). https://doi.org/10.1186/s13195-015-0130-5

Ferguson, C. J. (2009). An effect size primer: A guide for clinicians and researchers. *Professional Psychology: Research and Practice*, *40*(5), 532-538. https://psycnet.apa.org/doi/10.1037/a0015808

Fernández-Ballesteros, R., Benetos, A., & Robine, J. (2019). The concept of successful aging and related terms. In R. Fernández-Ballesteros, A. Benetos, & J. Robine (Eds.), *The Cambridge handbook of successful aging* (pp. 6-22). Cambridge University Press.

Ferrari, R. (2015). Writing narrative style literature reviews. *Medical Writing*, *24*(4), 230-235. https://doi.org/10.1179/2047480615Z.000000000329

Fierini, F. (2020). Mixed dementia: Neglected clinical entity or nosographic artifice? *Journal of the Neurological Sciences*, *410*, 116662. https://doi.org/10.1016/j.jns.2019.116662

Firth, N. C., Startin, C. M., Hithersay, R., Hamburg, S., Wijeratne, P. A., Mok, K. Y., Hardy, J., Alexander, D. C., LonDown, S. C., & Strydom, A. (2018). Aging related cognitive changes associated with Alzheimer's disease in Down syndrome. *Annals of Clinical and Translational Neurology*, *5*(6), 741-751. https://doi.org/10.1002/acn3.571

FitzGerald, J., Byrne, D., & Žnuderl, N. (2011). *The impact of changes in educational attainment on life expectancy in Ireland*. The Economic and Social Research Institute. Retrieved 2nd April 2023 from https://www.econstor.eu/bitstream/10419/100241/1/675456304.pdf

Fleming, V., Piro-Gambetti, B., Patrick, A., Zammit, M., Alexander, A., Christian, B. T., Handen, B., Cohen, A., Klunk, W., & Laymon, C. (2021). Physical activity and cognitive and imaging biomarkers of Alzheimer's disease in Down syndrome. *Neurobiology of Aging*, *107*, 118-127. https://doi.org/10.1016/j.neurobiolaging.2021.07.016

Fleming, V., Piro-Gambetti, B., Handen, B., Christian, B. T., Cohen, A., Tudorascu, D., Plante, D. T., Okonkwo, O., & Hartley, S. L. (2022). Physical activity and physical and mental health in middle-aged adults with Down syndrome. *Journal of Policy and Practice in Intellectual Disabilities*, *19*(4), 408-418. https://doi.org/10.1111/jppi.12434

Fleming, V. L., Peven, J., Helsel, B. C., Ptomey, L. T., Clina, J., Barry, A., Ances, B. M., Handen, B. L., Christian, B. T., & Laymon, C. (2025). Physical activity as a resistance or resilience mechanism in Down syndrome Alzheimer's disease. *Alzheimer's & Dementia: Translational Research & Clinical Interventions*, *11*(3), e70127. https://doi.org/10.1002/trc2.70127

Flor, L. S., Reitsma, M. B., Gupta, V., Ng, M., & Gakidou, E. (2021). The effects of tobacco control policies on global smoking prevalence. *Nature Medicine*, *27*(2), 239-243. https://doi.org/10.1038/s41591-020-01210-8

Flores-Aguilar, L., Iulita, M. F., Kovecses, O., Torres, M. D., Levi, S. M., Zhang, Y., Askenazi, M., Wisniewski, T., Busciglio, J., & Cuello, A. C. (2020). Evolution of neuroinflammation across the lifespan of individuals with Down syndrome. *Brain*, *143*(12), 3653-3671. https://doi.org/10.1093/brain/awaa326

Flygare Wallén, E., Ljunggren, G., Carlsson, A. C., Pettersson, D., & Wändell, P. (2018). High prevalence of diabetes mellitus, hypertension and obesity among persons with a recorded diagnosis of intellectual disability or autism spectrum disorder. *Journal of Intellectual Disability Research*, *62*(4), 269-280. https://doi.org/10.1111/jir.12462

Fonseca, L. M., Haddad, G. G., Mattar, G. P., Oliveira, M. C. d., Simon, S. S., Guilhoto, L. M., Busatto, G. F., Zaman, S., Holland, A. J., Hoexter, M. Q., & Bottino, C. M. (2019). The validity and reliability of the CAMDEX-DS for assessing dementia in adults with Down syndrome in Brazil. *Brazilian Journal of Psychiatry*, *41*(3), 225-233. https://doi.org/10.1590/1516-4446-2018-0033

Fonseca, L. M., Padilla, C., Jones, E., Neale, N., Haddad, G. G., Mattar, G. P., Barros, E., Clare, I. C. H., Busatto, G. F., Bottino, C. M. C., Hoexter, M. Q., Holland, A. J., & Zaman, S. (2020). Amnestic and non-amnestic symptoms of dementia: An international study of Alzheimer's disease in people with Down's syndrome. *International Journal of Geriatric Psychiatry*, *35*(6), 650-661. https://doi.org/10.1002/gps.5283

Fornito, A., Zalesky, A., & Breakspear, M. (2015). The connectomics of brain disorders. *Nature Reviews Neuroscience*, *16*(3), 159-172. https://doi.org/10.1038/nrn3901

Fortea, J., Carmona-Iragui, M., Benejam, B., Fernández, S., Videla, L., Barroeta, I., Alcolea, D., Pegueroles, J., Muñoz, L., & Belbin, O. (2018). Plasma and CSF biomarkers for the diagnosis of Alzheimer's disease in adults with Down syndrome: A cross-sectional study. *The Lancet Neurology*, *17*(10), 860-869. https://doi.org/10.1016/S1474-4422(18)30285-0

Fortea, J., Pegueroles, J., Alcolea, D., Belbin, O., Dols-Icardo, O., Vaque-Alcazar, L., Videla, L., Gispert, J. D., Suarez-Calvet, M., Johnson, S. C., Sperling, R., Bejanin, A., Lleo, A., & Montal, V. (2024). APOE4 homozygosity represents a distinct genetic form of Alzheimer's disease. *Nature Medicine*, *30*(5), 1284-1291. https://doi.org/10.1038/s41591-024-02931-w

Fortea, J., Zaman, S. H., Hartley, S., Rafii, M. S., Head, E., & Carmona-Iragui, M. (2021). Alzheimer's disease associated with Down syndrome: A genetic form of dementia. *The Lancet Neurology*, *20*(11), 930-942. https://doi.org/10.1016/S1474-4422(21)00245-3

Foster, L., & Walker, A. (2021). Active ageing across the life course: Towards a comprehensive approach to prevention. *BioMed Research International*, *2021*. https://doi.org/10.1155/2021/6650414

Franits, L. E. (2005). Nothing about us without us: Searching for the narrative of disability. *The American Journal of Occupational Therapy*, *59*(5), 577-579. https://doi.org/10.5014/ajot.59.5.577

Frank, L., Helsel, B., Dodd, D., Bodde, A. E., Danon, J. C., Sherman, J. R., Forsha, D. E., Szabo-Reed, A., Washburn, R. A., & Donnelly, J. E. (2023). The association between cardiovascular health and cognition in adults with Down syndrome. *Journal of Neurodevelopmental Disorders*, *15*(1), 43. https://doi.org/10.1186/s11689-023-09510-z

Fratiglioni, L., & Wang, H.-X. (2007). Brain reserve hypothesis in dementia. *Journal of Alzheimer's disease*, *12*(1), 11-22. https://doi.org/10.3233/JAD-2007-12103

Fu, J. F., Garimella, A., Lapointe, A., Aye, W. W. T., Chen, C. D., Lee, J. H., Krinsky?McHale, S. J., Zaman, S., Lott, I. T., Hom, C., Ances, B., Head, E., Mapstone, M., Lai, F., Handen, B. L., Laymon, C. M., Hartley, S. L., Christian, B. T., Rentz, D. M., & Johnson, K. A. (2025). Joint spatial associations of amyloid beta and tau pathology in Down syndrome and preclinical Alzheimer's disease: Cross-sectional associations with early cognitive impairments. *Alzheimer's & Dementia*, *21*(7), 1-13. https://doi.org/10.1002/alz.70424

Funahashi, S. (2017). Working memory in the prefrontal cortex. *Brain Sciences*, *7*(5), 49. https://doi.org/10.3390/brainsci7050049

Fuster, J. M. (2019). The prefrontal cortex in the neurology clinic. In M. D'Esposito & J. H. Grafman (Eds.), *Handbook of clinical neurology* (Vol. 163, pp. 3-15). Elsevier. https://doi.org/10.1016/B978-0-12-804281-6.00001-X

Gangadharan, S. K., Devapriam, J., & Bhaumik, S. (2009). People with learning disability, and ageing. *Psychiatry*, *8*(10), 382-386. https://doi.org/10.1016/j.mppsy.2009.06.019

Garcia, T. P., & Marder, K. (2017). Statistical approaches to longitudinal data analysis in neurodegenerative diseases: Huntington's disease as a model. *Current Neurology and Neuroscience Reports*, *17*(2), 14. https://doi.org/10.1007/s11910-017-0723-4

Gatchel, J. R., Rabin, J. S., Buckley, R. F., Locascio, J. J., Quiroz, Y. T., Yang, H.-S., Vannini, P., Amariglio, R. E., Rentz, D. M., & Properzi, M. (2019). Longitudinal association of depression symptoms with cognition and cortical amyloid among community-dwelling older adults. *JAMA Network Open*, *2*(8), e198964. https://doi.org/10.1001/jamanetworkopen.2019.8964

GBD Dementia Forecasting Collaborators. (2022). Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: An analysis for the Global Burden of Disease Study 2019. *The Lancet Public Health*, *7*(2), 105-125. https://doi.org/10.1016/S2468-2667(21)00249-8

Genon, S., Reid, A., Langner, R., Amunts, K., & Eickhoff, S. B. (2018). How to characterize the function of a brain region. *Trends in Cognitive Sciences*, *22*(4), 350-364. https://doi.org/10.1016/j.tics.2018.01.010

Gensous, N., Bacalini, M. G., Franceschi, C., & Garagnani, P. (2020). Down syndrome, accelerated aging and immunosenescence. *Seminars in Immunopathology, 42*(5), 635-645. https://doi.org/10.1007/s00281-020-00804-1

Gerstorf, D., Hülür, G., Drewelies, J., Willis, S. L., Schaie, K. W., & Ram, N. (2020). Adult development and aging in historical context. *American Psychologist*, *75*(4), 525-539. https://doi.org/10.1037/amp0000596

Ghezzo, A., Salvioli, S., Solimando, M. C., Palmieri, A., Chiostergi, C., Scurti, M., Lomartire, L., Bedetti, F., Cocchi, G., & Follo, D. (2014). Age-related changes of adaptive and neuropsychological features in persons with Down Syndrome. *PloS One*, *9*(11), e113111. https://doi.org/10.1371/journal.pone.0113111

Gilleard, C. (2007). Old age in ancient Greece: Narratives of desire, narratives of disgust. *Journal of Aging Studies*, *21*(1), 81-92. https://doi.org/10.1016/j.jaging.2006.02.002

Gjermestad, A., Luteberget, L., Midjo, T., & Witsø, A. E. (2017). Everyday life of persons with intellectual disability living in residential settings: A systematic review of qualitative studies. *Disability & Society*, *32*(2), 213-232. https://doi.org/10.1080/09687599.2017.1284649

Glantz, M. D., Bharat, C., Degenhardt, L., Sampson, N. A., Scott, K. M., Lim, C. C., Al-Hamzawi, A., Alonso, J., Andrade, L. H., & Cardoso, G. (2020). The epidemiology of alcohol use disorders cross-nationally: Findings from the World Mental Health Surveys. *Addictive Behaviors*, *102*, 106128. https://doi.org/10.1016/j.addbeh.2019.106128

Glass, T. A. (2003). Assessing the success of successful aging. *Annals of Internal Medicine*, *139*(5), 382-383. https://doi.org/10.7326/0003-4819-139-5_part_1-200309020-00015

Glasson, E., & Bittles, A. H. (2008). The impact of ageing in people with intellectual and developmental disability. In E. B. Bodzsar & C. Susanne (Eds.), *Ageing Related Problems in Past and Present Populations* (pp. 27-43). Plantin Publications & Press Ltd.

Gleiser, M. (2014). *The island of knowledge: The limits of science and the search for meaning*. Basic Books.

Glenner, G. G., & Wong, C. W. (1984). Alzheimer's disease: Initial report of the purification and characterization of a novel cerebrovascular amyloid protein. *Biochemical and Biophysical Research Communications*, *120*(3), 885-890. https://doi.org/https://doi-org.elib.tcd.ie/10.1016/j.bbrc.2012.08.020

Gligoroska, J. P., & Manchevska, S. (2012). The effect of physical activity on cognition–physiological mechanisms. *Materia Socio Medica*, *24*(3), 198-202. https://doi.org/10.5455/msm.2012.24.198-202

Gomez, W., Morales, R., Maracaja-Coutinho, V., Parra, V., & Nassif, M. (2020). Down syndrome and Alzheimer's disease: Common molecular traits beyond the amyloid precursor protein. *Aging*, *12*(1), 1011-1033. https://doi.org/10.18632/aging.102677

Gorelick, P. B., Scuteri, A., Black, S. E., DeCarli, C., Greenberg, S. M., Iadecola, C., Launer, L. J., Laurent, S., Lopez, O. L., & Nyenhuis, D. (2011). Vascular contributions to cognitive impairment and dementia: A statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*, *42*(9), 2672-2713. https://doi.org/10.1161/STR.0b013e3182299496

Gottesman, R. F., Schneider, A. L., Zhou, Y., Coresh, J., Green, E., Gupta, N., Knopman, D. S., Mintz, A., Rahmim, A., & Sharrett, A. R. (2017). Association between midlife vascular risk factors and estimated brain amyloid deposition. *Journal of the American Medical Association*, *317*(14), 1443-1450. https://doi.org/10.1001/jama.2017.3090

Götz, F. M., Gosling, S. D., & Rentfrow, P. J. (2022). Small effects: The indispensable foundation for a cumulative psychological science. *Perspectives on Psychological Science*, *17*(1), 205-215. https://doi.org/10.1177/1745691620984483

Grady, C. (2012). The cognitive neuroscience of ageing. *Nature Reviews Neuroscience*, *13*(7), 491-505. https://doi.org/10.1038/nrn3256

Grande, G., Qiu, C., & Fratiglioni, L. (2020). Prevention of dementia in an ageing world: Evidence and biological rationale. *Ageing Research Reviews*, *64*, 101045. https://doi.org/10.1016/j.arr.2020.101045

Gray, J. C., Thompson, M., Bachman, C., Owens, M. M., Murphy, M., & Palmer, R. (2020). Associations of cigarette smoking with gray and white matter in the UK Biobank. *Neuropsychopharmacology*, *45*(7), 1215-1222. https://doi.org/10.1038/s41386-020-0630-2

Green, S. B. (1991). How many subjects does it take to do a regression analysis. *Multivariate Behavioral Research*, *26*(3), 499-510. https://doi.org/10.1207/s15327906mbr2603_7

Griffin, S. C., Mezuk, B., Williams, A. B., Perrin, P. B., & Rybarczyk, B. D. (2020). Isolation, not loneliness or cynical hostility, predicts cognitive decline in older Americans. *Journal of Aging and Health*, *32*(1-2), 52-60. https://doi.org/10.1177/0898264318800587

Gutiérrez-Rojas, L., Porras-Segovia, A., Dunne, H., Andrade-González, N., & Cervilla, J. A. (2020). Prevalence and correlates of major depressive disorder: A systematic review. *Brazilian Journal of Psychiatry*, *42*(6), 657-672. https://doi.org/10.1590/1516-4446-2020-0650

Hakim, A. (2022). Perspectives on the complex links between depression and dementia. *Frontiers in Aging Neuroscience*, *14*, 821866. https://doi.org/10.3389/fnagi.2022.821866

Hamadelseed, O., Elkhidir, I. H., & Skutella, T. (2022). Psychosocial risk factors for Alzheimer's disease in patients with Down syndrome and their association with brain changes: A narrative review. *Neurology and Therapy*, *11*(3), 931-953. https://doi.org/10.1007/s40120-022-00361-9

Hardy, J. A., & Higgins, G. A. (1992). Alzheimer's disease: The amyloid cascade hypothesis. *Science*, *256*(5054), 184-185. https://doi.org/10.1126/science.1566067

Harrison, J. R., & Owen, M. J. (2016). Alzheimer's disease: The amyloid hypothesis on trial. *The British Journal of Psychiatry*, *208*(1), 1-3. https://doi.org/10.1192/bjp.bp.115.167569

Harrison, R. A., Bradshaw, J., Forrester-Jones, R., Mccarthy, M., & Smith, S. (2021). Social networks and people with intellectual disabilities: A systematic review. *Journal of Applied Research in Intellectual Disabilities*, *34*(4), 973-992. https://doi.org/10.1111/jar.12878

