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Multiple medication use in the middle and older age population

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PhD Thesis

December 2013

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Co-supervisor: Dr Kathleen Bennett

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Declarations

I declare that this thesis has not been submitted as an exercise for a degree at this or any other university.

The material of this thesis forms part of the data analysis from a prospective longitudinal study entitled 'The Irish Longitudinal Study on Ageing' (TILDA). I certify that I performed all work contained within this thesis, from project conception and design, analysis and interpretation of data to manuscript preparation. The hypotheses, design and governance of the TILDA study is under the direction of Professor Rose Anne Kenny. Professor Rose Anne Kenny and Dr Kathleen Bennett provided guidance and direction on the issues addressed within this thesis and acted as supervisors. Jure Peklar assisted on the cleaning and coding of the TILDA medication data, and Dr Chris Fox, Mr Ian Maidment and Dr David Smithard assisted with the coding of the anti-cholinergic properties of the medications.

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Summary

Polypharmacy in the older population is increasingly common and can represent necessary preventative therapies or potential inappropriate prescribing and be a risk factor for falls. In addition, medications with anti-cholinergic activity have recently been implicated with cognitive and functional decline in older adults, but few studies have examined their relationship with falls. Estimating the associated risks in observational studies is complex due to the accuracy of medication use ascertainment and confounding by indication.

This doctoral thesis considers the source of medication data, access to healthcare, and approaches to account for confounding, to examine the association between both polypharmacy and medications with anti-cholinergic activity and incident falls. The data were derived from The Irish Longitudinal Study on Ageing (TILDA) and the Health Service Executive - Primary Care Reimbursement Services pharmacy claims database. The findings are summarised below.

Study I. Interview ascertained medication use of 19 therapeutic classes was compared to pharmacy records for 2,621 participants. Agreement was good or very good for 15 medication classes, and moderate or poor for antiinflammatory and antirheumatic products, analgesics, psycholeptics, and ophthalmologicals. Participants were less likely to report a regularly dispensed medication if they were older, had more medications regularly dispensed, did not report an indicated health condition, or if the medication was less frequent dispensed, but results varied by therapeutic class. Memory and cognition were not associated with discordance between sources.

Study II. Multivariable regression was compared to propensity score methods to assess the association between free healthcare access and polypharmacy whilst accounting for underlying socioeconomic and health status differences. Polypharmacy was reported by 22% and 7% of the 1,932 and 3,864 participants aged 50-69 years with and without public healthcare coverage.

Public patients had a 21-38% greater risk of polypharmacy depending on the method used to account for confounding. Associations were mainly unaffected after also accounting for objective health measures, but significantly attenuated after accounting for frequency of healthcare visits.

Study III. Established falls risk-increasing medications were identified from previous systematic reviews. At wave 2 in TILDA, participants reported having any fall, the number of falls, and any injurious falls since the baseline interview. After adjustment for sociodemographics, baseline comorbidity, health and falls risk variables, polypharmacy including antidepressant use was associated with a greater risk of all falls outcomes, but both antidepressant use without polypharmacy, and polypharmacy without antidepressants were not. Benzodiazepine use was associated with a greater number of falls, independent of polypharmacy. However, injurious falls were more likely to occur with benzodiazepine use that also included polypharmacy. The other identified fall risk-increasing medication classes of antihypertensives, diuretics, and antipsychotics were not associated with any falling outcomes after adjustment for comorbidity.

Study IV. The regular use of medications with definite anti-cholinergic activity at baseline was not associated with an increased risk of having any fall over the next two years, but was associated with an increased risk of injurious falls and a greater number of falls after adjusting for the confounders. The use of additional medications with anti-cholinergic activity increased these risks further. Associations did not vary by age, sex, cognition, or falls history. Findings were replicated in those with linked pharmacy dispensing records (n=2402), and were robust to adjustment for baseline objective health measures.

Conclusions: Our findings represent an original contribution to pharmacoepidemiology methodological research, to research into medication related risk factors for falling, and demonstrate the contribution cohort studies can make to pharmacoepidemiology.

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Publications

This doctoral thesis is based on the following original papers, referred to in the text by their Roman numerals.

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II. Richardson K, Kenny RA, Bennett K. The effect of free healthcare on polypharmacy: A comparison of propensity score methods and multivariable regression to account for confounding. Submitted to *Pharmacoepidemiol Drug Saf.*

III. Richardson K, Bennett K, Kenny RA. Polypharmacy including falls risk-increasing medications and subsequent falls in community-dwelling middle and older aged adults. Submitted to *Age Ageing*.

IV. Richardson K, Bennett K, Maidment I, Fox C, Smithard D, Kenny RA. Use of medications with anti-cholinergic activity and injurious falls in community-dwelling adults aged 50 years and older. Submitted to *BMJ.*

Other related published work completed during my PhD include:

- Richardson K, Moore P, Peklar J, Galvin R, Bennett K, Kenny RA. "*Drug prescribing for the older population in Ireland: Opportunities for cost saving and improved healthcare*." Trinity College Dublin (2012). Available from http://www.tilda.ie.
- Peklar J, Henman M, Richardson K, Kos M, Kenny RA. Food supplement use in the community dwelling population aged 50 and over in the Republic of Ireland. *Complementary Therapies in Medicine* 2013; 21(4):333–41.

Abbreviations

ACB	Anti-cholinergic Cognitive Burden
AD	Antidepressant
ADL	Activities of Daily Living
ARMD	Age Related Macular Degeneration
ATC	Anatomic Therapeutic Chemical
BMI	Body Mass Index
BZD	Benzodiazepine
CES-D	Center for Epidemiologic Studies Depression Scale
CI	Confidence Interval
CNS	Central Nervous System
FS	Food Supplement
GMS	General Medical Services
HADS-A	Hospital Anxiety and Depression Scale – Anxiety subscale
HSE-PCRS	Health Service Executive - Primary Care Reimbursement Services
IADL	Instrumental Activities of Daily Living
IPTW	Inverse-Probability-of-Treatment-Weighted
IQR	Inter Quartile Range
IRR	Incidence Rate Ratio
MMSE	Mini Mental State Examination
OR	Odds Ratio
OTC	Over-the-counter
PP	Polypharmacy
PS	Propensity Score
RCT	Randomised Controlled Trial
RR	Relative Risk
SCQ	Self-completion questionnaire
SD	Standard Deviation
SE	Standard Error
TIA	Transient Ischaemic Attack
TILDA	The Irish Longitudinal Study on Ageing
TUG	Timed Up-and-Go
WHO	World Health Organisation

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1 Introduction

Chapter one provides an introduction to the topics related to multiple medication use in the older population covered in this thesis, including relevant literature reviews, and then outlines the objectives of my thesis. Chapter two describes the two datasets used for the thesis: The Irish Longitudinal Study on Ageing (TILDA) and the Health Service Executive - Primary Care Reimbursement Services (HSE-PCRS) pharmacy database. Chapter three, four, five, and six detail the four main research studies. Finally, chapter seven provides a discussion of the findings of the thesis.