Hartley, D., Blumenthal, T., Carrillo, M., DiPaolo, G., Esralew, L., Gardiner, K., Granholm, A.-C., Iqbal, K., Krams, M., & Lemere, C. (2015). Down syndrome and Alzheimer's disease: Common pathways, common goals. *Alzheimer's & Dementia*, *11*(6), 700-709. https://doi.org/10.1016/j.jalz.2014.10.007

Hartley, S. L., Fleming, V., Schworer, E. K., Peven, J., Handen, B. L., Krinsky-McHale, S., Hom, C., Lee, L., Tudorascu, D. L., & Laymon, C. (2023). Timing of Alzheimer's disease by intellectual disability level in Down syndrome. *Journal of Alzheimer's Disease*, *95*(1), 213-225. https://doi.org/10.3233/JAD-230200

Hartley, S. L., Handen, B. L., Devenny, D., Tudorascu, D., Piro-Gambetti, B., Zammit, M. D., Laymon, C. M., Klunk, W. E., Zaman, S., & Cohen, A. (2020). Cognitive indicators of transition to preclinical and prodromal stages of Alzheimer's disease in Down syndrome. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*, *12*(1), e12096. https://doi.org/10.1002/dad2.12096

Hatzidimitriadou, E., & Milne, A. (2005). Planning ahead: Meeting the needs of older people with intellectual disabilities in the United Kingdom. *Dementia*, *4*(3), 341-359. https://doi.org/10.1177/1471301205055027

Haveman, M., Heller, T., Lee, L., Maaskant, M., Shooshtari, S., & & Strydom, A. (2009). *Report on the State of Science on Health Risks and Ageing in People with Intellectual Disabilities*. IASSID. Retrieved 2nd Aril 2023 from https://iassidd.org/wp-content/uploads/2019/02/haveman-et-al-state-of-the-science.pdf

Head, E., & Ances, B. (2020). Biomarkers in Down syndrome can help us understand Alzheimer's disease. *The Lancet*, *395*(10242), 1951-1953. https://doi.org/10.1016/S0140-6736(20)30916-8

Head, E., Powell, D. K., & Schmitt, F. A. (2018). Metabolic and vascular imaging biomarkers in Down syndrome provide unique insights into brain aging and Alzheimer disease pathogenesis. *Frontiers in Aging Neuroscience*, *10*, 191. https://doi.org/10.3389/fnagi.2018.00191

Health Service Executive. (2011). *Time to move on from congregated settings: A strategy for community inclusion*. Health Service Executive. Retrieved 2/02/2023 from https://www.hse.ie/eng/services/list/4/disability/congregatedsettings/time-to-move-on-from-congregated-settings-%E2%80%93-a-strategy-for-community-inclusion.pdf

Heger, I. S., Deckers, K., Schram, M. T., Stehouwer, C. D., Dagnelie, P. C., van der Kallen, C. J., Koster, A., Eussen, S. J., Jansen, J. F., & Verhey, F. R. (2021). Associations of the lifestyle for brain health index with structural brain changes and cognition: Results from the Maastricht study. *Neurology*, *97*(13), e1300-e1312. https://doi.org/10.1212/WNL.0000000000012572

Heller, T., & Harris, S. P. (2011). *Disability through the life course*. Sage Publications.

Heller, T., & van Heumen, L. (2013). Aging with disability. In M. Wehmeyer (Ed.), *The Oxford handbook of positive psychology and disability* (pp. 409-423). Oxford University Press.

Heller, T., & van Heumen, L. (2021). Positive psychology and disability studies: Directions for research on aging with IDD. *Innovation in Aging, 17*(5), 224. https://doi.org/10.1093/geroni/igab046.867

Henderson, A., McSkimming, P., Kinnear, D., McCowan, C., McIntosh, A., Allan, L., & Cooper, S.-A. (2020). Changes over a decade in psychotropic prescribing for people with intellectual disabilities: Prospective cohort study. *British Medical Journal*, *10*(9), e036862. https://doi.org/10.1136/bmjopen-2020-036862

Hendrie, H. C., Albert, M. S., Butters, M. A., Gao, S., Knopman, D. S., Launer, L. J., Yaffe, K., Cuthbert, B. N., Edwards, E., & Wagster, M. V. (2006). The NIH Cognitive and Emotional Health Project. *Alzheimer's & Dementia*, *2*(1), 12-32. https://doi.org/10.1016/j.jalz.2005.11.004

Hevey, D., & McGee, H. M. (1998). The effect size statistic: Useful in health outcomes research? *Journal of Health Psychology*, *3*(2), 163-170. https://doi.org/10.1177/135910539800300201

Hilgenkamp, T. I. M., Reis, D., Van Wijck, R., & Evenhuis, H. M. (2012). Physical activity levels in older adults with intellectual disabilities are extremely low. *Research in Developmental Disabilities*, *33*(2), 477-483. https://doi.org/10.1016/j.ridd.2011.10.011

Hinde, K., & Mason, J. (2020). Health practitioner knowledge and confidence in diagnosis and treatment of mental health issues in people with intellectual disabilities. *Journal of Intellectual & Developmental Disability*, *45*(3), 269-278. https://doi.org/10.3109/13668250.2020.1730075

Hithersay, R., Startin, C. M., Hamburg, S., Mok, K. Y., Hardy, J., Fisher, E. M. C., Tybulewicz, V. L. J., Nizetic, D., & Strydom, A. (2019). Association of dementia With mortality among adults with Down syndrome older than 35 years. *JAMA Neurology*, *76*(2), 152-160. https://doi.org/10.1001/jamaneurol.2018.3616

Holt-Lunstad, J. (2018). Why social relationships are important for physical health: A systems approach to understanding and modifying risk and protection. *Annual Review of Psychology*, *69*(1), 437-458. https://doi.org/10.1146/annurev-psych-122216-011902

Holt-Lunstad, J., Smith, T. B., & Layton, J. B. (2010). Social relationships and mortality risk: A meta-analytic review. *PLoS Medicine*, *7*(7), e1000316. https://doi.org/10.1371/journal.pmed.1000316

Holt-Lunstad, J., & Steptoe, A. (2022). Social isolation: An underappreciated determinant of physical health. *Current Opinion in Psychology*, *43*, 232-237. https://doi.org/10.1016/j.copsyc.2021.07.012

Holzapfel, S. D., Ringenbach, S. D., Mulvey, G. M., Sandoval-Menendez, A. M., Birchfield, N., & Tahiliani, S. R. (2016). Differential effects of assisted cycling therapy on short-term and working memory of adolescents with Down syndrome. *Journal of Cognitive Psychology*, *28*(8), 990-1003. https://doi.org/10.1080/20445911.2016.1205592

House, A., Latchford, G., Russell, A. M., Bryant, L., Wright, J., Graham, E., Stansfield, A., Ajjan, R., & O'Dwyer, J. (2018). Development of a supported self-management intervention for adults with type 2 diabetes and a learning disability. *Pilot and Feasibility Studies*, *4*(106), 1-11. https://doi.org/10.1186/s40814-018-0291-7

Hsieh, K., Heller, T., Bershadsky, J., & Taub, S. (2015). Impact of adulthood stage and social-environmental context on body mass index and physical activity of individuals with intellectual disability. *Intellectual and Developmental Disabilities*, *53*(2), 100-113. https://doi.org/10.1352/1934-9556-53.2.100

Hsieh, K., Hilgenkamp, T. I., Murthy, S., Heller, T., & Rimmer, J. H. (2017). Low levels of physical activity and sedentary behavior in adults with intellectual disabilities. *International Journal of Environmental Research and Public Health*, *14*(12), 1503. https://doi.org/10.3390/ijerph14121503

Hsieh, K., Scott, H. M., & Murthy, S. (2020). Associated risk factors for depression and anxiety in adults with intellectual and developmental disabilities: Five-year follow up. *American Journal on Intellectual and Developmental Disabilities*, *125*(1), 49-63. https://doi.org/http://dx.doi.org/10.1352/1944-7558-125.1.49

Huang, T., Lam, X.J., Lim, C.T., Jusoh, N., Fakurazi, S., Cheah, P.S., & Ling, K.H. (2024). Understanding perspectives and research trends in Down syndrome neuropathogenesis: A bibliometric analysis. *Journal of Intellectual Disabilities*, 17446295241299160. https://doi.org/10.1177/17446295241299160

Hunt, L. J., Covinsky, K. E., Cenzer, I., Espejo, E., Boscardin, W. J., Leutwyler, H., Lee, A. K., & Cataldo, J. (2023). The epidemiology of smoking in older adults: A national cohort study. *Journal of General Internal Medicine*, *38*(7), 1697-1704. https://doi.org/10.1007/s11606-022-07980-w

Hyman, M. (2012). *How social networks control your health*. Retrieved 25th October 2023 from https://drhyman.com/blog/2012/01/31/how-social-networks-control-your-health.com

IASSIDD (2019). *Hearing impairment.* IASSID. Retrieved 18th November 2021 from https://view.officeapps.live.com/op/view.aspx?src=https%3A%2F%2Fiassidd.org%2Fwp-content%2Fuploads%2F2019%2F08%2Fconsensir_HEARING_IMPAIRMENT.doc&wdOrigin=BROWSELINK

Ibrahim, J. G., & Molenberghs, G. (2009). Missing data methods in longitudinal studies: A review. *TEST*, *18*(1), 1-43. https://doi.org/10.1007/s11749-009-0138-x

Ijezie, O. A., Healy, J., Davies, P., Balaguer-Ballester, E., & Heaslip, V. (2023). Quality of life in adults with Down syndrome: A mixed methods systematic review. *PloS One*, *18*(5), e0280014. https://doi.org/10.1371/journal.pone.0280014

Infurna, F. J., Gerstorf, D., & Lachman, M. E. (2020). Midlife in the 2020s: Opportunities and challenges. *American Psychologist*, *75*(4), 470-485. https://doi.org/https://psycnet.apa.org/doi/10.1037/amp0000591

IPAQ Research Committee. (2005). *Guidelines for data processing and analysis of the International Physical Activity Questionnaire (IPAQ)-short and long forms*. Retrieved 24th October 2024 from https://sites.google.com/view/ipaq/score

Iqbal, K., Liu, F., & Gong, C.-X. (2016). Tau and neurodegenerative disease: The story so far. *Nature Reviews Neurology*, *12*(1), 15-27. https://doi.org/10.1038/nrneurol.2015.225

Irala, J. d., Fernandez-Crehuet Navajas, R., & Serrano del Castillo, A. (1997). Abnormally wide confidence intervals in logistic regression: Interpretation of statistical program results. *Pan American Journal of Public Health*, *2*, 268-271. https://doi.org/https://iris.paho.org/handle/10665.2/9017

Iulita, M. F., Bejanin, A., Vilaplana, E., Carmona-Iragui, M., Benejam, B., Videla, L., Barroeta, I., Fernández, S., Altuna, M., Pegueroles, J., Montal, V., Valldeneu, S., Giménez, S., González-Ortiz, S., Torres, S., El Bounasri El Bennadi, S., Padilla, C., Rozalem Aranha, M., Estellés, T., . . . Fortea, J. (2023). Association of biological sex with clinical outcomes and biomarkers of Alzheimer's disease in adults with Down syndrome. *Brain Communications*, *5*(2), fcad027. https://doi.org/10.1093/braincomms/fcad074

Iulita, M. F., Chavez, D. G., Christensen, M. K., Tamayo, N. V., Plana-Ripoll, O., Rasmussen, S. A., Figuls, M. R., Alcolea, D., Videla, L., & Barroeta, I. (2022). Association of Alzheimer disease with life expectancy in people with Down syndrome. *JAMA Network Open*, *5*(5), e2212910-e2212910. https://doi.org/10.1001/jamanetworkopen.2022.12910

Izal, M., Nuevo, R., & Montorio, I. (2019). Successful aging and positive psychology: Two empirically related perspectives. *OBM Geriatrics*, *3*(4), 1-1. https://doi.org/http://dx.doi.org/10.21926/obm.geriatr.1904094

Jack, C. R., Andrews, S. J., Beach, T. G., Buracchio, T., Dunn, B., Graf, A., Hansson, O., Ho, C., Jagust, W., & McDade, E. (2024). Revised criteria for the diagnosis and staging of Alzheimer's disease. *Nature Medicine*, *30*, 2121-2124. https://doi.org/10.1038/s41591-024-02988-7

Jack, C. R., Bennett, D. A., Blennow, K., Carrillo, M. C., Feldman, H. H., Frisoni, G. B., Hampel, H., Jagust, W. J., Johnson, K. A., & Knopman, D. S. (2016). A/T/N: An unbiased descriptive classification scheme for Alzheimer disease biomarkers. *Neurology*, *87*(5), 539-547. https://doi.org/10.1212/WNL.0000000000002923

Jackson, E. (2013). Choosing a methodology: Philosophical underpinning. *Practitioner Research in Higher Education*, *7*(1), 49-62. https://doi.org/194.81.189.19/ojs/index.php/prhe

Jafari, A., Rajabi, A., Gholian-Aval, M., Peyman, N., Mahdizadeh, M., & Tehrani, H. (2021). National, regional, and global prevalence of cigarette smoking among women/females in the general population: A systematic review and meta-analysis. *Environmental Health and Preventive Medicine*, *26*(5), 1-13. https://doi.org/10.1186/s12199-020-00924-y

Jakobsen, J. C., Gluud, C., Wetterslev, J., & Winkel, P. (2017). When and how should multiple imputation be used for handling missing data in randomised clinical trials–A practical guide with flowcharts. *BMC Medical Research Methodology*, *17*(1), 162. https://doi.org/10.1186/s12874-017-0442-1

Jalali, A., Ziapour, A., Karimi, Z., Rezaei, M., Emami, B., Kalhori, R. P., Khosravi, F., Sameni, J. S., & Kazeminia, M. (2024). Global prevalence of depression, anxiety, and stress in the elderly population: A systematic review and meta-analysis. *BMC Geriatrics*, *24*(1), 809. https://doi.org/10.1186/s12877-024-05311-8

Janssen, F., Bardoutsos, A., & Vidra, N. (2020). Obesity prevalence in the long-term future in 18 European countries and in the USA. *Obesity Facts*, *13*(5), 514-527. https://doi.org/10.1159/000511023

Janssen, I., Katzmarzyk, P. T., & Ross, R. (2002). Body mass index, waist circumference, and health risk: Evidence in support of current National Institutes of Health guidelines. *Archives of Internal Medicine*, *162*(18), 2074-2079. https://doi.org/10.1001/archinte.162.18.2074

Jenkins, M. R., Peven, J. C., Kubic, L., Handen, B. L., Krinsky-McHale, S. J., Hom, C. L., Lee, A., Tudorascu, D. L., McLachlan, M., Zammit, M., Minhas, D., Luo, W., Laymon, C., Lee, J. H., Lott, I., Cohen, A., Ances, B. M., Rosas, H. D., Lai, F., . . . the Down syndrome Alzheimer Biomarker Consortium. (2025). Behavioral and psychological symptoms of dementia and Alzheimer's disease progression in Down syndrome. *Journal of Neurodevelopmental Disorders*, *17*(1), 19. https://doi.org/10.1186/s11689-025-09604-w

Jeste, D. V., Alexopoulos, G. S., Bartels, S. J., Cummings, J. L., Gallo, J. J., Gottlieb, G. L., Halpain, M. C., Palmer, B. W., Patterson, T. L., & Reynolds, C. F. (1999). Consensus statement on the upcoming crisis in geriatric mental health: Research agenda for the next 2 decades. *Archives of General Psychiatry*, *56*(9), 848-853. https://doi.org/doi:10.1001/archpsyc.56.9.848

Jeste, D. V., Depp, C. A., & Vahia, I. V. (2010). Successful cognitive and emotional aging. *World Psychiatry*, *9*(2), 78-84. https://doi.org/10.1002/j.2051-5545.2010.tb00277.x

Jeste, D. V., Savla, G. N., Thompson, W. K., Vahia, I. V., Glorioso, D. K., Martin, A. v. S., Palmer, B. W., Rock, D., Golshan, S., & Kraemer, H. C. (2013). Association between older age and more successful aging: Critical role of resilience and depression. *American Journal of Psychiatry*, *170*(2), 188-196. https://doi.org/10.1176/appi.ajp.2012.12030386

Jha, P. (2020). The hazards of smoking and the benefits of cessation: A critical summation of the epidemiological evidence in high-income countries. *Elife*, *9*, e49979. https://doi.org/10.7554/eLife.49979

Johansen, M. C., Langton-Frost, N., & Gottesman, R. F. (2020). The role of cardiovascular disease in cognitive impairment. *Current Geriatrics Reports*, *9*, 1-9. https://doi.org/10.1007/s13670-020-00309-7

Johnson, B. T., & Acabchuk, R. L. (2018). What are the keys to a longer, happier life? Answers from five decades of health psychology research. *Social Science & Medicine*, *196*, 218-226. https://doi.org/10.1016/j.socscimed.2017.11.001

Jorm, A. F. (2002). Prospects for the prevention of dementia. *Australasian Journal on Ageing*, *21*(1), 9-13. https://doi.org/10.1111/j.1741-6612.2002.tb00408.x

Kadam, R. A. (2017). Informed consent process: A step further towards making it meaningful! *Perspectives in Clinical Research*, *8*(3), 107-112. https://doi.org/10.4103/picr.PICR_147_16

Kahana, E., & Kahana, B. (2003). Contextualizing successful aging: New directions in an age-old search. In R. A. Settersten (Ed.), *Invitation to the life course: Toward new understandings of later life* (pp. 225-255). Routledge.