1.1 Medication use in the older population

Due to population ageing the global population of adults aged over 65 years is expected to increase from around 420 million in 2000 to nearly one billion in 2050 (1). In Ireland, the proportion of the population aged over 65 years is expected to double over the next 35 years from 11% in 2006 to 22% in 2041 (2). Increasing life expectancy and associated greater morbidity, as well as new drug treatments and indications, all contribute to the development of multiple medication use as people age. Medication usage among the middle aged and older population is increasing both internationally and in Ireland where, in 2010, the medicines' budget was in excess of €1 billion for the over 50s, accounting for two thirds of the total (3,4).

Many medications are taken concurrently over the long term for the prevention or management of chronic diseases in older people. The most commonly used medications in European older adults are from the cardiovascular, central nervous system, and gastrointestinal classes, with usage increasing with age (5). Polypharmacy is a measure of multiple medication use. The definition varies in the literature, making international comparisons of prevalence rates difficult, but it is most commonly defined as the concurrent use of five or more medications (6),

and excessive polypharmacy defined as 10 or more medications (7). Table 1.1 shows different prevalence estimates of polypharmacy in older adults across population-based studies. In adults aged over 65 years, estimates of the prevalence of polypharmacy range from 13-53%.

Table 1.1. Polypharmacy prevalence estimates in older adults from population-based studies

Population (reference)	Medication reporting	Age, year (N)	Definition of polypharmacy	Polypharmacy prevalence
Lieto, Finland (8)	Nurse interview in	Aged 65+	5+ Rx drugs	
community dwelling	health centre / home, prescriptions 'currently taking'	1990-1 (n=1131)		19%
		1998-9 (n=1197)		25%
	/all taken in past 7 days			
England and Wales (9)	In home interviews	Aged 65+	5+ Rx/OTC/FS	13%
6 centres (inc. Institutions) The Cognitive Function and Ageing Study (MRC CFAS)	"current use"	1991-3 (n=12423)		
Canada Population	Telephone survey	Aged 65+, 1998-9	5+ Rx/OTC/FS	
Health Survey (10)	"current use"	Community (n=2851)		13%
		Institutionised (n=1711)		53%
US (11), community dwelling	In home interviews	Aged 65+	5+ Rx drugs	M 31%
National Social Life, Health, and Aging	"on a regular schedule, like	2005-6 (n=1960)		F 35%
Project (NSHAP)	every day or every week"		5+ Rx/OTC/FS	M ~52%
				F ~57%
Emilia-Romagna region,	Pharmacy records	Aged 65+	5+ Rx drugs	39%
Italy (12)		2007 (n=887,165)	on 1+ day	
Canada Survey of	Telephone survey	Aged 65+	5+ Rx	27%
Experiences with	"regular or ongoing basis"	2008 (n=3132)		
Primary Health Care (13)				
Kuopio, Finland (14)	Nurse interview and	Aged 75+	PP:	
community-dwelling	medical record check,	1998 (n=601)	6+ Rx/OTC/FS	PP 61%
	"Drugs and vitamins taken regularly or as-needed"		Excessive PP: 10+	EPP 28%
		2000 (n=167)	Rx/OTC/FS	PP 67%
				EPP 28%
Sweden (15) (including Institutions)	Interview (visit, proxy, phone),	Aged 77+	5+ Rx/OTC	42%
Swedish Panel Study	"on a regular basis or as	2002 (n=621)		
of Living Conditions of the	needed during the 2 weeks			
Oldest Old (SWEOLD)	prior to the interview."			
Sweden (16)	Pharmacy prescription	Aged 75-89	5+ Rx drugs	57%
GP practices	Records	2005 (n=626,258)	10+ Rx drugs	18%

Rx=prescribed; OTC=Over-the-counter; PP=polypharmacy; EPP=excessive polypharmacy; FS=food supplements; M=male; F=female.

Multiple medication use in the older population is increasingly common (3), and can represent necessary preventative therapies or potential inappropriate prescribing. Polypharmacy has been associated with inappropriate prescribing and adverse drug reactions (6,17), and is implicated in several health outcomes including functional impairment, falls and fractures, hospitalization, and mortality (9,18). The differing pharmacokinetics and pharmacodynamics in the elderly population also make them more vulnerable to the effects of inappropriate prescribing and adverse drug reactions (7). However, there are also many medications prescribed that improve the quality of life of individuals with specific conditions.

1.2 Pharmacoepidemiology

Pharmacoepidemiology is the study of medication use or the effects of medication use in the population. Table 1.2 describes the types of data sources used in pharmacoepidemiology studies and their typical properties. Providing evidence on the long term consequences of medication use in older populations is vital, however, there is a lack of high-quality evidence to guide prescribing (18). Although randomised controlled trials (RCTs) provide the highest quality evidence, older people and those with concomitant diseases are often excluded from drug trials. Electronic medical and administrative databases (e.g. Clinical Practice Research Datalink, disease specific registries) can provide detailed information on long-term medication use in the population, but are often missing detailed outcome and confounding information. Population-based longitudinal studies provide a good alternative to assess the effects of medication usage in a community setting, but medication use data is often not recorded continuously. For example, medication use may not be available at the exact time of the outcome of interest, but rather only at the last interview date. If associations are found between medication exposures and outcomes, they would likely be underestimates compared to if the medication exposure was available at the time of the outcome. Population-based longitudinal studies need careful analysis and interpretation to overcome the limitations due to the observational nature of these studies.

Consideration needs to be made as to the source of medication data, any differences in healthcare access, and methods used to control for confounding (particularly confounding by indication).

Table 1.2. Typical features of data sources for pharmacoepidemiology studies

Data source	Population	Medications	Outcomes	Confounders	Typical no. Patients
RCT	Patients Recruited	Detailed recording	Detailed recording	Randomised	Hundreds
Electronic medical record database	Population accessing services	Prescribed or dispensed	GP recorded or hospitalisation, mortality	GP recorded, missing lifestyle, frailty	Millions
Population-based cohort study	Population that Responded	Self-report	Detailed, but self-report	Detailed, but self-report	Thousands

1.3 Measuring medication use

Pharmacoepidemiological studies require reliable and valid ascertainment of medication use. Misclassification of medication use can bias estimates of the risks of taking medications either towards or away from the null (19). Prescription records, pharmacy records and self-report data are often used to obtain information on medication use in the population. Prescription and pharmacy records are potentially recorded more accurately, but may not represent actual use or be available for the whole population. Self-report (via a self-completed questionnaire, telephone interview, or face-to-face interview) provides information on medicines actually used as well as non-prescription use. However, self-reporting may be inaccurate, but can be supplemented by a medication inventory, whereby all medication packages are presented to interviewers, reducing any recall problems. Comparison between pharmacy records and self-reported data is essential for improved understanding of the relative merits of each and the extent of potential misclassification of medication use in pharmacoepidemiological studies. In addition, understanding of the predictors of poor concordance will help improve medication use data

collection in the future and help better appreciate any biases in the data when performing pharmacoepidemiological studies.

1.3.1 Studies examining medication agreement

Few studies have investigated the agreement between pharmacy records and self-report in older populations (20–22). When these sources were compared for cardiovascular medication use in the Rotterdam Elderly Study of over 55 year olds, 80% of the prescriptions matched in both sources (20). Self-reported psychotropic use was compared in the Finnish intervention study of over 75 year olds, but agreement varied according to whether 4, 6 or 12 month time windows were examined in the pharmacy data (22). The Three-City Study in France compared all medication classes, and found that self-reported medication use was better reported using 60-day than 30-day reimbursement pharmacy records (21). These and other studies in the general population report mostly good agreement between self-report and pharmacy records, but agreement varies significantly by therapeutic group, with least agreement for medications taken topically, as-needed, or for shorter periods (21,23,24). A study comparing all prescription records to self-reported medication use in Danish adults aged over 75 years found disagreement concerning drugs taken, doses and regimens (25). Greater disagreement was reported for use of hypnotics, analgesics, bronchodilators and diuretics.

1.3.1.1 Studies examining predictors of poor concordance

In the older population, only the Rotterdam Elderly Study has examined predictors of discordance, and found neither age, sex, education nor socio-economic status were associated (20). Studies in various settings reported worse recall of medications for those who were older (26–29), unmarried (26), and with less education (26,30). Yet medication recall often does not vary by gender (20,26–28,30), or income (29). Despite the potential importance of memory and

cognition in recall ability, few studies have examined these and those that have found mixed results (25,31,32).

1.4 Confounding in pharmacoepidemiology

When examining the association between an exposure and an outcome, a confounder is a variable that is related to both the exposure and outcome, but is not on the causal pathway between the two. Effect estimates may be under- or over-estimates of the true association if this confounding is not accounted for. The biggest threat to the validity of pharmacoepidemiology studies is confounding by indication. When examining the effects of medication use, it is difficult to untangle the effect of the medication from that of the underlying indication or medical condition.

1.4.1 Addressing confounding

In epidemiology, the traditional approach to address confounding is either by the design (e.g. matching, restriction) and/or by analysis via multivariate regression, whereby confounders are adjusted for in a regression model. More recently, propensity scores and instrumental variable analysis have become popular alternatives (33,34). Instrumental variable analysis attempts to mimic randomisation within an RCT by the choice of an appropriate instrument. An instrument is a variable that is associated with the exposure (treatment), unrelated to the confounders, but neither directly nor indirectly related to the outcome, except through its association with the exposure (34,35). In the simplest case, instrumental variable analysis then substitutes the instrument for actual exposure. An instrument sometimes used in health services research is geographical location, where treatment rates vary by region, but the effectiveness of treatment does not (36). However, it is often difficult to identify strong instruments in medical research (37). In addition, simulation studies have shown even with strong instruments, instrumental variables

analysis often leads to more bias than multivariable regression and residual confounding may still exist (38,39).

Propensity score analysis attempts to mimic the design of an RCT by increasing the comparability between the unexposed and exposed groups on their measured confounders (40). The propensity score is defined as the conditional probability of exposure (or treatment) given an individual's covariates. These conditional probabilities are commonly calculated using multivariable logistic regression. There are different approaches to using the estimated propensity score, including adjustment for the propensity score (continuous or categorised according to percentiles) in a multivariable regression, matching on the propensity score, or inverse probability weighting by the propensity score. The choice of method is influenced by whether the study objectives are to make statements about the whole population, or just the exposed patients. For example, when selecting unexposed patients to match characteristics (e.g. based on a propensity score) of the exposed patients, effect estimates will apply to a population representing the exposed patients. However, multivariable regression will produce effect estimates applicable to the total population (the exposed and unexposed).

Approaches towards variable selection differ between propensity score methods and multivariable regression. Multivariable regression typically aims to seek a parsimonious model to avoid multicollinearity between potential confounders (41), whereas recent studies using propensity score techniques have advocated using a greater number of potential confounders (42). However, studies generally report similar findings when using either propensity score methods or multivariable regression (33,43,44).

1.4.2 Confounding by healthcare system use

When conducting pharmacoepidemiology studies in settings with differential healthcare access, such as Ireland (see chapter 2.2 for more information), the possibility of 'confounding by

healthcare system use' needs to be considered (42). This occurs where access to healthcare confounds the association between medication use and health outcomes.

In the Republic of Ireland, eligibility for free public healthcare is means tested, and reports suggest free healthcare leads to increased use of primary care (45). Certain classes of medications have been shown to be inappropriately prescribed in the Irish public healthcare system, or more frequently prescribed to those with lower incomes (46–48). The Irish government has proposed plans to introduce universal health insurance for all Irish residents, which includes free physician visits in the future (49). Understanding the effects of free healthcare on medication use is important for informing such policy debates.