Kahana, E., Kahana, B., & Kercher, K. (2003). Emerging lifestyles and proactive options for successful ageing. *Ageing International*, *28*(2), 155-180. https://doi.org/10.1007/s12126-003-1022-8

Kahana, E., Kahana, B., & Lee, J. E. (2014). Proactive approaches to successful aging: One clear path through the forest. *Gerontology*, *60*(5), 466-474. https://doi.org/10.1159/000360222

Kaiser, A. (2013). A review of longitudinal datasets on ageing. *Journal of Population Ageing*, *6*(1), 5-27. https://doi.org/10.1007/s12062-013-9082-3

Kalat, J. W. (2015). *Biological psychology*. Cengage Learning.

Kalinin, S., González-Prieto, M., Scheiblich, H., Lisi, L., Kusumo, H., Heneka, M. T., Madrigal, J. L., Pandey, S. C., & Feinstein, D. L. (2018). Transcriptome analysis of alcohol-treated microglia reveals downregulation of beta amyloid phagocytosis. *Journal of Neuroinflammation*, *15*, 141. https://doi.org/10.1186/s12974-018-1184-7

Kaup, A. R., Byers, A. L., Falvey, C., Simonsick, E. M., Satterfield, S., Ayonayon, H. N., Smagula, S. F., Rubin, S. M., & Yaffe, K. (2016). Trajectories of depressive symptoms in older adults and risk of dementia. *JAMA Psychiatry*, *73*(5), 525-531. https://doi.org/10.1001/jamapsychiatry.2016.0004

Kim, D. J., Massa, M. S., Clarke, R., Scarlett, S., O'Halloran, A. M., Kenny, R. A., & Bennett, D. (2022). Variability and agreement of frailty measures and risk of falls, hospital admissions and mortality in TILDA. *Scientific Reports*, *12*(1), 4878. https://doi.org/10.1038/s41598-022-08959-7

Kitwood, T. (1993). Person and process in dementia. *International Journal of Geriatric Psychiatry*, *8*(7), 541-545. https://doi.org/10.1002/gps.930080702

Kleineidam, L., Thoma, M. V., Maercker, A., Bickel, H., Mösch, E., Hajek, A., König, H.-H., Eisele, M., Mallon, T., Luck, T., Röhr, S., Weyerer, S., Werle, J., Pentzek, M., Fuchs, A., Wiese, B., Mamone, S., Scherer, M., Maier, W., . . . Wagner, Michael. (2018). What is successful aging? A psychometric validation study of different construct definitions. *The Gerontologist*, *59*(4), 738-748. https://doi.org/10.1093/geront/gny083

Koritsas, S., & Iacono, T. (2016). Weight, nutrition, food choice, and physical activity in adults with intellectual disability. *Journal of Intellectual Disability Research*, *60*(4), 355-364. https://doi.org/10.1111/jir.12254

Kremen, W. S., Beck, A., Elman, J. A., Gustavson, D. E., Reynolds, C. A., Tu, X. M., Sanderson-Cimino, M. E., Panizzon, M. S., Vuoksimaa, E., & Toomey, R. (2019). Influence of young adult cognitive ability and additional education on later-life cognition. *Proceedings of the National Academy of Sciences*, *116*(6), 2021-2026. https://doi.org/10.1073/pnas.1811537116

Krinsky-McHale, S. J., Devenney, D. A., Gu, H., Jenkins, E. C., Kittler, P., Vundavalli, V. M., Schupf, N., Scotto, L., Tycko, B., Urv, T. K., Ye, L., Zigman, W. B. & Silverman, W. (2008). Successful aging in a 70-year-old man with Down syndrome: A case study. *Intellectual and Developmental Disabilities*, *46*, 215-228. https://doi.org/10.1352/2008.46:215-228

Kubis-Kubiak, A., Dyba, A., & Piwowar, A. (2020). The interplay between diabetes and alzheimer's disease: In the hunt for biomarkers. *International Journal of Molecular Sciences*, *21*(8), 2744. https://doi.org/10.3390/ijms21082744

Kumari, S. (2008). Multicollinearity: Estimation and elimination. *Journal of Contemporary Research in Management*, *3*(1), 87-95. https://doi.org/http://jcrm.psgim.ac.in/index.php/jcrm/article/view/11

Lachman, M. E., Teshale, S., & Agrigoroaei, S. (2015). Midlife as a pivotal period in the life course: Balancing growth and decline at the crossroads of youth and old age. *International Journal of Behavioral Development*, *39*(1), 20-31. https://doi.org/10.1177/0165025414533223

Lanctôt, K. L., Agüera-Ortiz, L., Brodaty, H., Francis, P. T., Geda, Y. E., Ismail, Z., Marshall, G. A., Mortby, M. E., Onyike, C. U., & Padala, P. R. (2017). Apathy associated with neurocognitive disorders: Recent progress and future directions. *Alzheimer's & Dementia*, *13*(1), 84-100. https://doi.org/10.1016/j.jalz.2016.05.008

Lane, C. A., Barnes, J., Nicholas, J. M., Sudre, C. H., Cash, D. M., Parker, T. D., Malone, I. B., Lu, K., James, S.-N., & Keshavan, A. (2019). Associations between blood pressure across adulthood and late-life brain structure and pathology in the neuroscience substudy of the 1946 British birth cohort (Insight 46): An epidemiological study. *The Lancet Neurology*, *18*(10), 942-952. https://doi.org/10.1016/S1474-4422(19)30228-5

Larsson, S. C., Traylor, M., Malik, R., Dichgans, M., Burgess, S., & Markus, H. S. (2017). Modifiable pathways in Alzheimer's disease: Mendelian randomisation analysis. *British Medical Journal*, *359*, j5375. https://doi.org/10.1136/bmj.j5375

Lautarescu, B. A., Holland, A. J., & Zaman, S. H. (2017). The early presentation of dementia in people with Down syndrome: A systematic review of longitudinal studies. *Neuropsychology Review*, *27*(1), 31-45. https://doi.org/10.1007/s11065-017-9341-9

Lennartsson, C., Rehnberg, J., & Dahlberg, L. (2021). The association between loneliness, social isolation and all-cause mortality in a nationally representative sample of older women and men. *Aging & Mental Health*, *26*(9), 1-8. https://doi.org/10.1080/13607863.2021.1976723

Lennox, N., Beange, H., Parmenter, T., Santos-Teachout, R., Evenhuis, H., Kerr, M., McElduff, A., Fraser, W., Böhmer, C., & Davis, R. (2002). *Health guidelines for adults with an intellectual disability*. IASSID. Retrieved 14th March 2021 from https://healthmattersprogram.org/wp-content/uploads/2020/06/Health-Guidelines-and-Screenings-2.pdf

Lim, E., Nielsen, N., Lapane, L., Barooah, A., Xu, S., Qu, S., McPhillips, E., Dubé, C. E., & Lapane, K. (2023). Health effects of social connectedness in older adults living in congregate long-term care settings: A systematic review of quantitative and qualitative evidence. *International Journal of Older People Nursing*, *18*(6), e12577. https://doi.org/10.1111/opn.12577

Lin, X., & Li, H. (2021). Obesity: Epidemiology, pathophysiology, and therapeutics. *Frontiers in Endocrinology*, *12*, 706978. https://doi.org/10.3389/fendo.2021.706978

Lindsay, S. (2016). A scoping review of the experiences, benefits, and challenges involved in volunteer work among youth and young adults with a disability. *Disability and Rehabilitation*, *38*(16), 1533-1546. https://doi.org/10.3109/09638288.2015.1107634

Livingston, G., Huntley, J., Liu, K. Y., Costafreda, S. G., Selbæk, G., Alladi, S., Ames, D., Banerjee, S., Burns, A., & Brayne, C. (2024). Dementia prevention, intervention, and care: 2024 report of the Lancet standing commission. *The Lancet*, *404*(20452), 572-628. https://doi.org/10.1016/S0140-6736(24)01296-0

Livingston, G., Huntley, J., Sommerlad, A., Ames, D., Ballard, C., Banerjee, S., Brayne, C., Burns, A., Cohen-Mansfield, J., & Cooper, C. (2020). Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *The Lancet*, *396*(10248), 413-446. https://doi.org/10.1016/S0140-6736(20)30367-6

Livingston, G., Sommerlad, A., Orgeta, V., Costafreda, S. G., Huntley, J., Ames, D., Ballard, C., Banerjee, S., Burns, A., & Cohen-Mansfield, J. (2017). Dementia prevention, intervention, and care. *The Lancet*, *390*(10113), 2673-2734. https://doi.org/10.1016/S0140-6736%2817%2931363-6

Loomba, R., Abraham, M., Unalp, A., Wilson, L., Lavine, J., Doo, E., Bass, N. M., & Network, N. S. C. R. (2012). Association between diabetes, family history of diabetes, and risk of nonalcoholic steatohepatitis and fibrosis. *Hepatology*, *56*(3), 943-951. https://doi.org/10.1002/hep.25772

Lott, I. T., & Head, E. (2019). Dementia in Down syndrome: Unique insights for Alzheimer disease research. *Nature Reviews Neurology*, *15*(3), 135-147. https://doi.org/10.1038/s41582-018-0132-6

Loughrey, D. G., Kelly, M. E., Kelley, G. A., Brennan, S., & Lawlor, B. A. (2018). Association of age-related hearing loss with cognitive function, cognitive impairment, and dementia. *JAMA Otolaryngology–Head & Neck Surgery*, *144*(2), 115. https://doi.org/10.1001/jamaoto.2017.2513

Lourida, I., Hannon, E., Littlejohns, T. J., Langa, K. M., Hyppönen, E., Kuzma, E., & Llewellyn, D. J. (2019). Association of lifestyle and genetic risk with incidence of dementia. *Journal of the American Medical Association*, *322*(5), 430-437. https://doi.org/10.1001/jama.2019.9879

Lubben, J. (2017). Addressing social isolation as a potent killer! *Public Policy & Aging Report*, *27*(4), 136-138. https://doi.org/10.1093/ppar/prx026

Lushniak, B. D., Samet, J. M., Pechacek, T. F., Norman, L. A., & Taylor, P. A. (2014). *The health consequences of smoking—50 years of progress: A report of the surgeon general*. Retrieved 24th May 2021 from https://stacks.cdc.gov/view/cdc/21569/cdc_21569_ds1.pdf

Lynch, L., McCarron, M., McCallion, P., & Burke, E. (2021). Sedentary behaviour levels in adults with an intellectual disability: a systematic review and meta-analysis. *HRB Open Research*, *4*, 69. https://doi.org/10.12688/hrbopenres.13326.1

Lynch, L., McCarron, M., McCallion, P., & Burke, E. (2024). A longitudinal exploration of self-reported TV behaviours as a surrogate for sedentary behaviour in older adults with an intellectual disability from the intellectual disability supplement to the Irish longitudinal study on aging (IDS-TILDA) study. *Journal of Intellectual Disabilities*, *29*(1), 50-65. https://doi.org/10.1177/17446295241230578

Lynch, L., McCarron, M., McCallion, P., & Burke, E. (2025). To identify and compare ActivPAL objectively measured activity levels with self-reported activity from the international physical activity questionnaire in older adults with intellectual disability. *Journal of Applied Research in Intellectual Disabilities*, *38*(1), e13327. https://doi.org/10.1111/jar.13327

Mackey, S., Allgaier, N., Chaarani, B., Spechler, P., Orr, C., Bunn, J., Allen, N. B., Alia-Klein, N., Batalla, A., & Blaine, S. (2019). Mega-analysis of gray matter volume in substance dependence: General and substance-specific regional effects. *American Journal of Psychiatry*, *176*(2), 119-128. https://doi.org/10.1176/appi.ajp.2018.17040415

Madley-Dowd, P., Hughes, R., Tilling, K., & Heron, J. (2019). The proportion of missing data should not be used to guide decisions on multiple imputation. *Journal of Clinical Epidemiology*, *110*, 63-73. https://doi.org/10.1016/j.jclinepi.2019.02.016

Maharani, A., Dawes, P., Nazroo, J., Tampubolon, G., & Pendleton, N. (2018). Longitudinal relationship between hearing aid use and cognitive function in older Americans. *Journal of the American Geriatrics Society*, *66*(6), 1130-1136. https://doi.org/10.1111/jgs.15363

Mahmoud, R., Kimonis, V., & Butler, M. G. (2022). Genetics of obesity in humans: A clinical review. *International Journal of Molecular Sciences*, *23*(19), 11005. https://doi.org/10.3390/ijms231911005

Mahy, J., Shields, N., Taylor, N., & Dodd, K. (2010). Identifying facilitators and barriers to physical activity for adults with Down syndrome. *Journal of Intellectual Disability Research*, *54*(9), 795-805. https://doi.org/10.1111/j.1365-2788.2010.01308.x

Makino, K., Lee, S., Bae, S., Chiba, I., Harada, K., Katayama, O., Shinkai, Y., Makizako, H., & Shimada, H. (2021). Diabetes and prediabetes inhibit reversion from mild cognitive impairment to normal cognition. *Journal of the American Medical Directors Association*, *22*(9), 1912-1918. e1912. https://doi.org/10.1016/j.jamda.2021.02.033

Maltese, G., McAuley, S. A., Trawley, S., & Sinclair, A. J. (2024). Ageing well with diabetes: The role of technology. *Diabetologia*, *67*(10), 2085-2102. https://doi.org/10.1007/s00125-024-06240-2

Man, J., Kangas, M., Trollor, J., & Sweller, N. (2017). Clinical competencies and training needs of psychologists working with adults with intellectual disability and comorbid mental ill health. *Clinical Psychologist*, *21*(3), 206-214. https://doi.org/10.1111/cp.12092

Manthey, J., Shield, K. D., Rylett, M., Hasan, O. S., Probst, C., & Rehm, J. (2019). Global alcohol exposure between 1990 and 2017 and forecasts until 2030: A modelling study. *The Lancet*, *393*(10190), 2493-2502. https://doi.org/10.1016/S0140-6736(18)32744-2

Marconi, V., Pizzolato, F., Donati, D., & Schena, F. (2018). Physical activity levels in people with intellectual disability attending daily centers. *Sport Sciences for Health*, *14*(2), 257-264. https://doi.org/10.1007/s11332-017-0414-1

Martin, F. C., & Romero Ortuño, R. (2019). Longitudinal studies of ageing: From insights to impacts: Commentary to accompany themed collection on longitudinal studies. *Age and Ageing*, *48*(4), 481-485. https://doi.org/10.1093/ageing/afz028

Martin, P., Kelly, N., Kahana, B., Kahana, E., Willcox, B. J., Willcox, D. C., & Poon, L. W. (2015). Defining successful aging: A tangible or elusive concept? *The Gerontologist*, *55*(1), 14-25. https://doi.org/10.1093/geront/gnu044

Matranga, D., Bono, F., & Maniscalco, L. (2021). Statistical advances in epidemiology and public health. *International Journal of Environmental Research and Public Health 18*(7). https://doi.org/10.3390/ijerph18073549

McCallion, P., & McCarron, M. (2004). Ageing and intellectual disabilities: A review of recent literature. *Current Opinion in Psychiatry*, *17*(5), 349-352. https://doi.org/10.1097/01.yco.0000139968.14695.95

McCarron, M. (2011). *Growing older with an intellectual disability in Ireland 2011: First results from the Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing (IDS-TILDA)*. School of Nursing and Midwifery, Trinity College Dublin. Retrieved 21/04/2021 from https://www.tcd.ie/tcaid/assets/pdf/idstildareport2011.pdf

McCarron, M., Haigh, M., McCallion, P., Carroll, R., Burke, E., McGlinchey, E., O'Donovan, M.A., McCausland, D., & Sheerin, F. (2017). *Health, wellbeing and social inclusion: Ageing with an intellectual disability in Ireland*. School of Nursing and Midwifery, Trinity College Dublin. Retrieved 21st April 2021 from https://www.tcd.ie/tcaid/assets/pdf/wave3report.pdf