Few studies have examined the effect on health insurance coverage on health outcomes. Prospective studies in North America have shown that differences in health insurance coverage result in differential rates of mortality, disability, and declines in self-rated health (50,51). Uninsured US citizens restrict medication use; particularly medications used to manage or prevent cardiovascular disease (52,53), and this cost-related restriction can lead to declines in health (54). In Ireland, it could be the case that those without free healthcare restrict their medication use, or conversely, that over-prescribing may occur among those with free healthcare, possibly enabled through free medical practitioner visits.

1.5 Outcomes: Falling in older adults

Fall-related injuries are of major public health concern (55). Population-based studies in North America and Europe report around 30% of community-dwelling persons aged over 65 years fall annually (56,57), with around half experiencing multiple falls or resulting in injury (57,58). Injuries can range from serious fractures, head injury and joint dislocations, to less serious soft-tissue bruises, cuts, and abrasions (57,59). Falls are associated with increased rates of hospitalisation, institutionalisation, and disability (59–62). They can also lead to loss of independence, fear of falling, decreased activity, social isolation, and poorer quality of life (56,62,63).

Risk factors for falls are multifactorial and involve a complex interplay between many intrinsic and extrinsic factors. Intrinsic health status has commonly been associated with falling, including depression, comorbidity, urinary incontinence, pain, impaired vision, and cognitive impairment (64,65). Table 1.3 displays the results of pooled associations of risk factors for falls from a meta-analysis of prospective studies (64). Many risk factors were associated with falls, but the strongest included history of falls, gait problems, walking aids use, vertigo, and Parkinson disease.

Table 1.3. Pooled odds ratios (with 95% confidence intervals) for the association of risk factors for any fall in community-dwelling older people

Characteristic	No. Studies	OR	(95% CI)
Age (per 5-year)	18	1.12	(1.07–1.17)
Sex – women	22	1.30	(1.18–1.42)
Living alone	11	1.33	(1.21–1.45)
Low education	7	1.01	(0.88–1.16)
Low body mass index	3	1.17	(0.93–1.46)
History of falls	18	2.77	(2.37–3.25)
Physical limitation	10	1.20	(1.04–1.38)
Physical disability	9	1.56	(1.22–1.99)
Instrumental disability	6	1.46	(1.20–1.77)
Walking aid use	11	2.18	(1.79–2.65)
Cognition impairment	10	1.36	(1.12–1.65)
Depression	17	1.63	(1.36–1.94)
History of stroke	5	1.61	(1.31–1.98)
Urinary incontinence	13	1.40	(1.26–1.57)
Rheumatic disease	9	1.47	(1.28–1.70)
Dizziness/vertigo	6	1.80	(1.39–2.33)
Hypotension	4	1.24	(0.90–1.71)
Diabetes	8	1.19	(1.08–1.31)
Parkinson disease	5	2.71	(1.08–6.84)
No. comorbidities	10	1.23	(1.16–1.30)
Poor self-rated health	6	1.50	(1.15–1.96)
Pain	2	1.39	(1.19–1.62)
Fear of falling	9	1.55	(1.14–2.09)
Gait problems	5	2.06	(1.82–2.33)
Vision impairment	15	1.35	(1.18–1.54)
Hearing impairment	7	1.21	(1.05–1.39)

Adapted from Deandrea 2010 meta-analysis (64)

1.5.1 Medication use and falls

The use of certain medications have been suggested as modifiable extrinsic risk factors for falling. Various medication classes have been repeatedly associated with falls in observational studies (66–69). Table 1.4 provides a summary of the results of meta-analyses (66–68).

Table 1.4 Pooled odds ratios (with 95% confidence intervals) for the association between medication classes and falls.

Medication class	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Antihypertensives	1.24 (1.01-1.50)*	n/a
Diuretics	1.07 (1.01-1.14)*	0.99 (0.78-1.25)*
Beta-blockers	1.01 (0.86-1.17)*	n/a
ACE inhibitors	1.20 (0.92-1.58)*	n/a
Calcium channel blockers	0.94 (0.77-1.14)**	n/a
Nonsteroidal anti-inflammatories	1.21 (1.01-1.44)**	n/a
Narcotics	0.96 (0.78-1.18)*	n/a
Aspirin	1.12 (0.80-1.57)*	n/a
Antipsychotics	1.59 (1.37-1.83)*	1.39 (0.94-2.00)*
Benzodiazepines	1.57 (1.43-1.72)*	1.41 (1.20-1.71)*
Antidepressants	1.68 (1.47-1.91)*	1.36 (1.13-1.76)*
Tricyclic antidepressant	1.51 (1.14-2.00)†	n/a

n/a = not available
*Results from Woolcott 2009 meta-analysis (68).
**Results from Leipzig 1999 meta-analysis II (67).
† Results from Leipzig 1999 meta-analysis I (66).

Psychotropics, particularly antipsychotics, antidepressants and benzodiazepines, are the medications with the strongest associations with falls risk (66,68,69). Possible explanations include that the sedative, autonomic and extrapyramidal effects, and the effects on alpha-adrenergic receptors of psychotropics increase the risk of falling (70–74).

The use of cardiovascular medications, particularly, antihypertensives and diuretics have been associated with falls (67,68). There is less research into these medication classes, particularly for specific classes, but associations could be due to factors like orthostatic hypotension (69). A recent study of primary care data found thiazide use associated with falls, but suggests the associations for other antihypertensives are due to confounding (75).

Polypharmacy is also an important risk factor for falling (18). However, recent studies suggest that the association may not be significant when indications for the medicines are considered (65), and that polypharmacy only poses a risk if it includes falls risk-increasing medications (76).

1.5.2 Medications with anti-cholinergic activity and falls

The anti-cholinergic activity of certain medications may also contribute to a higher falls risk. Anti-cholinergic medications block muscarinic cholinergic receptors in the brain thereby inhibiting the parasympathetic nervous system (77). These medications are prescribed for a variety of conditions including incontinence (e.g. Oxybutin), depression (e.g. Amitriptyline) and psychosis (e.g. Olanzapine) (78–80). However, there are a wide range of medications that also exhibit anti-cholinergic activity in vitro, including anti-arrythmics, anti-histamines, anti-ulcer drugs, anti-diarrhoeals, and muscle relaxants, and if used in combination could increase the risk of an adverse effect (81). Possible anti-cholinergic side-effects in the elderly are listed in table 1.5. Common side-effects, such as constipation, dry mouth, urinary disorders, and memory loss, often develop gradually and may get overlooked as they mimic the aging process (79). Other side-effects that may influence falls risk include blurred vision, increased heart rate, and Central Nervous System effects such as sedation, confusion, behavioural excitation and hallucinations (79,80). The use of medicines with anti-cholinergic activity is common in older adults (81), who are more susceptible to their effects, given age-related deficits in drug metabolism, elimination, and in the integrity of basal forebrain cholinergic neurons (deficits are related to cognitive decline and dementia) (80,82).

1.5.2.1 Studies examining medications with anti-cholinergic activity and falls

Few studies have investigated the association between use of medications with anti-cholinergic activity and falls (83). A prospective study of 6,343 community-dwelling adults aged 65 years and

older in France reported no association between baseline use of medication with anti-cholinergic activity and falling (84). They, however, reported a positive association for regular anti-cholinergic medication use, but this definition included use post-falling. Over 4-years follow-up of 414 elderly psychiatric inpatients, falling was reported more frequently for those currently taking anti-cholinergic medications, but only crude associations were provided (71). Falls were recorded prospectively via monthly diaries for 12 months in 602 nursing home residents aged over 70 years in Australia, and baseline use of an anti-cholinergic or sedative medication use was associated with a greater falls risk (85).

Table 1.5. Potential side effects of anti-cholinergic medications in older adults

Mild	**Moderate**	**Severe**
Pupil dilation	Visual disturbances	Risk of falls
	Dizziness	Acute angle closure glaucoma
Mouth dryness	Disturbing dry mouth/thirst	Difficulty chewing, swallowing
	Speech difficulty	Impaired taste
	Reduced appetite	Mucosal damage
		Dental decay
	Oesophagitis	Faecal impaction
	Reduced gastric secretions and emptying	Altered absorption of medications
	Constipation	Paralytic ileus, pseudo-obstruction
Urinary hesitancy		Urinary retention
		Urinary tract infection
	Increased heart rate	Arrhythmia
		Exacerbation of angina
		Congestive heart failure
Decreased sweating		Heatstroke
Drowsiness	Excitement	Agitation and disorientation
Fatigue	Restlessness	
Mild amnesia	Confusion	Hallucinations, delirium
Inability to concentrate	Memory impairment	Ataxia, seizures
		Exacerbation of cognitive impairment

Adapted from Mintzer and Burns 2000 (86)

1.6 Summary

Observational studies are needed to provide evidence on the long term consequences of medication use in older populations. However, several methodological issues exist when analysing observational data. Little research has been devoted to considering and comparing the source of medication use data in older adults and examining reasons for discrepancies between sources. It is not known whether medication use varies in Ireland by eligibility to public healthcare, and hence whether this could confound any associations between medication use and health outcomes. In terms of accounting for confounding, few studies have examined the effect of variable selection on propensity score methods in comparison to multivariate regression.

Certain medication classes, in particular psychotropics, have been recurrently associated with falls in population-based studies. Polypharmacy has also been associated with falls, but studies suggest the association may not be significant when indications for the medicines are considered, and that polypharmacy only poses a risk if it includes falls risk-increasing medications. The anti-cholinergic activity of medications is a factor that could contribute to the association between psychotropic use and increased falls risk, and warrants further research.

1.7 Objectives

This research aims to demonstrate the value of performing pharmacoepidemiology in cohort studies and explore its limitations through an applied example of medication use as a risk factor for falling. The following details the objectives of the research undertaken using data from The Irish Longitudinal Study on Ageing (TILDA) and the HSE-PCRS pharmacy database, outlined by study:

Study I. (a) To assess the agreement between in-home interview and pharmacy data on prescription medications used regularly within fifteen therapeutic medication classes

(b) To examine patient-level predictors of discordance, including demographic factors (age, sex, education, marital status), cognitive function and mental health.

Study II. (a) To assess whether the rate of polypharmacy differs for adults with and without public healthcare coverage, and (i) to examine this further by assessing whether the use of major therapeutic classes differs by access to public healthcare.

(b) To compare approaches to account for confounding and examine the degree of additional effect modification after controlling for objective measures of health.

(c) To assess whether access to free medical practitioner visits and hospital services is a mediating factor.

Study III. (a) To assess the association between polypharmacy including established fall risk-increasing medications and subsequent falls, number of falls and injurious falls over two years of follow-up.

Study IV. (a) To assess the association between the use of medications with anti-cholinergic activity and subsequent falls and injurious falls over two years of follow-up.

(b) To examine the associations using both self-reported regular medication use data and linked pharmacy dispensing records in a subset.

2 Data sources

The following details the data sources and the assessment of medication use used in the thesis of: (i) the Irish Longitudinal Study on Ageing and (ii) the Health Service Executive - Primary Care Reimbursement Services pharmacy database.

2.1 The Irish Longitudinal study on Ageing

The Irish Longitudinal study on Ageing (TILDA) is a prospective study, representative of the community-dwelling over 50 year olds in Ireland. In its first wave undertaken from September 2009 to January 2011, TILDA recruited 8,175 individuals aged 50 years and over. Households in Ireland were assigned into geographic clusters, and a stratified randomly sample of clusters were approached to maintain a population representative sample. Each of the selected addresses was visited by a trained interviewer, who ascertained the eligibility of the address, and attempted to contact a household member and determine whether any individuals aged 50 or over lived at the address. All individuals aged 50 years or older and their partners (even if aged less than 50 years) were invited to be included in the study. Each participant underwent an extensive in home face-to-face interview, and was invited to complete a self-completion questionnaire (SCQ) and attend a nurse conducted health assessment. The overall response rate to the in home interview was 62.0%. The numbers who responded were compared to the 2006 Irish census and the 2010 Quarterly National Household Survey, and responders were found to have slightly higher education levels (87). Study weights are provided to weight TILDA participants back to national estimates based on educational attainment, age, sex, marital status, and geographic location.

TILDA was approved by the Faculty of Health Sciences Research Ethics Committee of Trinity College Dublin. Participants with dementia or with a cognitive impairment severe enough to prevent them from being able to personally consent to the study (determined at the discretion

of the interviewer) were excluded. The sample is described in further detail elsewhere (87), and the questionnaires are available from www.tcd.ie/tilda.