McCarron, M., Haigh, M, Dann, G, McCallion, P. Eds. (2023). *Longitudinal dynamics in the ageing of people with an intellectual disability*. School of Nursing and Midwifery, Trinity College Dublin. Retrieved 11th May 2024 from https://www.tcd.ie/tcaid/assets/pdf/idstildawave5report.pdf

McCarron, M., McCallion, P., Reilly, E., Dunne, P., Carroll, R. & Mulryan, N. (2017). A prospective 20-year longitudinal follow-up of dementia in persons with Down syndrome. *Journal of Intellectual Disability Research*, *61*(9), 843-852. https://doi.org/10.1111/jir.12390

McCarron, M., McCausland, D., McGlinchey, E., Bowman, S., Foley, M., Haigh, M., Burke, E., & McCallion, P. (2022). Recruitment and retention in longitudinal studies of people with intellectual disability: A case study of the Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing (IDS-TILDA). *Research in Developmental Disabilities*, *124*, 104197. https://doi.org/10.1016/j.ridd.2022.104197

McCarron, M., Swinburne, J., Burke, E., McGlinchey, E., Carroll, R., & McCallion, P. (2013). Patterns of multimorbidity in an older population of persons with an intellectual disability: Results from the Intellectual Disability Supplement to the Irish longitudinal Study on Aging (IDS-TILDA). *Research in Developmental Disabilities*, *34*, 521-527. https://doi.org/10.1016/j.ridd.2012.07.029

McCausland, D. (2016). *Social participation for older people with an intellectual disability in Ireland*. In M. McCarron, M. Haigh, P. McCallion, R. Carroll, E. Burke, E. McGlinchey, M.A. O'Donovan, D. McCausland, & F. Sheerin (Eds.), *Health, wellbeing and social inclusion: Ageing with an intellectual disability in Ireland*. School of Nursing and Midwifery (pp.30-61). Trinity College Dublin. Retrieved 21st April 2024 from https://www.tcd.ie/tcaid/assets/pdf/wave3report.pdf

McCausland, D., Haigh, M., McCallion, P., & McCarron, M. (2024). IRB challenges in multisite studies: A case report and commentary from the Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing (IDS-TILDA). *HRB Open Research*, *7*(3). https://doi.org/10.12688/hrbopenres.13854.1

McCausland, D., McCallion, P., Brennan, D., & McCarron, M. (2018). Interpersonal relationships of older adults with an intellectual disability in Ireland. *Journal of Applied Research in Intellectual Disabilities*, *31*(1), e140-e153. https://doi.org/10.1111/jar.12352

McCausland, D., McCallion, P., Carroll, R., & McCarron, M. (2021). The nature and quality of friendship for older adults with an intellectual disability in Ireland. *Journal of Applied Research in Intellectual Disabilities*, *34*(3), 763-776. https://doi.org/10.1111/jar.12851

McConkey, R., Bunting, B., Keogh, F., & Garcia Iriarte, E. (2019). The impact on social relationships of moving from congregated settings to personalized accommodation. *Journal of Intellectual Disabilities*, *23*(2), 149-159. https://doi.org/10.1177/1744629517716546

McConkey, R., Keogh, F., Bunting, B., Garcia Iriarte, E., & Watson, S. F. (2016). Relocating people with intellectual disability to new accommodation and support settings: Contrasts between personalized arrangements and group home placements. *Journal of Intellectual Disabilities*, *20*(2), 109-120. https://doi.org/10.1177/1744629515624639

McCrory, C., Finucane, C., O'Hare, C., Frewen, J., Nolan, H., Layte, R., Kearney, P. M., & Kenny, R. A. (2016). Social disadvantage and social isolation are associated with a higher resting heart rate: Evidence from the Irish longitudinal study on ageing. *Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, *71*(3), 463-473. https://doi.org/10.1093/geronb/gbu163

McGillicuddy, N. B. (2006). A review of substance use research among those with mental retardation. *Mental Rtardation and Developmental Disabilities Research Reviews*, *12*(1), 41-47. https://doi.org/10.1002/mrdd.20092

McGlinchey, E., McCallion, P., & McCarron, M. (2020). Down syndrome and dementia: Advances in the field. *Current Opinion in Psychiatry*, *33*(3), 278-283. https://doi.org/10.1097/YCO.0000000000000589

McGlinchey, E., McCarron, M., Holland, A., & McCallion, P. (2019). Examining the effects of computerised cognitive training on levels of executive function in adults with Down syndrome. *Journal of Intellectual Disability Research*, *63*(9), 1137-1150. https://doi.org/10.1111/jir.12626

McKee, A. M., & Morley, J. E. (2021). Obesity in the elderly. In A. S. Feingold & B. Anawalt (Eds.), *Endotext*. South Dartmouth.

McKee, S. A., & Weinberger, A. H. (2013). How can we use our knowledge of alcohol-tobacco interactions to reduce alcohol use? *Annual Review of Clinical Psychology*, *9*(1), 649-674. https://doi.org/10.1146/annurev-clinpsy-050212-185549

McLeod, S. (2023). *What does effect size tell you?* Retrieved 07th October 2024 from https://www.simplypsychology.org/effect-size.html#:~:text=According%20to%20Cohen%20%281988%2C%201992%29%2C%20the%20effect%20size,and%20large%20if%20r%20varies%20more%20than%200.5.

McVea, A., DiFilippo, A., McLachlan, M., Betcher, B., Zammit, M., Betthauser, T. J., Converse, A., Murali, D., Stone, C., & Hartley, S. (2025). PET-measured amyloid beta accumulates at an accelerated rate in Down syndrome compared to neurotypical populations. *Alzheimer's & Dementia*, *21*(6), e70357. https://doi.org/10.1002/alz.70357

McVilly, K., McGillivray, J., Curtis, A., Lehmann, J., Morrish, L., & Speight, J. (2014). Diabetes in people with an intellectual disability: A systematic review of prevalence, incidence and impact. *Diabetic Medicine*, *31*(8), 897-904. https://doi.org/10.1111/dme.12494

Mehta, H., & Glover, G. (2019). *Psychotropic drugs and people with learning disabilities or autism*. Public Health England. Retrieved 18th March 2024 from https://www.gov.uk/government/publications/psychotropic-drugs-and-people-with-learning-disabilities-or-autism

Mela, V., Mota, B. C., Milner, M., McGinley, A., Mills, K. H., Kelly, Á. M., & Lynch, M. A. (2020). Exercise-induced re-programming of age-related metabolic changes in microglia is accompanied by a reduction in senescent cells. *Brain, Behavior, and Immunity*, *87*, 413-428. https://doi.org/10.1016/j.bbi.2020.01.012

Melbøe, L., & Hardonk, S. (2022). Expanding opportunities for work and citizenship: Participation of people with intellectual disabilities in voluntary work. *Scandinavian Journal of Disability Research*, *24*(1). https://doi.org/10.16993/sjdr.837

Melville, C. A., Cooper, S. A., Morrison, J., Allan, L., Smiley, E., & Williamson, A. (2007). The prevalence and determinants of obesity in adults with intellectual disabilities. *Obesity Reviews*, *8*(3), 223-230. https://doi.org/10.1111/j.1467-789X.2006.00296.x

Mendonca, G. V., Pereira, F. D., & Fernhall, B. (2010). Reduced exercise capacity in persons with Down syndrome: Cause, effect, and management. *Therapeutics and Clinical Risk Management*, *6*, 601-610. https://doi.org/10.2147/TCRM.S10235

Meuwese-Jongejeugd, A., Vink, M., van Zanten, B., Verschuure, H., Eichhorn, E., Koopman, D., Bernsen, R., & Evenhuis, H. (2006). Prevalence of hearing loss in 1598 adults with an intellectual disability: Cross-sectional population based study. *International Journal of Audiology*, *45*(11), 660-669. https://doi.org/10.1080/14992020600920812

Mewton, L., Visontay, R., Hoy, N., Lipnicki, D. M., Sunderland, M., Lipton, R. B., Guerchet, M., Ritchie, K., Najar, J., & Scarmeas, N. (2023). The relationship between alcohol use and dementia in adults aged more than 60 years: A combined analysis of prospective, individual-participant data from 15 international studies. *Addiction*, *118*(3), 412-424. https://doi.org/10.1111/add.16035

Mihaila, I., Handen, B. L., Christian, B. T., Lao, P. J., Cody, K. A., Klunk, W. E., Tudorascu, D. L., Cohen, A. D., Okonkwo, O. C., & Hartley, S. L. (2019). Leisure activity, brain β-amyloid, and episodic memory in adults with Down syndrome. *Developmental Neurobiology*, *79*(7), 738-749. https://doi.org/10.1002/dneu.22677

Miller, A. H., & Raison, C. L. (2016). The role of inflammation in depression: From evolutionary imperative to modern treatment target. *Nature Reviews Immunology*, *16*(1), 22-34. https://doi.org/10.1038/nri.2015.5

Mills, K. T., Stefanescu, A., & He, J. (2020). The global epidemiology of hypertension. *Nature Reviews Nephrology*, *16*(4), 223-237. https://doi.org/10.1038/s41581-019-0244-2

Mongan, D., Millar, S. R., & Galvin, B. (2021). *The 2019-20 Irish National Drug and Alcohol Survey: Main findings.* Health Research Board. Retrieved 24th September 2024 from https://www.drugsandalcohol.ie/34287

Montross, L. P., Depp, C., Daly, J., Reichstadt, J., Golshan, S., Moore, D., Sitzer, D., & Jeste, D. V. (2006). Correlates of self-rated successful aging among community-dwelling older adults. *The American Journal of Geriatric Psychiatry*, *14*(1), 43-51. https://doi.org/10.1097/01.JGP.0000192489.43179.31

Moreau, M., Benhaddou, S., Dard, R., Tolu, S., Hamzé, R., Vialard, F., Movassat, J., & Janel, N. (2021). Metabolic diseases and Down syndrome: How are they linked together? *Biomedicines*, *9*(2), 221. https://doi.org/10.3390/biomedicines9020221

Moreno-Agostino, D., Wu, Y.-T., Daskalopoulou, C., Hasan, M. T., Huisman, M., & Prina, M. (2021). Global trends in the prevalence and incidence of depression: A systematic review and meta-analysis. *Journal of Affective Disorders*, *281*, 235-243. https://doi.org/10.1016/j.jad.2020.12.035

Mosconi, L. (2020). *The XX brain: The groundbreaking science empowering women to maximize cognitive health and prevent Alzheimer's disease*. Avery.

Mossello, E., Boncinelli, M., Caleri, V., Cavallini, M. C., Palermo, E., Di Bari, M., Tilli, S., Sarcone, E., Simoni, D., & Biagini, C. A. (2008). Is antidepressant treatment associated with reduced cognitive decline in Alzheimer's disease? *Dementia and Geriatric Cognitive Disorders*, *25*(4), 372-379. https://doi.org/10.1159/000121334

Muller, P., & Woods, L. (2022). Multiple imputation to minimise bias from missing stage information in estimates of early cancer diagnosis in England: A population-based study. *Cancer Epidemiology*, *79*, 102198. https://doi.org/10.1016/j.canep.2022.102198

Mungas, D., Fletcher, E., Gavett, B. E., Widaman, K., Zahodne, L. B., Hohman, T. J., Mayeda, E. R., Dowling, N. M., Johnson, D. K., & Farias, S. T. (2021). Comparison of education and episodic memory as modifiers of brain atrophy effects on cognitive decline: Implications for measuring cognitive reserve. *Journal of the International Neuropsychological Society*, *27*(5), 401-411. https://doi.org/10.1017/S1355617720001095

Mungas, D., Gavett, B., Fletcher, E., Farias, S. T., DeCarli, C., & Reed, B. (2018). Education amplifies brain atrophy effect on cognitive decline: Implications for cognitive reserve. *Neurobiology of Aging*, *68*, 142-150. https://doi.org/10.1016/j.neurobiolaging.2018.04.002

Murata, C., Saito, T., Tsuji, T., Saito, M., & Kondo, K. (2017). A 10-year follow-up study of social ties and functional health among the old: The AGES project. *International Journal of Environmental Research and Public Health*, *14*(7), 717. https://doi.org/10.3390/ijerph14070717

Murphy, K., & Bantry-White, E. (2021). Behind closed doors: Human rights in residential care for people with an intellectual disability in Ireland. *Disability & Society*, *36*(5), 750-771. https://doi.org/10.1080/09687599.2020.1768052

Nagdee, M. (2011). Dementia in intellectual disability: A review of diagnostic challenges. *African Journal of Psychiatry*, *14*(3), 194-199. https://doi.org/http://dx.doi.org/10.4314/ajpsy.v14i3.1

Naik, S., Banerjee, A., Bapi, R. S., Deco, G., & Roy, D. (2017). Metastability in senescence. *Trends in Cognitive Sciences*, *21*(7), 509-521. https://doi.org/10.1016/j.tics.2017.04.007

National Academies of Sciences, (2020). *Social isolation and loneliness in older adults: Opportunities for the health care system*. National Academies Press.

National Health Service. (2019). *Learning disability Mortality Review (LeDeR) programme: Action from learning*. National Health Services. Retrieved 28th February 2021 from https://www.england.nhs.uk/wp-content/uploads/2019/05/action-from-learning.pdf

National Institute on Alcohol Abuse and Alcoholism (NIAAA). (2021). *Alcohol's effects on health*. NIAAA. Retrieved 23rd September 2024 from https://www.niaaa.nih.gov/publications/brochures-and-fact-sheets/alcohol-use-disorder-comparison-between-dsm

Neale, N., Padilla, C., Fonseca, L. M., Holland, T., & Zaman, S. (2018). Neuroimaging and other modalities to assess Alzheimer's disease in Down syndrome. *NeuroImage: Clinical*, *17*, 263-271. https://doi.org/10.1016/j.nicl.2017.10.022

Nelson, M. E., Jester, D. J., Petkus, A. J., & Andel, R. (2021). Cognitive reserve, Alzheimer's neuropathology, and risk of dementia: A systematic review and meta-analysis. *Neuropsychology Review*, *31*(2), 233-250. https://doi.org/10.1007/s11065-021-09478-4

Newall, N. E., & Menec, V. H. (2019). Loneliness and social isolation of older adults: Why it is important to examine these social aspects together. *Journal of Social and Personal Relationships*, *36*(3), 925-939. https://doi.org/10.1177/0265407517749045

Ngandu, T., Lehtisalo, J., Solomon, A., Levälahti, E., Ahtiluoto, S., Antikainen, R., Bäckman, L., Hänninen, T., Jula, A., & Laatikainen, T. (2015). A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): A randomised controlled trial. *The Lancet*, *385*(9984), 2255-2263. https://doi.org/10.1016/S0140-6736(15)60461-5

Nguyen, H., Chua, K.-C., Dregan, A., Vitoratou, S., Bayes-Marin, I., Olaya, B., & Prina, A. M. (2020). Factors associated with multimorbidity patterns in older adults in England: Findings from the English Longitudinal Study of Aging (ELSA). *Journal of Aging and Health*, *32*(9), 1120-1132. https://doi.org/10.1177/0898264319891026

NHS Digital. (2021). *Health and Care of People with Learning Disabilities, Experimental Statistics: 2020 to 2021*. National Health Service, UK. Retrieved 21st October 2023 from https://digital.nhs.uk/data-and-information/publications/statistical/health-and-care-of-people-with-learning-disabilities/experimental-statistics-2020-to-2021

Nianogo, R. A., Rosenwohl-Mack, A., Yaffe, K., Carrasco, A., Hoffmann, C. M., & Barnes, D. E. (2022). Risk factors associated with Alzheimer disease and related dementias by sex and race and ethnicity in the US. *JAMA Neurology*, *79*(6), 584-591. https://doi.org/10.1001/jamaneurol.2022.0976

Norton, S., Matthews, F. E., Barnes, D. E., Yaffe, K., & Brayne, C. (2014). Potential for primary prevention of Alzheimer's disease: An analysis of population-based data. *The Lancet Neurology*, *13*(8), 788-794. https://doi.org/10.1016/S1474-4422(14)70136-X

O'Brien, J. (1992). Developing high quality services for people with developmental disabilities. In V. J. Bradley & H. A. Bersani (Eds.), *Quality assurance for individuals with developmental disabilities* (pp. 17-31). Paul H. Brookes.