Below follows a description of the ascertainment of variables used in this thesis.

2.1.1 Self-reported medication use

Interviewers asked participants in their homes "to record all medications that you take on a regular basis, like every day or every week", and to provide medication packages so that interviewers could copy down the correct medication names. Assistance from relatives was permitted. Medications were assigned WHO Anatomic Therapeutic Chemical (ATC) Classification codes (88). Polypharmacy was defined as regular use of five or more medicines (excluding dietary supplements) (6).

2.1.2 Interview ascertained socio-demographics

Participants reported their age, sex, living situation (living alone, living with a spouse, living with others), marital status (married, single, widowed, divorced/separated), education (none/primary, junior certificate, leaving certificate, third/higher), location (Dublin, other city, rural), employment status (retired, part-time employed, full-time employed, self-employed, unemployed, incapacity, unpaid work), annual household income (<€10k, €10-20k, €20-40k, €40-70k, ≥€70k), and house value (renting, <€100k, €100-199k, €200-399k, €400-699k, >€700k).

2.1.3 Interview ascertained health variables

Doctor diagnosed health conditions were reported for the following: hypertension, angina, heart attack, heart failure, diabetes, transient ischaemic attack, high cholesterol, heart murmur, arrhythmia, stroke, other cardiovascular disease, cataracts, glaucoma, age related macular

degeneration, chronic lung disease, asthma, osteoporosis, cancer, arthritis, stomach ulcer, liver disease, varicose ulcer, Parkinson's disease, dementia, memory problems, anxiety, depression, or other psychological disorder (emotional problem, mood swings, hallucinations, schizophrenia, or other).

Participants self-reported urinary incontinence in the past 12 months, sleep problems (trouble falling asleep most of the time), and their vision and hearing (both excellent, very good, good, fair, or poor). Participants were asked if they were 'often troubled with pain?', and if so 'How bad is the pain most of the time?'. This was then categorised as mild, moderate or severe. Disability was reported as any limitations in Instrumental Activities of Daily Living (IADL) or Activities of Daily Living (ADLs) and the number of mobility impairments from a list of 11 (such as walking, climbing stairs, reaching, lifting). Falls related history included falls in the last year, injurious falls, fractures (hip or wrist) or blackouts or fainting.

Frequency of healthcare visits were recorded by the number of medical practitioner visits, hospital outpatient and inpatient visits in the previous year.

Depressive symptoms were assessed using the Centre for Epidemiologic Studies Depression Scale (89). Cognition was assessed using the animal naming test, where participants were asked to name as many different animals as possible in one minute. Delayed recall was measured as the number of words recalled from ten presented earlier in the interview. Participants also indicated their smoking status (current, past, never).

2.1.4 Self-completion questionnaire variables

A total of 6,912 (85%) participants returned a self-completion questionnaire. This included questions about perceptions of ageing, alcohol use, social activities, and quality of life. Anxiety symptoms were also assessed using the Hospital Anxiety and Depression Scale – Anxiety subscale (90).

2.1.5 Health assessment variables

Health assessments were either performed in a dedicated university centre or in the participant's home if travel was impracticable (*n*=5,898, 72%). Timed Up-and-Go (TUG) whereby participants rose from a chair, walked 3m, and returned to sitting was used as a measure of functional mobility (91). Handgrip strength was taken as the average for each hand measured using a Baseline dynamometer. Global cognition was assessed using the mini–mental state examination (MMSE) (92). Uncontrolled hypertension was defined as a systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg from the average of two seated readings (irrespective of antihypertensive use). Height and weight were measured using standard procedures for body mass index (BMI). Further details about the health assessment procedures can be found elsewhere (93).

2.1.5.1 Health assessment variables only recorded at the university centres

A total of 5,036 (62%) participants attended a university health assessment centre in Dublin or Cork. Here, a 4.88m gait mat was used to assess gait speed (cm/s) at usual walking pace. Orthostatic blood pressure was measured using continuous beat-to-beat plethysmography (Finometer) during active stand. Orthostatic hypotension severity was graded by sustained failure to return to at least 90% of baseline systolic blood pressure at 40 seconds post stand, and at 110 seconds post stand (94).

2.1.6 TILDA two-year follow-up

In TILDA's second wave (April - December 2012), 6831 participants were re-interviewed in their home. A total of 207 participants had died since wave 1, and 1,137 dropped out due to refusal or non-contact. To adjust for any differential dropout, study attrition weights are provided

based on age, gender, education, marital status, smoking status, medication use, and cognition, as well as their two-way interactions. See chapters 5 and 6 for more discussion on differential dropout. The mean (SD) time between the baseline and second interview was 24.3 (2.8) months, range 15.9 - 36.8 months.

2.2 Health Service Executive - Primary Care Reimbursement Services database

Approximately 40% of the Irish population is entitled to free healthcare (95). Among those under 70 years, eligibility is means tested and is available to those for whom medical expenses would cause undue hardship. For adults aged over 70 years higher thresholds were introduced in January 2009. Most eligible individuals (93%) are issued a 'medical card', enabling free medical practitioner and hospital visits and prescription medications at minimal cost (free before Oct 2010; €0.50 per item from Oct 2010 and €1.50 per item since Jan 2013). The remaining 7% are eligible for a General Practitioner Visit Card, enabling free medical practitioner visits, but no benefits regarding other services or prescription medications. Personal prescription expenditure is capped for all individuals (€120 per month in 2010, €144 per month since Jan 2013), but private insurance plans generally provide only limited benefits towards medical practitioner visit costs and none towards prescription medication costs.

The Health Service Executive - Primary Care Reimbursement Services (HSE-PCRS) pharmacy database contains information on all prescribed drugs dispensed under the Medical Card scheme. Data includes patient's age, gender and for each medicine dispensed; the non-proprietary drug name, proprietary drug name, strength and quantity dispensed. All prescription items are coded using the World Health Organisation (WHO) Anatomical Therapeutic Chemical (ATC) classification system (88).

3 Study I - Agreement between patient interview data on prescription medication use and pharmacy records in the over 50s varied by therapeutic group and reporting of indicated health conditions

3.1 Abstract

Objective: To estimate the agreement between interview ascertained medication use and pharmacy records among the population aged over 50, and to identify patient-level predictors of discordance.