O'Donovan, M., Demetriou, E., Whittle, E., Duke, Z., Aitken, T., & Guastella, A. (2021). *Home and living options for people with disabilities: A systematic review and environmental scan of strategies to support transition from group homes and congregate care, and those which prevent movement to congregate settings.* Sydney: Centre for Disability Studies/The University of Sydney. Retrieved 26th September 2024 from https://individualisedliving.com.au/wp-content/uploads/sites/3/2022/01/ndia_report_final_28june2021-cover-and-disclaimer.pdf

O'Dwyer, M., Peklar, J., Mulryan, N., McCallion, P., McCarron, M., & Henman, M. C. (2017). Prevalence, patterns and factors associated with psychotropic use in older adults with intellectual disabilities in Ireland. *Journal of Intellectual Disability Research*, *61*(10), 969-983. https://doi.org/10.1111/jir.12391

Oke, J., Akinkunmi, W., & Etebefia, S. (2019). Use of correlation, tolerance and variance inflation factor for multicollinearity test. *Global Scientific Journals*, *7*(5), 652-659.

Okely, J. A., Akeroyd, M. A., Allerhand, M., Starr, J. M., & Deary, I. J. (2019). Longitudinal associations between hearing loss and general cognitive ability: The Lothian Birth Cohort 1936. *Psychology and Aging*, *34*(6), 766-779. https://doi.org/10.1037/pag0000385

Olshansky, S. J., Perry, D., Miller, R. A., & Butler, R. N. (2007). Pursuing the longevity dividend: Scientific goals for an aging world. *Annals of the New York Academy of Sciences*, *1114*(1), 11-13. https://doi.org/10.1196/annals.1396.050

Olson, A., Leko, M. M., & Roberts, C. A. (2016). Providing students with severe disabilities access to the general education curriculum. *Research and Practice for Persons with Severe Disabilities*, *41*(3), 143-157. https://doi.org/10.1177/1540796916651975

Oppewal, A., & Hilgenkamp, T. I. (2019). Physical fitness is predictive for 5-year survival in older adults with intellectual disabilities. *Journal of Applied Research in Intellectual Disabilities*, *32*(4), 958-966. https://doi.org/10.1111/jar.12589

Oreskovic, N. M., Cottrell, C., Torres, A., Patsiogiannis, V., Santoro, S., Nichols, D., Moore, C., & Skotko, B. G. (2020). Physical activity patterns in adults with Down syndrome. *Journal of Applied Research in Intellectual Disabilities*, *33*(6), 1457-1464. https://doi.org/10.1111/jar.12773

Ozyigit, A. (2021). The impact of years of schooling on dementia: Panel data evidence from Europe. *Universal Journal of Public Health*, *9*(1), 18-25. https://doi.org/.13189/ujph.2021.090102

Pal, K., Mukadam, N., Petersen, I., & Cooper, C. (2018). Mild cognitive impairment and progression to dementia in people with diabetes, prediabetes and metabolic syndrome: A systematic review and meta-analysis. *Social Psychiatry and Psychiatric Epidemiology*, *53*(11), 1149-1160. https://doi.org/10.1007/s00127-018-1581-3

Pallant, J. (2020). *SPSS survival manual: A step by step guide to data analysis using IBM SPSS* (7th ed.). Routledge. https://doi.org/10.4324/9781003117452

Pape, S. E., Baksh, R. A., Startin, C., Hamburg, S., Hithersay, R., & Strydom, A. (2021). The association between physical activity and CAMDEX-DS changes prior to the onset of Alzheimer's disease in Down Syndrome. *Journal of Clinical Medicine*, *10*(9), 1882. https://doi.org/10.3390/jcm10091882

Parra, P., Costa, R., de Asúa, D. R., Moldenhauer, F., & Suárez, C. (2017). Atherosclerotic surrogate markers in adults with Down syndrome: A case-control study. *The Journal of Clinical Hypertension*, *19*(2), 205-211. https://doi.org/10.1111/jch.12890

Parrini, M., Ghezzi, D., Deidda, G., Medrihan, L., Castroflorio, E., Alberti, M., Baldelli, P., Cancedda, L., & Contestabile, A. (2017). Aerobic exercise and a BDNF-mimetic therapy rescue learning and memory in a mouse model of Down syndrome. *Scientific Reports*, *7*(1), 16825. https://doi.org/10.1038/s41598-017-17201-8

Patel, V., Saxena, S., Lund, C., Thornicroft, G., Baingana, F., Bolton, P., Chisholm, D., Collins, P. Y., Cooper, J. L., & Eaton, J. (2018). The Lancet Commission on global mental health and sustainable development. *The Lancet*, *392*(10157), 1553-1598. https://doi.org/1016/S0140-6736(18)31612-X

Peel, N. M., McClure, R. J., & Bartlett, H. P. (2005). Behavioral determinants of healthy aging. *American Journal of Preventive Medicine*, *28*(3), 298-304. https://doi.org/10.1016/j.amepre.2004.12.002

Peeters, G., Kenny, R. A., & Lawlor, B. (2020). Late life education and cognitive function in older adults. *International Journal of Geriatric Psychiatry*, *35*(6), 633-639. https://doi.org/10.1002/gps.5281

Penninkilampi, R., Casey, A.-N., Singh, M. F., & Brodaty, H. (2018). The association between social engagement, loneliness, and risk of dementia: A systematic review and meta-analysis. *Journal of Alzheimer's disease*, *66*(4), 1619-1633. https://doi.org/10.3233/JAD-180439

Petersen, R. C., Mormino, E., & Schneider, J. A. (2024). Alzheimer Disease—What's in a Name? *JAMA Neurology*, *81*(12), 1245-1246. https://doi.org/10.1001/jamaneurol.2024.3766

Petersen, R. C., Weintraub, S., Sabbagh, M., Karlawish, J., Adler, C. H., Dilworth-Anderson, P., Frank, L., Hummel, C. H., Taylor, A., & Initiative, D. N. (2023). A new framework for dementia nomenclature. *JAMA Neurology*, *80*(12), 1364-1370. https://doi.org/10.1001/jamaneurol.2023.3664

Peven, J. C., Handen, B. L., Laymon, C. M., Fleming, V., Piro-Gambetti, B., Christian, B. T., Klunk, W., Cohen, A. D., Okonkwo, O., & Hartley, S. L. (2022). Physical activity, memory function, and hippocampal volume in adults with Down syndrome. *Frontiers in Integrative Neuroscience*, *16*, 919711. https://doi.org/10.3389/fnint.2022.919711

Phelan, E. A., Anderson, L. A., Lacroix, A. Z., & Larson, E. B. (2004). Older adults' views of "successful aging"—How do they compare with researchers' definitions? *Journal of the American Geriatrics Society*, *52*(2), 211-216. https://doi.org/10.1111/j.1532-5415.2004.52056.x

Picciotti, P. M., Carfì, A., Anzivino, R., Paludetti, G., Conti, G., Brandi, V., Bernabei, R., & Onder, G. (2017). Audiologic assessment in adults with Down syndrome. *American Journal on Intellectual and Developmental Disabilities*, *122*(4), 333-341. https://doi.org/10.1352/1944-7558-122.4.333

Pinto, R. M., Witte, S. S., Wall, M. M., & Filippone, P. L. (2018). Recruiting and retaining service agencies and public health providers in longitudinal studies: Implications for community-engaged implementation research. *Methodological Innovations*, *11*(1), 2059799118770996. https://doi.org/10.1177/2059799118770996

Piro-Gambetti, B., Schworer, E. K., Handen, B., Glukhovskaya, M., & Hartley, S. L. (2024). Does employment complexity promote healthy cognitive aging in Down syndrome? *Journal of Intellectual Disabilities*, *28*(2), 499-513. https://doi.org/10.1177/17446295231169379

Ponroy Bally, B., & Murai, K. K. (2021). Astrocytes in Down syndrome across the lifespan. *Frontiers in Cellular Neuroscience*, *15*, 702685. https://doi.org/10.3389/fncel.2021.702685

Popa-Wagner, A., Buga, A.-M., Popescu, B., & Muresanu, D. (2015). Vascular cognitive impairment, dementia, aging and energy demand: A vicious cycle. *Journal of Neural Transmission*, *122*, 47-54. https://doi.org/10.1007/s00702-013-1129-3

Pounds, O., Theodore, K., & Dodd, K. (2025). Factors associated with Alzheimer's dementia diagnosis and survival in Down syndrome. *Journal of Intellectual Disability Research*, *69*(6), 489-501. https://doi.org/10.1111/jir.13230

Prakash, R. S., Voss, M. W., Erickson, K. I., & Kramer, A. F. (2015). Physical activity and cognitive vitality. *Annual Review of Psychology*, *66*(1), 769-797. https://doi.org/10.1146/annurev-psych-010814-015249

Pressman, S. D., Cohen, S., Miller, G. E., Barkin, A., Rabin, B. S., & Treanor, J. J. (2005). Loneliness, social network size, and immune response to influenza vaccination in college freshmen. *Health Psychology*, *24*(3), 297-306. https://doi.org/https://psycnet.apa.org/doi/10.1037/0278-6133.24.3.297

Probst, C., Kilian, C., Sanchez, S., Lange, S., & Rehm, J. (2020). The role of alcohol use and drinking patterns in socioeconomic inequalities in mortality: A systematic review. *The Lancet Public Health*, *5*(6), e324-e332. https://doi.org/10.1016/S2468-2667(20)30052-9

Pruchno, R. A., Wilson-Genderson, M., Rose, M., & Cartwright, F. (2010). Successful aging: Early influences and contemporary characteristics. *The Gerontologist*, *50*(6), 821-833. https://doi.org/10.1093/geront/gnq041

Ptomey, L. T., Szabo, A. N., Willis, E. A., Gorczyca, A. M., Greene, J. L., Danon, J. C., & Donnelly, J. E. (2018). Changes in cognitive function after a 12-week exercise intervention in adults with Down syndrome. *Disability and Health Journal*, *11*(3), 486-490. https://doi.org/10.1016/j.dhjo.2018.02.003

Qazvini, M. (2023). Survival analysis of longitudinal data: The case of English population aged 50 and over. *Journal of Demographic Economics*, *89*(3), 419-463. https://doi.org/10.1017/dem.2023.3

Qiu, C., & Fratiglioni, L. (2018). Aging without dementia is achievable: Current evidence from epidemiological research. *Journal of Alzheimer's disease*, *62*(3), 933-942. https://doi.org/10.3233/JAD-171037

Rafii, M. S., & Fortea, J. (2023). Down syndrome in a new era for Alzheimer disease. *Journal of the American Medical Association*, *330*(22), 2157-2158. https://doi.org/10.1001/jama.2023.22924

Rafnsson, S. B., Orrell, M., D'Orsi, E., Hogervorst, E., & Steptoe, A. (2020). Loneliness, social integration, and incident dementia over 6 years: Prospective findings from the English Longitudinal Study of Ageing. *The Journals of Gerontology: Series B*, *75*(1), 114-124. https://doi.org/10.1093/geronb/gbx087

Ranganathan, P., Pramesh, C., & Aggarwal, R. (2017). Common pitfalls in statistical analysis: Logistic regression. *Perspectives in Clinical Research*, *8*(3), 148-151. https://doi.org/10.4103/picr.PICR_87_17

Raymo, C., & Richardson, W. (1998). Science and Religion: Skeptics and true believers. The exhilarating connection between science and religion. *Science-AAAS-Weekly Paper Edition*, *281*(5385), 1969-1969.

Rehm, J., Hasan, O. S., Black, S. E., Shield, K. D., & Schwarzinger, M. (2019). Alcohol use and dementia: A systematic scoping review. *Alzheimer's Research & Therapy*, *11*(1), 1-11. https://doi.org/10.1186/s13195-018-0453-0

Reinhardt, G. Y., Vidovic, D., & Hammerton, C. (2021). Understanding loneliness: A systematic review of the impact of social prescribing initiatives on loneliness. *Perspectives in Public Health*, *141*(4), 204-213. https://doi.org/10.1177/1757913920967040

Ribenfors, F., Blood, L., Hatton, C., & Marriott, A. (2025). 'It's got its ups and downs': What people with intellectual disabilities living in supported living and residential care like and dislike about their home. *Journal of Applied Research in Intellectual Disabilities*, *38*(1), e13313. https://doi.org/10.1111/jar.13313

Richardson, S., Karunananthan, S., & Bergman, H. (2011). I may be frail but I ain't no failure. *Canadian Geriatrics Journal*, *14*(1), 24-28. https://doi.org/10.5770/cgj.v14i1.4

Ringenbach, S., Holzapfel, S., Mulvey, G., Jimenez, A., Benson, A., & Richter, M. (2016). The effects of assisted cycling therapy (ACT) and voluntary cycling on reaction time and measures of executive function in adolescents with Down syndrome. *Journal of Intellectual Disability Research*, *60*(11), 1073-1085. https://doi.org/10.1111/jir.12275

Ringenbach, S. D., Chen, C., Albert, A., Lichtsinn, K., & Alberts, J. L. (2013). Assisted cycle therapy (ACT): Implications for improvements in motor control. In M. Leitner & M. Fuchs (Eds.), *Motor behavior and control: New research* (pp. 103-114). Nova Science Publishers Inc.

Ringenbach, S. D., Holzapfel, S., Mulvey, G. M., & Pandya, S. (2015). Assisted cycling therapy for persons with Down syndrome—Implications for improvements in cognitive functioning. In S. Dey (Ed.), *Health problems in Down syndrome* (pp. 71-84). InTech. https://doi.org/10.5772/60636

Robertson, J., Emerson, E., Baines, S., & Hatton, C. (2020). Self-reported smoking, alcohol and drug use among adolescents and young adults with and without mild to moderate intellectual disability. *Journal of Intellectual & Developmental Disability*, *45*(1), 35-45. https://doi.org/10.3109/13668250.2018.1440773

Rodrigues, A. N., Coelho, L. C., Goncalves, W. L., Gouvea, S. A., Vasconcellos, M. J. R., Cunha, R. S., & Abreu, G. R. (2011). Stiffness of the large arteries in individuals with and without Down syndrome. *Vascular Health and Risk Management*, *7*, 375-381. https://doi.org/10.2147/VHRM.S21273

Roebuck, M. (2021). Housing for people with intellectual disabilities: A scoping review. *Journal on Developmental Disabilities*, *26*(2), 1-23.

Rowe, J. W., & Kahn, R. L. (1997). Successful aging. *The Gerontologist*, *37*(4), 433-440. https://doi.org/10.1093/geront/37.4.433

Roy-Vallejo, E., Alonso, E., Galvan-Roman, J., Ibanez, P., Moldenhauer, F., Fernández, C. S., & de Asúa, D. R. (2020). Hemodynamic profile of Spanish adults with Down syndrome. *Revista Clínica Española (English Edition)*, *220*(5), 275-281. https://doi.org/10.1016/j.rceng.2019.09.005

Roy-Vallejo, E., Galván-Román, J. M., Moldenhauer, F., & Real de Asua, D. (2020). Adults with Down syndrome challenge another paradigm: When aging no longer entails arterial hypertension. *The Journal of Clinical Hypertension*, *22*(7), 1127-1133. https://doi.org/10.1111/jch.13930

Ruze, R., Liu, T., Zou, X., Song, J., Chen, Y., Xu, R., Yin, X., & Xu, Q. (2023). Obesity and type 2 diabetes mellitus: Connections in epidemiology, pathogenesis, and treatments. *Frontiers in Endocrinology*, *14*, 1161521. https://doi.org/10.3389/fendo.2023.1161521

Ryan, J. (2017). Ageing and intellectual disability: Editorial. *Frontline*, *105*, 1.

Sabia, S., Fayosse, A., Dumurgier, J., Schnitzler, A., Empana, J.-P., Ebmeier, K. P., Dugravot, A., Kivimäki, M., & Singh-Manoux, A. (2019). Association of ideal cardiovascular health at age 50 with incidence of dementia: 25 year follow-up of Whitehall II cohort study. *British Medical Journal*, *366*, l4414. https://doi.org/10.1136/bmj.l4414

Sachdev, P. S., Blacker, D., Blazer, D. G., Ganguli, M., Jeste, D. V., Paulsen, J. S., & Petersen, R. C. (2014). Classifying neurocognitive disorders: The DSM-5 approach. *Nature Reviews Neurology*, *10*(11), 634-642. https://doi.org/10.1038/nrneurol.2014.181

Saini, F., Dell'Acqua, F., & Strydom, A. (2022). Structural connectivity in Down syndrome and Alzheimer's disease. *Frontiers in Neuroscience*, *16*, 908413. https://doi.org/10.3389/fnins.2022.908413

Salinas, J., Beiser, A., Himali, J. J., Satizabal, C. L., Aparicio, H. J., Weinstein, G., Mateen, F. J., Berkman, L. F., Rosand, J., & Seshadri, S. (2017). Associations between social relationship measures, serum brain-derived neurotrophic factor, and risk of stroke and dementia. *Alzheimer's & Dementia: Translational Research & Clinical Interventions*, *3*(2), 229-237. https://doi.org/10.1016/j.trci.2017.03.001

Salse-Batán, J., Sanchez-Lastra, M., Suárez-Iglesias, D., & Pérez, C. A. (2022). Effects of exercise training on obesity-related parameters in people with intellectual disabilities: Systematic review and meta-analysis. *Journal of Intellectual Disability Research*, *66*(5), 413-441. https://doi.org/10.1111/jir.12928

Santabárbara, J., Bueno-Notivol, J., Lipnicki, D. M., de la Cámara, C., López-Antón, R., Lobo, A., & Gracia-García, P. (2021). A novel score for predicting Alzheimer's disease risk from late life psychopathological and health risk factors. *International Journal of Environmental Research and Public Health*, *18*(4), 1802. https://doi.org/10.3390/ijerph18041802

Santos, F., Zurek, J., & Janicki, M. (2021). Are persons with intellectual and developmental disabilities being embraced in healthy aging interventions? *Innovation in Aging*, *5*(Suppl 1), 224. https://doi.org/10.1093/geroni/igab046.868

Scheirs, J. G. M., Muller, A., Manders, N. C. P., & van der Zanden, C. D. (2022). The prevalence and diagnosis of depression in people with mild or borderline intellectual disability: Multiple instrument testing tells us more. *Journal of Mental Health Research in Intellectual Disabilities*, *16*(1), 54-66. https://doi.org/10.1080/19315864.2022.2029642

Schupf, N., Lee, J. H., Pang, D., Zigman, W. B., Tycko, B., Krinsky-McHale, S., & Silverman, W. (2018). Epidemiology of estrogen and dementia in women with Down syndrome. *Free Radical Biology and Medicine*, *114*, 62-68. https://doi.org/10.1016/j.freeradbiomed.2017.08.019

Schupf, N., Zigman, W., Kapell, D., Lee, J., Kline, J., & Levin, B. (1997). Early menopause in women with Down's syndrome. *Journal of Intellectual Disability Research*, *41*(3), 264-267. https://doi.org/10.1046/j.1365-2788.1997.03838.x

Selkoe, D. J. (1991). Amyloid protein and Alzheimer's disease. *Scientific American*, *265*(5), 68-79. https://doi.org/https://www.jstor.org/stable/24938799

Sheerin, F., Fleming, S., Burke, E., Byrne, K., Cleary, M., Doyle, C., & Keenan, P. (2022). Exploring mental health issues in people with an intellectual disability. *Learning Disability Practice*, *25*(4). https://doi.org/10.7748/ldp.2019.e1999

Shen, C., Rolls, E. T., Cheng, W., Kang, J., Dong, G., Xie, C., Zhao, X.-M., Sahakian, B. J., & Feng, J. (2022). Associations of social isolation and loneliness with later dementia. *Neurology*, *99*(2), e164-e175. https://doi.org/10.1212/WNL.0000000000200583

Shen, C., Zhang, R., Yu, J., Sahakian, B. J., Cheng, W., & Feng, J. (2025). Plasma proteomic signatures of social isolation and loneliness associated with morbidity and mortality. *Nature Human Behaviour*, *9*, 569-583. https://doi.org/10.1038/s41562-024-02078-1

Shield, K., Manthey, J., Rylett, M., Probst, C., Wettlaufer, A., Parry, C. D., & Rehm, J. (2020). National, regional, and global burdens of disease from 2000 to 2016 attributable to alcohol use: A comparative risk assessment study. *The Lancet Public Health*, *5*(1), e51-e61. https://doi.org/10.1016/S2468-2667(19)30231-2

Shrestha, N. (2020). Detecting multicollinearity in regression analysis. *American Journal of Applied Mathematics and Statistics*, *8*(2), 39-42. https://doi.org/10.12691/ajams-8-2-1

Siddaway, A. P., Wood, A. M., & Hedges, L. V. (2019). How to do a systematic review: A best practice guide for conducting and reporting narrative reviews, meta-analyses, and meta-syntheses. *Annual Review of Psychology*, *70*(1), 747-770. https://doi.org/10.1146/annurev-psych-010418-102803

Silveira, E. A., Mendonça, C. R., Delpino, F. M., Souza, G. V. E., de Souza Rosa, L. P., de Oliveira, C., & Noll, M. (2022). Sedentary behavior, physical inactivity, abdominal obesity and obesity in adults and older adults: A systematic review and meta-analysis. *Clinical Nutrition ESPEN*, *50*, 63-73. https://doi.org/10.1016/j.clnesp.2022.06.001

Simplican, S. C., Leader, G., Kosciulek, J., & Leahy, M. (2015). Defining social inclusion of people with intellectual and developmental disabilities: An ecological model of social networks and community participation. *Research in Developmental Disabilities*, *38*, 18-29. https://doi.org/10.1016/j.ridd.2014.10.008

Sims, J. R., Zimmer, J. A., Evans, C. D., Lu, M., Ardayfio, P., Sparks, J., Wessels, A. M., Shcherbinin, S., Wang, H., & Nery, E. S. M. (2023). Donanemab in early symptomatic Alzheimer disease: The TRAILBLAZER-ALZ 2 randomized clinical trial. *Journal of the American Medical Association*, *330*(6), 512-527. https://doi.org/10.1001/jama.2023.13239

Skudlik, S., Hirt, J., Döringer, T., Thalhammer, R., Lüftl, K., Prodinger, B., & Müller, M. (2023). Challenges and care strategies associated with the admission to nursing homes in Germany: A scoping review. *BMC Nursing*, *22*(1), 5. https://doi.org/10.1186/s12912-022-01139-y

Snyder, H. M., Bain, L. J., Brickman, A. M., Carrillo, M. C., Esbensen, A. J., Espinosa, J. M., Fernandez, F., Fortea, J., Hartley, S. L., & Head, E. (2020). Further understanding the connection between Alzheimer's disease and Down syndrome. *Alzheimer's & Dementia*, *16*(7), 1065-1077. https://doi.org/10.1002/alz.12112

Sommerlad, A., Kivimäki, M., Larson, E. B., Röhr, S., Shirai, K., Singh-Manoux, A., & Livingston, G. (2023). Social participation and risk of developing dementia. *Nature Aging*, *3*(5), 532-545. https://doi.org/10.1038/s43587-023-00387-0

Song, S., Stern, Y., & Gu, Y. (2022). Modifiable lifestyle factors and cognitive reserve: A systematic review of current evidence. *Ageing Research Reviews*, *74*, 101551. https://doi.org/10.1016/j.arr.2021.101551

Spector, A., & Orrell, M. (2010). Using a biopsychosocial model of dementia as a tool to guide clinical practice. *International Psychogeriatrics*, *22*(6), 957-965. https://doi.org/10.1017/S1041610210000840

Staff, R. T., Hogan, M. J., Williams, D. S., & Whalley, L. (2018). Intellectual engagement and cognitive ability in later life (the “use it or lose it” conjecture): Longitudinal, prospective study. *British Medical Journal*, *363*, k4925. https://doi.org/10.1136/bmj.k4925

Stanley, T. D., Carter, E. C., & Doucouliagos, H. (2018). What meta-analyses reveal about the replicability of psychological research. *Psychological Bulletin*, *144*(12), 1325-1346. https://doi.org/http://dx.doi.org.elib.tcd.ie/10.1037/bul0000169

Startin, C. M., D’Souza, H., Ball, G., Hamburg, S., Hithersay, R., Hughes, K. M., Massand, E., Karmiloff-Smith, A., & Thomas, M. S. (2020). Health comorbidities and cognitive abilities across the lifespan in Down syndrome. *Journal of Neurodevelopmental Disorders*, *12*(4), 1-13. https://doi.org/10.1186/s11689-019-9306-9

Statistical Point. (2025). *The Durbin-Watson Test: Definition and Example*. Retrieved 7th February 2025 from https://statisticalpoint.com/durbin-watson-test/

Stephens, J. F. (2018). *United Nations speech*. Retrieved 24/09/2025 from https://speakola.com/ideas/john-franklin-stephens-united-nations-2018

Steptoe, A., Shankar, A., Demakakos, P., & Wardle, J. (2013). Social isolation, loneliness, and all-cause mortality in older men and women. *Proceedings of the National Academy of Sciences*, *110*(15), 5797-5801. https://doi.org/10.1073/pnas.1219686110

Stern, Y. (2012). Cognitive reserve in ageing and Alzheimer's disease. *The Lancet Neurology*, *11*(11), 1006-1012. https://doi.org/10.1016/S1474-4422(12)70191-6

Stern, Y. (2021). How can cognitive reserve promote cognitive and neurobehavioral health? *Archives of Clinical Neuropsychology*, *36*(7), 1291-1295. https://doi.org/10.1093/arclin/acab049

Stern, Y., Arenaza-Urquijo, E. M., Bartrés-Faz, D., Belleville, S., Cantilon, M., Chetelat, G., Ewers, M., Franzmeier, N., Kempermann, G., & Kremen, W. S. (2020). Whitepaper: Defining and investigating cognitive reserve, brain reserve, and brain maintenance. *Alzheimer's & Dementia*, *16*(9), 1305-1311. https://doi.org/10.1016/j.jalz.2018.07.219

Stern, Y., Barnes, C. A., Grady, C., Jones, R. N., & Raz, N. (2019). Brain reserve, cognitive reserve, compensation, and maintenance: Operationalization, validity, and mechanisms of cognitive resilience. *Neurobiology of Aging*, *83*, 124-129. https://doi.org/10.1016/j.neurobiolaging.2019.03.022

Sterne, J. A., White, I. R., Carlin, J. B., Spratt, M., Royston, P., Kenward, M. G., Wood, A. M., & Carpenter, J. R. (2009). Multiple imputation for missing data in epidemiological and clinical research: Potential and pitfalls. *British Medical Journal*, *338*, b2393. https://doi.org/10.1136/bmj.b2393

Steventon, J. J., Foster, C., Furby, H., Helme, D., Wise, R. G., & Murphy, K. (2020). Hippocampal blood flow is increased after 20 min of moderate-intensity exercise. *Cerebral Cortex*, *30*(2), 525-533. https://doi.org/10.1093/cercor/bhz104

Stillman, C. M., Cohen, J., Lehman, M. E., & Erickson, K. I. (2016). Mediators of physical activity on neurocognitive function: A review at multiple levels of analysis. *Frontiers in Human Neuroscience*, *10*, 626. https://doi.org/10.3389/fnhum.2016.00626

Stoltzner, S. E., Grenfell, T. J., Mori, C., Wisniewski, K. E., Wisniewski, T. M., Selkoe, D. J., & Lemere, C. A. (2000). Temporal accrual of complement proteins in amyloid plaques in Down's syndrome with Alzheimer's disease. *The American Journal of Pathology*, *156*(2), 489-499. https://doi.org/10.1016/S0002-9440(10)64753-0

Strawbridge, W. J., Wallhagen, M. I., & Cohen, R. D. (2002). Successful aging and well-being: Self-rated compared with Rowe and Kahn. *The Gerontologist*, *42*(6), 727-733. https://doi.org/https://psycnet.apa.org/doi/10.1093/geront/42.6.725

Sun, H., Saeedi, P., Karuranga, S., Pinkepank, M., Ogurtsova, K., Duncan, B. B., Stein, C., Basit, A., Chan, J. C., & Mbanya, J. C. (2022). IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Research and Clinical Practice*, *183*, 109119. https://doi.org/10.1016/j.diabres.2021.109119

Sutherland, M. T., Riedel, M. C., Flannery, J. S., Yanes, J. A., Fox, P. T., Stein, E. A., & Laird, A. R. (2016). Chronic cigarette smoking is linked with structural alterations in brain regions showing acute nicotinic drug-induced functional modulations. *Behavioral and Brain Functions*, *12*(16), 1-15. https://doi.org/10.1186/s12993-016-0100-5

Swan, G. E., & Lessov-Schlaggar, C. N. (2007). The effects of tobacco smoke and nicotine on cognition and the brain. *Neuropsychology Review*, *17*, 259-273. https://doi.org/10.1007/s11065-007-9035-9

Swerts, C., Vandevelde, S., VanDerNagel, J. E., Vanderplasschen, W., Claes, C., & De Maeyer, J. (2017). Substance use among individuals with intellectual disabilities living independently in Flanders. *Research in Developmental Disabilities*, *63*, 107-117. https://doi.org/10.1016/j.ridd.2016.03.019

Tabachnick, B. G., & Fidell, L. (2013). *Using multivariate statistics: Pearson new international edition* (Vol. 6). Pearson Boston, MA.

Taggart, L., Truesdale, M., Dunkley, A., House, A., & Russell, A. (2018). Health promotion and wellness initiatives targeting chronic disease prevention and management for adults with intellectual and developmental disabilities: Recent advancements in type 2 diabetes. *Current Developmental Disorders Reports*, *5*, 132-142. https://doi.org/10.1007/s40474-018-0142-5

Tari, A. R., Walker, T. L., Huuha, A. M., Sando, S. B., & Wisloff, U. (2025). Neuroprotective mechanisms of exercise and the importance of fitness for healthy brain ageing. *The Lancet*, *405*(10484), 1093-1118. https://doi.org/10.1016/S0140-6736(25)00184-9

Teague, S., Youssef, G. J., Macdonald, J. A., Sciberras, E., Shatte, A., Fuller-Tyszkiewicz, M., Greenwood, C., McIntosh, J., Olsson, C. A., & Hutchinson, D. (2018). Retention strategies in longitudinal cohort studies: A systematic review and meta-analysis. *BMC Medical Research Methodology*, *18*, 1-22. https://doi.org/10.1186/s12874-018-0586-7

Temple, V., Jozsvai, E., Konstantareas, M., & Hewitt, T. A. (2001). Alzheimer dementia in Down's syndrome: The relevance of cognitive ability. *Journal of Intellectual Disability Research*, *45*(1), 47-55. https://doi.org/10.1111/j.1365-2788.2001.00299.x

Teo, R. H., Cheng, W. H., Cheng, L. J., Lau, Y., & Lau, S. T. (2023). Global prevalence of social isolation among community-dwelling older adults: A systematic review and meta-analysis. *Archives of Gerontology and Geriatrics*, *107*, 104904. https://doi.org/10.1016/j.archger.2022.104904

Thom, R. P., Palumbo, M. L., Thompson, C., McDougle, C. J., & Ravichandran, C. T. (2021). Selective serotonin reuptake inhibitors for the treatment of depression in adults with Down syndrome: A preliminary retrospective chart review study. *Brain Sciences*, *11*(9), 1216-1216. https://doi.org/10.3390/brainsci11091216

Tomioka, K., Iwamoto, J., Saeki, K., & Okamoto, N. (2011). Reliability and validity of the International Physical Activity Questionnaire (IPAQ) in elderly adults: The Fujiwara-kyo Study. *Journal of Epidemiology*, *21*(6), 459-465. https://doi.org/10.2188/jea.JE20110003

Tomlinson, J., Medlinskiene, K., Cheong, V.-L., Khan, S., & Fylan, B. (2019). Patient and public involvement in designing and conducting doctoral research: The whys and the hows. *Research Involvement and Engagement*, *5*(23), 1-12. https://doi.org/10.1186/s40900-019-0155-1

Torr, J., Strydom, A., Patti, P., & Jokinen, N. (2010). Aging in Down syndrome: Morbidity and mortality. *Journal of Policy & Practice in Intellectual Disabilities*, *7*(1), 70-81. https://doi.org/10.1111/j.1741-1130.2010.00249.x

Tramutola, A., Lanzillotta, C., Di Domenico, F., Head, E., Butterfield, D. A., Perluigi, M., & Barone, E. (2020). Brain insulin resistance triggers early onset Alzheimer disease in Down syndrome. *Neurobiology of Disease*, *137*, 104772. https://doi.org/10.1016/j.nbd.2020.104772

Tsiouris, J. A., Patti, P. J., & Flory, M. J. (2014). Effects of antidepressants on longevity and dementia onset among adults with Down syndrome: A retrospective study. *The Journal of Clinical Psychiatry*, *75*(7), 5682. https://doi.org/10.4088/JCP.13m08562

Tsou, A. Y., Bulova, P., Capone, G., Chicoine, B., Gelaro, B., Harville, T. O., Martin, B. A., McGuire, D. E., McKelvey, K. D., Peterson, M., Tyler, C., Wells, M., & Whitten, M. S. (2020). Medical care of adults with Down syndrome. *Journal of the American Medical Association*, *324*(15), 1543. https://doi.org/10.1001/jama.2020.17024

Tudor-Locke, C., Craig, C. L., Aoyagi, Y., Bell, R. C., Croteau, K. A., De Bourdeaudhuij, I., Ewald, B., Gardner, A. W., Hatano, Y., & Lutes, L. D. (2011). How many steps/day are enough? For older adults and special populations. *International Journal of Behavioral Nutrition and Physical Activity*, *8*(80), 1-19. https://doi.org/10.1186/1479-5868-8-80