Study Design and Setting: The Irish Longitudinal study on Ageing (TILDA) is representative of community-dwelling adults aged 50 and older in Ireland. Interview ascertained medication data from 2,621 participants were linked to pharmacy dispensing records. Kappa statistics measured the agreement between the two sources for nineteen therapeutic classes. Logistic regression assessed the effect of patient-level characteristics on survey under- and over-reporting of regularly dispensed medications.

Results: Agreement was good or very good (kappa=0.64-0.86) for fifteen medication classes, and moderate or poor for antiinflammatory and antirheumatic products (kappa=0.54), analgesics (kappa=0.50), psycholeptics (kappa=0.59), and ophthalmologicals (kappa=0.37). Not reporting an indicated health condition, less frequent dispensing, older age, and more medications regularly dispensed were associated with survey under-reporting, but results varied by therapeutic class. Memory and cognition were not associated with discordance.

Conclusion: Ascertaining medication use via patient interview seems a valid method for most medication classes and also captures non-prescription and supplement use. However, medications applied topically and as-needed may be under-reported. The source of medication data should be carefully considered when performing pharmacoepidemiological studies.

3.2 Introduction

Pharmacoepidemiological studies require reliable and valid ascertainment of medication use. Misclassification can bias risk estimates of medication use either towards or away from the null (19), i.e. either under- or over-estimate the true medication effects.

Pharmacy records and self-report data are often used to obtain information on medication use. Pharmacy records are potentially recorded more accurately, but may not represent actual use or be available for the population. Self-report (via a self-completed questionnaire, telephone interview, or face-to-face interview) provides information on medicines actually used as well as non-prescription use. Self-reporting may be inaccurate, but can be supplemented by a medication inventory, whereby all medication packages are presented to interviewers, reducing any recall problems. Comparison between pharmacy records and self-reported data is essential for improved understanding of the relative merits of each and the extent of potential misclassification of medication use in pharmacoepidemiological studies. Few studies have investigated the agreement between pharmacy records and self-report in older populations (20–22). For cardiovascular medications, only the Rotterdam Elderly Study has examined predictors of discordance, and found neither age, sex, education nor socio-economic status were associated (20).

These and other studies in the general population report mostly good agreement between self-report and pharmacy records, but agreement has varied significantly by therapeutic group, with less agreement for medications taken topically, as-needed, or for shorter periods (21,23,24). Studies in various settings report worse recall for those who are older (26–29), unmarried (26), and with less education (26,30). Yet medication recall often does not vary by gender (20,26–28,30), or income (29). Despite the potential importance of memory and cognition in recall ability, few studies have examined these and find mixed results (25,31,32).

We compared the agreement between in-home interview and pharmacy data on prescription medications used regularly within a population-based study of ageing in Ireland. Commonly used classes of medications were selected for comparison. Patient-level predictors of discordance were examined, including demographic factors previously reported on, as well conducting the most thorough examination to date of the role of cognitive function and mental health.

3.3 Methods

3.3.1 Study population

Data were retrieved from the Irish Longitudinal study on Ageing (TILDA) which is representative of the community-dwelling over 50s in Ireland. In its first wave undertaken from 2009 to 2011, TILDA recruited 8,175 individuals with each participant undergoing an extensive in home face-to-face interview, and being invited to complete a self-completion questionnaire (SCQ) and attend a health assessment. Households were selected from a stratified clustered sample of Irish residential addresses resulting in an overall response rate of 62.0%. A description of the sample and preliminary findings are available elsewhere (87).

In Ireland, the Medical Card scheme provides free GP and hospital visits and prescription medications at minimal cost to approximately 40% of the population (approximately 1.7 million). Medical Cards are available to those aged under 70 with low incomes or for whom medical expenses would cause undue hardship. For those aged over 70, the income threshold is higher resulting in most being eligible.

TILDA participants reporting Medical Card scheme coverage (n=3,975) were asked for consent to link their medical records and to provide their unique Medical Card number (n=2,862) to allow linkage. TILDA was approved by the Faculty of Health Sciences Research Ethics Committee of Trinity College Dublin, and participants provided written informed consent prior to

participation in the study. Participants with dementia or with a cognitive impairment severe enough to prevent being able to personally consent to the study (determined at the discretion of the interviewer) were not included in the study.

3.3.1.1 Self-reported medication data

Interviewers asked participants in their homes "to record all medications that you take on a regular basis, like every day or every week", and to provide medication packages to copy down the correct medication names. Assistance from relatives was permitted. Medications were assigned WHO Anatomic Therapeutic Chemical (ATC) Classification codes (88). An experienced pharmacist (JP) coded each medication as likely prescribed or not based on the proprietary name. Medications included in this analysis were those likely prescribed.

3.3.1.2 Self-reported health data

Within the home interview, the number of doctor diagnosed chronic diseases (categorised as 0, 1, 2, or >2) were reported from the following: heart disease, cataracts, hypertension, high cholesterol, stroke, diabetes, lung disease, asthma, arthritis, osteoporosis, cancer, Parkinson's disease, peptic ulcer or hip fracture. Participants also self-reported pain (moderate or severe), urinary incontinence in the past 12 months, and sleep problems (trouble falling asleep most of the time). We examined whether participants reported one of the main indicated health condition(s) in the survey for each therapeutic group they were regularly dispensed.

Depression was defined as scoring 16 or greater on the Center for Epidemiologic Studies Depression Scale (CES-D) during the interview (89). Anxiety was defined as scoring 8 or greater on the Hospital Anxiety and Depression Scale – Anxiety subscale (HADS-A) within the SCQ (90). Poor delayed recall was defined as recalling three or fewer words from ten presented earlier in the

interview. Poor cognition was defined as a mini–mental state examination (MMSE) score of 24 or lower in the health assessment (92).

3.3.2 Pharmacy records

The Health Service Executive - Primary Care Reimbursement Services (HSE-PCRS) pharmacy database contains information on all prescribed drugs dispensed under the Medical Card scheme. Data includes patient's age, gender and for each medicine dispensed; the non-proprietary drug name, proprietary drug name, strength and quantity dispensed. All prescription items are coded using the WHO ATC classification system. Pharmacy claims data were extracted for the 6 months prior to each participant's TILDA interview. A medication was considered used regularly if it was dispensed at least three times in the past six months with at least one dispensing episode in the past month.