Tyrer, F., Ling, S., Bhaumik, S., Gangadharan, S., Khunti, K., Gray, L., & Dunkley, A. (2020). Diabetes in adults with intellectual disability: Prevalence and associated demographic, lifestyle, independence and health factors. *Journal of Intellectual Disability Research*, *64*(4), 287-295. https://doi.org/10.1111/jir.12718

Urv, T. K., Zigman, W. B., & Silverman, W. (2008). Maladaptive behaviors related to dementia status in adults with Down syndrome. *American Journal on Mental Retardation*, *113*(2), 73-86. https://doi.org/10.1352/0895-8017(2008)113[73:MBRTDS]2.0.CO;2

Valtorta, N. K., Kanaan, M., Gilbody, S., & Hanratty, B. (2016). Loneliness, social isolation and social relationships: What are we measuring? A novel framework for classifying and comparing tools. *British Medical Journal*, *6*(4), e010799. https://doi.org/10.1136/bmjopen-2015-010799

Valtorta, N. K., Kanaan, M., Gilbody, S., Ronzi, S., & Hanratty, B. (2016). Loneliness and social isolation as risk factors for coronary heart disease and stroke: Systematic review and meta-analysis of longitudinal observational studies. *Heart*, *102*(13), 1009-1016. https://doi.org/10.1136/heartjnl-2015-308790

van Asselt-Goverts, A. E., Embregts, P. J. C. M., & Hendriks, A. H. C. (2013). Structural and functional characteristics of the social networks of people with mild intellectual disabilities. *Research in Developmental Disabilities*, *34*(4), 1280-1288. https://doi.org/10.1016/j.ridd.2013.01.012

van Asselt-Goverts, A., Embregts, P., & Hendriks, A. (2015). Social networks of people with mild intellectual disabilities: Characteristics, satisfaction, wishes and quality of life. *Journal of Intellectual Disability Research*, *59*(5), 450-461. https://doi.org/10.1111/jir.12143

Van Dyck, C. H., Swanson, C. J., Aisen, P., Bateman, R. J., Chen, C., Gee, M., Kanekiyo, M., Li, D., Reyderman, L., & Cohen, S. (2023). Lecanemab in early Alzheimer's disease. *New England Journal of Medicine*, *388*(1), 9-21. https://doi.org/10.1056/NEJMoa2212948

Vecchio, L. M., Meng, Y., Xhima, K., Lipsman, N., Hamani, C., & Aubert, I. (2018). The neuroprotective effects of exercise: Maintaining a healthy brain throughout aging. *Brain Plasticity*, *4*(1), 17-52. https://doi.org/10.3233/BPL-180069

Veldsman, M., Tai, X.-Y., Nichols, T., Smith, S., Peixoto, J., Manohar, S., & Husain, M. (2020). Cerebrovascular risk factors impact frontoparietal network integrity and executive function in healthy ageing. *Nature Communications*, *11*(1), 4340. https://doi.org/10.1038/s41467-020-18201-5

Verdile, G., Fuller, S. J., & Martins, R. N. (2015). The role of type 2 diabetes in neurodegeneration. *Neurobiology of isDease*, *84*, 22-38. https://doi.org/10.1016/j.nbd.2015.04.008

Vernooij-Dassen, M., Moniz-Cook, E., Verhey, F., Chattat, R., Woods, B., Meiland, F., Franco, M., Holmerova, I., Orrell, M., & de Vugt, M. (2021). Bridging the divide between biomedical and psychosocial approaches in dementia research: The 2019 INTERDEM manifesto. *Aging & Mental Health*, *25*(2), 206-212. https://doi.org/10.1080/13607863.2019.1693968

Videla, L., Benejam, B., Barroeta, I., Fernandez, S., Altuna, M., Arranz, J., Rodríguez-Baz, Í., Arriola-Infante, J. E., Maure-Blesa, L., & del Hoyo Soriano, L. (2025). The Down Alzheimer Barcelona Neuroimaging Initiative (DABNI) and its contributions to understanding Alzheimer's disease in Down syndrome: A decade of discovery. *Alzheimer's & Dementia*, *21*(6), e70259. https://doi.org/10.1002/alz.70259

Videla, L., Benejam, B., Pegueroles, J., Carmona-Iragui, M., Padilla, C., Fernández, S., Barroeta, I., Altuna, M., Valldeneu, S., & Garzón, D. (2022). Longitudinal clinical and cognitive changes along the Alzheimer disease continuum in Down syndrome. *JAMA Network Open*, *5*(8), e2225573-e2225573. https://doi.org/https://doi:10.1001/jamanetworkopen.2022.25573

Villiers-Tuthill, A., Copley, A., McGee, H., & Morgan, K. (2016). The relationship of tobacco and alcohol use with ageing self-perceptions in older people in Ireland. *BMC Public Health*, *16*, 627. https://doi.org/10.1186/s12889-016-3158-y

Vu, M., Schleiden, L. J., Harlan, M. L., & Thorpe, C. T. (2020). Hypertension management in nursing homes: Review of evidence and considerations for care. *Current Hypertension Reports*, *22*, 1-14. https://doi.org/10.1007/s11906-019-1012-1

Walker, E., Ploubidis, G., & Fancourt, D. (2019). Social engagement and loneliness are differentially associated with neuro-immune markers in older age: Time-varying associations from the English Longitudinal Study of Ageing. *Brain, Behavior, and Immunity*, *82*, 224-229. https://doi.org/10.1016/j.bbi.2019.08.189

Walker, J., Dosen, A., Buitelaar, J., & Janzing, J. (2011). Depression in Down syndrome: A review of the literature. *Research in Developmental Disabilities*, *32*(5), 1432-1440. https://doi.org/10.1016/j.ridd.2011.02.010

Walker, K. A., Sharrett, A. R., Wu, A., Schneider, A. L., Albert, M., Lutsey, P. L., Bandeen-Roche, K., Coresh, J., Gross, A. L., & Windham, B. G. (2019). Association of midlife to late-life blood pressure patterns with incident dementia. *Journal of the American Medical Association*, *322*(6), 535-545. https://doi.org/10.1001/jama.2019.10575

Walton, C., & Kerr, M. (2016). Severe intellectual disability: Systematic review of the prevalence and nature of presentation of unipolar depression. *Journal of Applied Research in Intellectual Disabilities*, *29*(5), 395-408. https://doi.org/10.1111/jar.12203

Wang, F., Gao, Y., Han, Z., Yu, Y., Long, Z., Jiang, X., Wu, Y., Pei, B., Cao, Y., & Ye, J. (2023). A systematic review and meta-analysis of 90 cohort studies of social isolation, loneliness and mortality. *Nature Human Behaviour*, *7*(8), 1307-1319. https://doi.org/10.1038/s41562-023-01617-6

Wang, L., Leonards, C. O., Sterzer, P., & Ebinger, M. (2014). White matter lesions and depression: A systematic review and meta-analysis. *Journal of Psychiatric Research*, *56*, 56-64. https://doi.org/10.1016/j.jpsychires.2014.05.005

Wang, Y., Beydoun, M. A., Min, J., Xue, H., Kaminsky, L. A., & Cheskin, L. J. (2020). Has the prevalence of overweight, obesity and central obesity levelled off in the United States? Trends, patterns, disparities, and future projections for the obesity epidemic. *International Journal of Epidemiology*, *49*(3), 810-823. https://doi.org/10.1093/ije/dyz273

Ward, M., May, P., Normand, C., Kenny, R. A., & Nolan, A. (2021). Mortality risk associated with combinations of loneliness and social isolation. Findings from The Irish Longitudinal Study on Ageing (TILDA). *Age and Ageing*, *50*(4), 1329-1335. https://doi.org/10.1093/ageing/afab004

Wenzel, K. C., Van Puymbroeck, M., Lewis, S., McGuire, F., & Vidotto, J. (2024). Characteristics and cognition of older adults engaged in lifelong learning. *Educational Gerontology*, *50*(5), 423-442. https://doi.org/10.1080/03601277.2023.2299647

Werner, S., & Stawski, M. (2012). Mental health: Knowledge, attitudes and training of professionals on dual diagnosis of intellectual disability and psychiatric disorder. *Journal of Intellectual Disability Research*, *56*(3), 291-304. https://doi.org/10.1111/j.1365-2788.2011.01429.x

Westrop, S. C., Melville, C. A., Muirhead, F., & Mcgarty, A. M. (2019). Gender differences in physical activity and sedentary behaviour in adults with intellectual disabilities: A systematic review and meta-analysis. *Journal of Applied Research in Intellectual Disabilities*, *32*(6), 1359-1374. https://doi.org/10.1111/jar.12648

White, L. R., Boyle, P. A., Foster, T. C., Gazzaley, A. H., & Disterhoft, J. F. (2019). How do we validate approaches that aim to harness reserve to improve the aging brain? *Neurobiology of Aging*, *83*, 145-149. https://doi.org/10.1016/j.neurobiolaging.2019.03.024

Whitelock, V., Rutters, F., Rijnhart, J. J., Nouwen, A., & Higgs, S. (2021). The mediating role of comorbid conditions in the association between type 2 diabetes and cognition: A cross-sectional observational study using the UK Biobank cohort. *Psychoneuroendocrinology*, *123*, 104902. https://doi.org/10.1016/j.psyneuen.2020.104902

Wicherts, J. M., Veldkamp, C. L., Augusteijn, H. E., Bakker, M., Van Aert, R. C., & Van Assen, M. A. (2016). Degrees of freedom in planning, running, analyzing, and reporting psychological studies: A checklist to avoid p-hacking. *Frontiers in Psychology*, *7*, 1832. https://doi.org/10.3389/fpsyg.2016.01832

Wiegmann, C., Mick, I., Brandl, E. J., Heinz, A., & Gutwinski, S. (2020). Alcohol and dementia–What is the link? A systematic review. *Neuropsychiatric Disease and Treatment*, *16*, 87-99. https://doi.org/10.2147/NDT.S198772

Wilkinson, L. (1999). Statistical methods in psychology journals: Guidelines and explanations. *American Psychologist*, *54*(8), 594-604. https://doi.org/http://dx.doi.org.elib.tcd.ie/10.1037/0003-066X.54.8.594

Willems, M., Van Berlaer, G., Maes, L., Leyssens, L., Koehler, B., & Marks, L. (2021). Outcome of 10 years of ear and hearing screening in people with intellectual disability in Europe: A multicentre study. *Journal of Applied Research in Intellectual Disabilities*, *35*(1), 123-133. https://doi.org/10.1111/jar.12923

Wilson, B. S., Tucci, D. L., Merson, M. H., & O'Donoghue, G. M. (2017). Global hearing health care: New findings and perspectives. *The Lancet*, *390*(10111), 2503-2515. https://doi.org/10.1016/s0140-6736(17)31073-5

Wilson, L. R., Vatansever, D., Annus, T., Williams, G. B., Hong, Y. T., Fryer, T. D., Nestor, P. J., Holland, A. J., & Zaman, S. H. (2019). Differential effects of Down's syndrome and Alzheimer's neuropathology on default mode connectivity. *Human Brain Mapping*, *40*(15), 4551-4563. https://doi.org/10.1002/hbm.24720

Wilson, N. J., Jaques, H., Johnson, A., & Brotherton, M. L. (2017). From social exclusion to supported inclusion: Adults with intellectual disability discuss their life experiences of a structured social group. *Journal of Applied Research in Intellectual Disabilities*, *30*(5), 847-858. https://doi.org/10.1111/jar.12275

Wilson, R. S., Boyle, P. A., Yu, L., Barnes, L. L., Schneider, J. A., & Bennett, D. A. (2013). Life-span cognitive activity, neuropathologic burden, and cognitive aging. *Neurology*, *81*(4), 314-321. https://doi.org/10.1212/WNL.0b013e31829c5e8a

Wilson, R. S., Krueger, K. R., Arnold, S. E., Schneider, J. A., Kelly, J. F., Barnes, L. L., Tang, Y., & Bennett, D. A. (2007). Loneliness and risk of Alzheimer disease. *Archives of General Psychiatry*, *64*(2), 234-240. https://doi.org/10.1001/archpsyc.64.2.234

Wissing, M. B., Dijkstra, R., van der Wal, I. A., Grootendorst, E. S., Hobbelen, J. S., van der Putten, A. A., De Deyn, P. P., Waninge, A., & Dekker, A. D. (2022). Dementia in people with severe/profound intellectual (and multiple) disabilities: Applicability of items in dementia screening instruments for people with intellectual disabilities. *Journal of Mental Health Research in Intellectual Disabilities*, *15*(4), 322-363. https://doi.org/10.1080/19315864.2022.2111737

Wissing, M. B. G., Fokkens, A. S., Dijkstra, R., Hobbelen, J. S. M., Van Der Putten, A. A. J., De Deyn, P. P., Waninge, A., & Dekker, A. D. (2022). Dementia in people with severe/profound intellectual (and multiple) disabilities: Practice-based observations of symptoms. *Journal of Mental Health Research in Intellectual Disabilities*, 1-30. https://doi.org/10.1080/19315864.2022.2061092

Wissing, M. B. G., Ulgiati, A. M., Hobbelen, J. S. M., De Deyn, P. P., Waninge, A., & Dekker, A. D. (2022). The neglected puzzle of dementia in people with severe/profound intellectual disabilities: A systematic literature review of observable symptoms. *Journal of Applied Research in Intellectual Disabilities*, *35*(1), 24-45. https://doi.org/10.1111/jar.12920

World Health Organisation. (2000). *Obesity: Preventing and managing the global epidemic*. World Health Organization. Retrieved 27th September 2021 from https://iris.who.int/handle/10665/42330

World Health Organisation. (2024). *Anatomical Therapeutic Chemical (ATC) Classification*. World Health Organisation,. Retrieved 30/04/2024 from https://www.who.int/tools/atc-ddd-toolkit/atc-classification

World Health Organization. (2008). *Waist circumference and waist-hip ratio: Report of a WHO expert consultation*. World Health Organisation. Retrieved 27th September 2021 from https://www.who.int/publications/i/item/9789241501491

World Health Organization. (2019a). *Risk Reduction of Cognitive Decline and Dementia: WHO Guidelines*. World Health Organisation. Retrieved 7th April 2024 from https://www.who.int/publications/i/item/9789241550543

World Health Organization. (2019b). *WHO report on the global tobacco epidemic, 2019: Offer help to quit tobacco use*. World Health Organization. Retrieved 13th June 2024 from https://www.who.int/publications/i/item/9789241516204

World Health Organization. (2020a). *Ensuring ethical standards and procedures for research with human beings.* World Health Organsation Retrieved 20th February 2021 from https://www.who.int/activities/ensuring-ethical-standards-and-procedures-for-research-with-human-beings

World Health Organization. (2020b). *Guidelines on physical activity and sedentary behaviour.* World Health Organisation. Retrieved 5th May 2021 from https://www.who.int/publications/i/item/9789240015128

World Health Organization. (2021). *Social isolation and loneliness among older people: Advocacy brief*. World Health Organisation. Retrieved 3rd March 2021 from https://www.who.int/publications/i/item/9789240030749

World Health Organization. (2022a). *Dementia*. World Health Organisation. Retrieved 9th September 2022 from https://www.who.int/health-topics/dementia#tab=tab_1

World Health Organization. (2022b). *Optimizing brain health across the life course: WHO position paper*. World Health Organisation. Retrieved 10th October 2022 from https://www.who.int/publications/i/item/9789240054561

World Health Organization. (2023). *WHO report on the global tobacco epidemic, 2023: Protect people from tobacco smoke*. World Health Organisation. Retrieved 13th June 2024 from https://www.who.int/publications/i/item/9789240077164

Xiang, X., Lai, P. H. L., Bao, L., Sun, Y., Chen, J., Dunkle, R. E., & Maust, D. (2021). Dual trajectories of social isolation and dementia in older adults: A population-based longitudinal study. *Journal of Aging and Health*, *33*(1-2), 63-74. https://doi.org/10.1177/0898264320953693

Yeo, B. S. Y., Song, H. J. J. M. D., Toh, E. M. S., Ng, L. S., Ho, C. S. H., Ho, R., Merchant, R. A., Tan, B. K. J., & Loh, W. S. (2023). Association of hearing aids and cochlear implants with cognitive decline and dementia: A systematic review and meta-analysis. *JAMA Neurology*, *80*(2), 134-141. https://doi.org/.1001/jamaneurol.2022.4427

Young, Y., Frick, K. D., & Phelan, E. A. (2009). Can successful aging and chronic illness coexist in the same individual? A multidimensional concept of successful aging. *Journal of the American Medical Directors Association*, *10*(2), 87-92. https://doi.org/10.1016/j.jamda.2008.11.003

Yu, J.-T., Xu, W., Tan, C.-C., Andrieu, S., Suckling, J., Evangelou, E., Pan, A., Zhang, C., Jia, J., & Feng, L. (2020). Evidence-based prevention of Alzheimer's disease: Systematic review and meta-analysis of 243 observational prospective studies and 153 randomised controlled trials. *Journal of Neurology, Neurosurgery & Psychiatry*, *91*(11), 1201-1209. https://doi.org/10.1136/jnnp-2019-321913

Yu, R.-C., Proctor, D., Soni, J., Pikett, L., Livingston, G., Lewis, G., Schilder, A., Bamiou, D., Mandavia, R., & Omar, R. (2024). Adult-onset hearing loss and incident cognitive impairment and dementia–A systematic review and meta-analysis of cohort studies. *Ageing Research Reviews*, *98*, 102346. https://doi.org/10.1016/j.arr.2024.102346

Zahodne, L. B., Mayeda, E. R., Hohman, T. J., Fletcher, E., Racine, A. M., Gavett, B., Manly, J. J., Schupf, N., Mayeux, R., & Brickman, A. M. (2019). The role of education in a vascular pathway to episodic memory: Brain maintenance or cognitive reserve? *Neurobiology of Aging*, *84*, 109-118. https://doi.org/10.1016/j.neurobiolaging.2019.08.009

Zeki Al Hazzouri, A., Caunca, M. R., Nobrega, J. C., Elfassy, T., Cheung, Y. K., Alperin, N., Dong, C., Elkind, M. S., Sacco, R. L., & DeCarli, C. (2018). Greater depressive symptoms, cognition, and markers of brain aging: Northern Manhattan Study. *Neurology*, *90*(23), e2077-e2085. https://doi.org/10.1212/WNL.0000000000005639

Zhenrong, R., Jiajia, W., Guangjin, Y., & Chanjuan, Y. (2024). Prevalence of social isolation in the elderly: A systematic review and meta-analysis. *Geriatric Nursing*, *58*, 87-97. https://doi.org/10.1016/j.gerinurse.2024.05.008

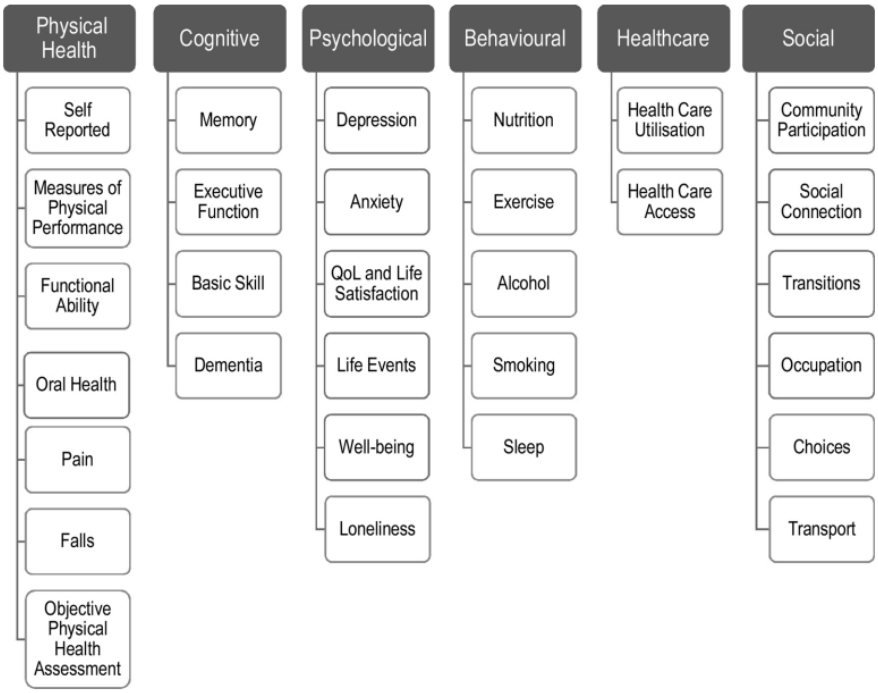
Zhou, B., Perel, P., Mensah, G. A., & Ezzati, M. (2021). Global epidemiology, health burden and effective interventions for elevated blood pressure and hypertension. *Nature Reviews Cardiology*, *18*(11), 785-802. https://doi.org/10.1038/s41569-021-00559-8

Zigman, W. B. (2013). Atypical aging in Down syndrome. *Developmental Disabilities Research Reviews*, *18*(1), 51-67. https://doi.org/10.1002/ddrr.1128

Appendix A: Sample of Search Strategy

Main Theme	Secondary Theme	Search Terms
Ageing Theory	Biopsychosocial	Biopsychosocial model OR biopsychosocial approach AND aging theory OR ageing theory
	Positive Psychology	Ageing theory OR aging theory AND positive psychology OR positive ageing
Down syndrome	Ageing	Down syndrome OR Down's syndrome OR trisomy 21 AND ageing OR aging OR older OR elderly
Alzheimer's Disease	Demographics	Alzheimer's Disease OR Alzheimer's OR Alzheimer OR Dementia OR Cognitive Decline AND Prevalence OR Incidence OR Demographics OR Epidemiology
	Physiological Pathways	Alzheimer's Disease OR Alzheimer's OR Alzheimer OR Dementia OR Cognitive Decline AND physiological pathways OR physiology OR biological mechanisms OR pathophysiology OR neurodegeneration OR biomarkers
	Down syndrome	Down syndrome OR Down's syndrome OR trisomy 21 AND DSAD OR Down syndrome related Alzheimer's Disease OR Alzheimer OR Alzheimer's OR dementia OR cognitive decline OR cognitive reserve

Appendix B: IDS-TILDA Conceptual Framework



Note: The six domains of functioning assessed in the IDS-TILDA research. From: "Recruitment and retention in longitudinal studies of people with intellectual disability: A case study of the Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing (IDS-TILDA)" by McCarron et al. (2022), *Research in Developmental Disabilities*, 124, Figure 1, p. 104197. https://doi.org/10.1016/j.ridd.2022.104197. Copyright 2022 Elsevier Ltd.

Appendix C: The Values Framework underpinning IDS-TILDA Research

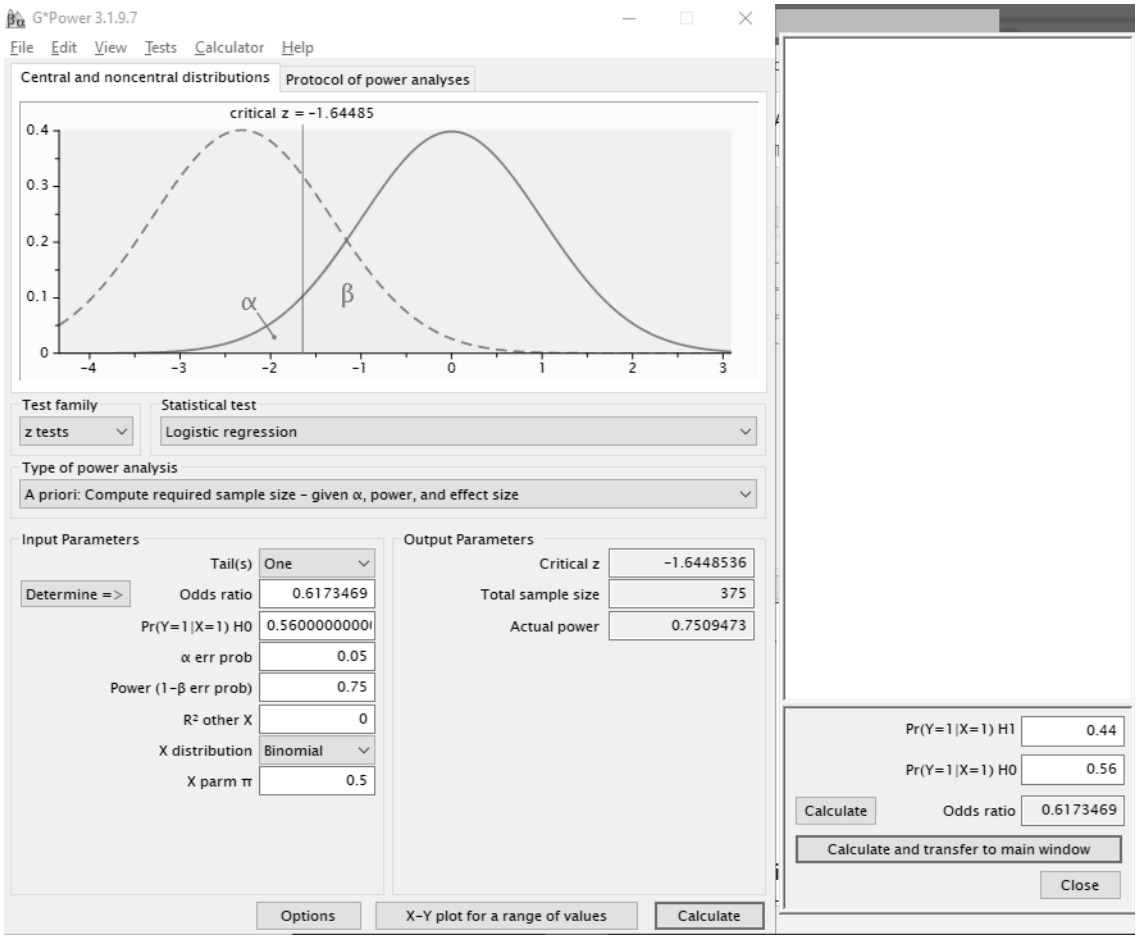
Note: The values underpinning the IDS-TILDA study framework. From: "Recruitment and retention in longitudinal studies of people with intellectual disability: A case study of the Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing (IDS-TILDA)", by McCarron et al. (2022), *Research in Developmental Disabilities*, 124, Figure 2, p. 104197. https://doi.org/10.1016/j.ridd.2022.104197. Copyright 2022 Elsevier Ltd.

Appendix D: Summary Overview of Multicollinearity Diagnostics for Lagged Dataset

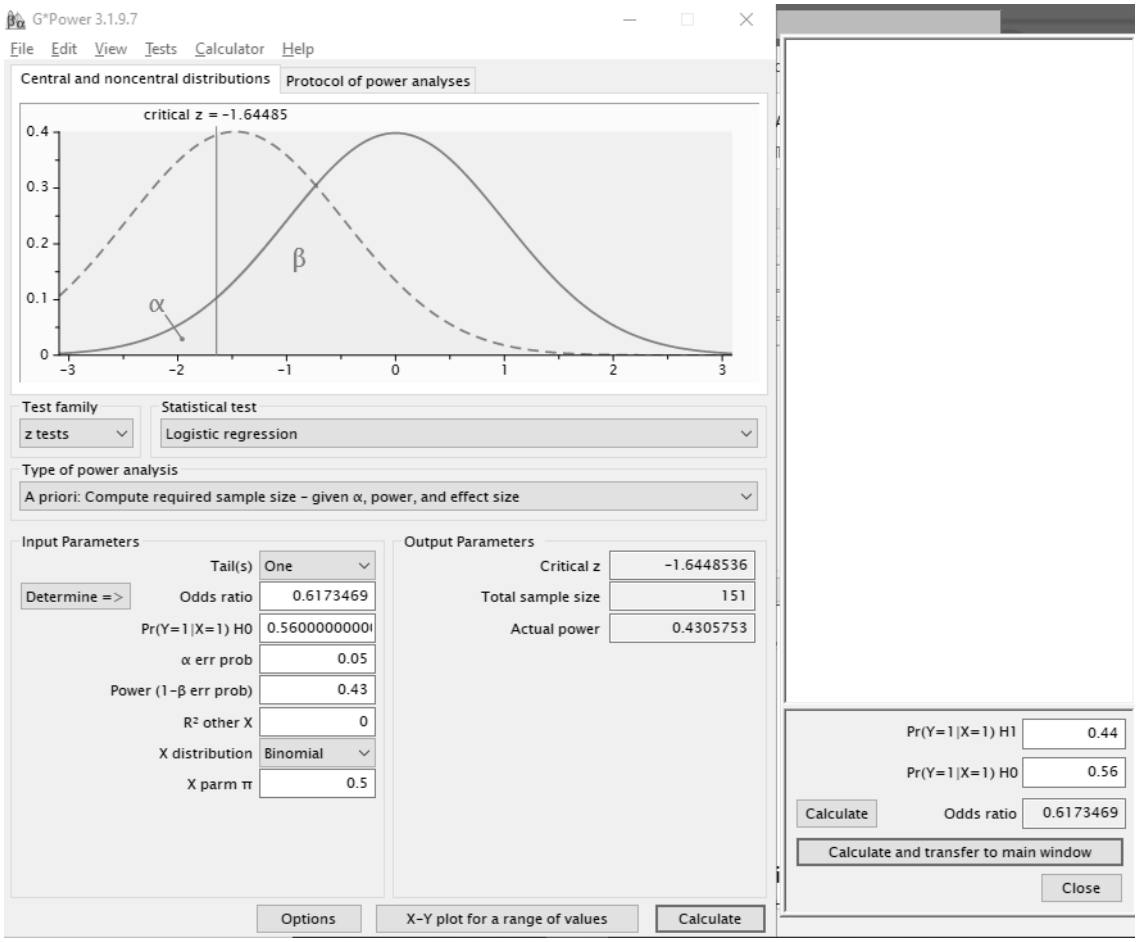
Independent Variable	Collinearity Statistics	
	Tolerance	*VIF*
Gender	.839	1.192
Level Intellectual Disability	.488	2.051
Residential Status	.587	1.703
No Education	.569	1.758
Hearing Loss	.843	1.187
Hypertension	.655	1.527
Frequent Alcohol	.896	1.117
Obesity	.839	1.192
Smoker	.821	1.218
Depression	.817	1.224
Social Isolation	.758	1.319
Physical Inactivity	.729	1.372
Diabetes	.681	1.468

Incorporating Demographics of Gender, Level Intellectual Disability and Residential Status

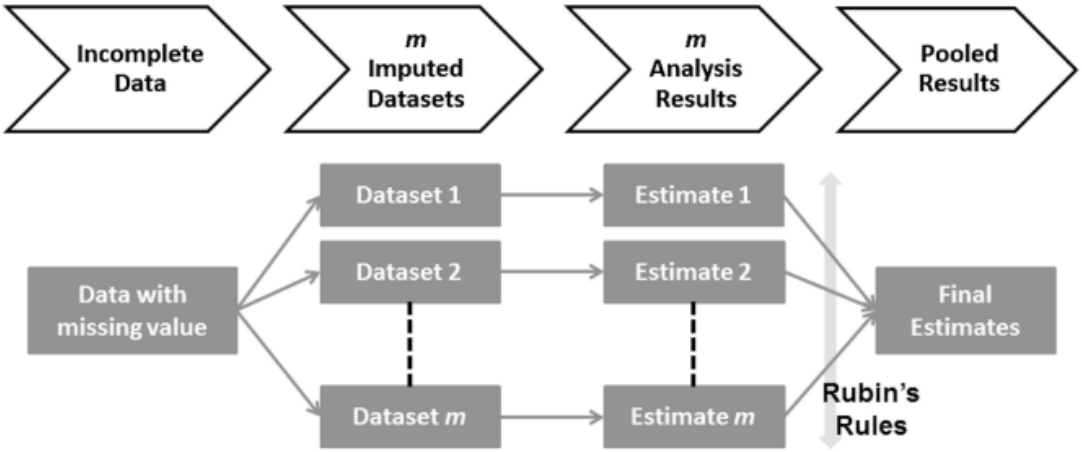
Appendix E: G-Power Analysis: Number of Participants required for 75% Power (1-tailed)



Appendix F: G-Power Analysis: Power Estimation for this Study Sample Size (1-tailed)



Appendix G: Visual Overview of Multiple Imputation by Chained Equations (MICE)



Note: An overview of the process of using Multiple Imputation by Chained Equations (MICE) to handle missing data. Rubin's rules combine parameter estimates from the multiple imputed databases to give a set of pooled results. From: "Multiple imputation: A mature approach to dealing with missing data" by Chevret et al. (2015), *Intensive Care Medicine*, 41 (2), Figure 1, p.350. https://doi.org/10.1007/s00134-014-3624-x. Copyright 2015 by Springer Nature.

Appendix H: MICE Imputation Constraints for Lagged Regression Dataset

	Role in Imputation	
Independent Variable	**Dependent**	**Predictor**
Gender	Yes	Yes
Level ID	Yes	Yes
Residential Status	Yes	Yes
No Education	Yes	No
Hearing Loss	Yes	Yes
Hypertension	Yes	Yes
Frequent Alcohol	Yes	Yes
Obesity	Yes	Yes
Smoker	Yes	Yes
Depression	Yes	Yes
Social Isolation	Yes	Yes
Physical Inactivity	Yes	Yes
Diabetes	Yes	Yes