3.3.3 Linkage

The TILDA ('survey') and HSE-PCRS ('pharmacy') datasets were linked by matching the 8 digit unique Medical Card number and additionally at least two of birth month, birth year and sex. If birth year was the only mismatch, the discrepancy had to be within 10 years. One-digit modifications to the Medical Card number were allowed to enable successful linkage. Once the linkage was completed, all unique identifiers were removed from the merged data set for analysis. The selection process for participants with linked pharmacy records (n=2,621) is displayed in figure 3.1. The majority (95%) additionally matched on sex, birth year and month.

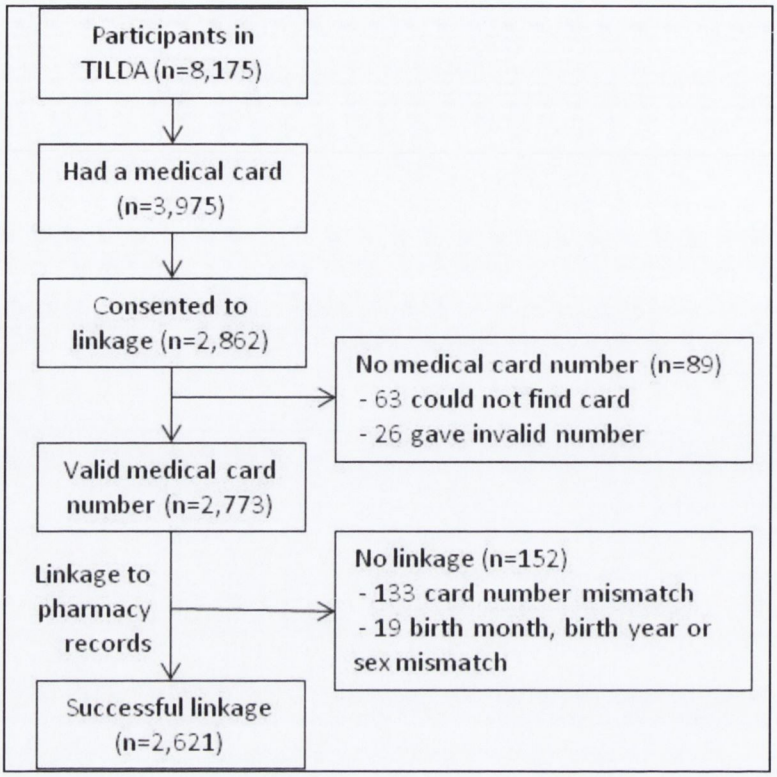


Figure 3.1. Selection of participants with pharmacy record linkage

3.3.3.1 Medication-level and person-level matching

Medications from pharmacy records and self-reported data were compared using the ATC code both at the medication level and within classes at the person level. At the medication-level, medications were compared on the full 5th level ATC code.

At the person-level, participants were separately categorised if they reported regular medication use or were regularly dispensed medications from each of nineteen ATC 2nd level therapeutic classes (classes with >5% prevalence in either dataset). As we suspected better reporting for medications dispensed more frequently, we defined high frequency dispensing as six or more dispensing episodes within that class in the previous 6 months, and low frequency dispensing as 3-5 dispensing episodes in the previous 6 months.

3.3.4 Statistical methods

Frequencies of patient characteristics were compared between those with and without data linkage using multivariable logistic regression. For the medication-level matching, the proportions of survey reported medications that were regularly dispensed and ever dispensed in the last 6 months, were summarised in ATC 1st level classes.

The following analyses were all performed at the person-level by comparing use within nineteen therapeutic classes. Agreement between the pharmacy and survey data was assessed using the kappa statistic as neither source was considered a gold standard. Interpretation of the value of kappa was guided as follows: poor (<0.20), fair (0.20-0.40), moderate (0.41-0.60), good (0.61-0.80), and very good (0.81-1.00) (96).

Logistic regression was used to examine patient-level characteristics associated with both survey under-reporting (omitted in the survey when regularly dispensed) and survey over-reporting (reported in the survey when never dispensed in the last 6 months) in each therapeutic group. Patient-level characteristics included sex, age, marital status (married or not), low education (none/primary), the number of medications regularly dispensed, low dispensing frequency (3-5 versus 6+ episodes), indication reported, depression, anxiety, poor recall and poor cognition. We adjusted for multiple testing by controlling the False Discovery Rate at 0.05 for each factor investigated (97). Multivariate logistic regression was performed for each therapeutic class by adjusting for age, sex, annual household income, number of medications regularly dispensed, dispensing frequency, indication reported, and any statistically significant predictors ($p<0.05$) in the univariate analysis.

Sensitivity analyses performed for the agreement analyses included: 1) a stricter definition of 'regular use' within the pharmacy records of 4+ prescriptions in the last 6 months including one in the last month, and 2) including all medications reported in the survey (i.e. not just those likely prescribed). The effect of interviewer variation on the prediction of survey under-

and over-reporting was tested by adding a random effect for the 126 interviewers administering the surveys. Analyses were performed using SAS Version 9.1 and Stata Version 12.0.

3.4 Results

The characteristics of 2,621 participants with linked pharmacy records compared to those without are displayed in table 3.1. Participants with linked pharmacy records were mostly women (56%) and had an average (SD) age of 69 (10) years. See supplementary material (chapter 3.6) for a comparison of the differences between those with and without pharmacy linkage.

Table 3.1. Characteristics of participants with linked pharmacy records by Medical Card coverage

	Medical Card		
	Linkage (N=2,621)	No linkage (N=1,354)	No Medical Card (N=4,114)
Sex – women	1,465 (56%)	780 (58%)	2,138 (52%)
Age (years), mean (SD)	69.1 (10.0)	67.8 (10.2)	59 (6.6)
Married	1,475 (56%)	743 (55%)	3,189 (78%)
Primary/no education	1,252 (48%)	593 (44%)	613 (15%)
Not employed	2,305 (88%)	1,117 (82%)	1,750 (43%)
Household income < €20,000†	1,187 (45%)	602 (45%)	551 (13%)
3+ chronic health conditions	1,032 (39%)	424 (31%)	676 (16%)
Poor cognition (MMSE≤24) †	136 (5%)	55 (4%)	41 (1%)
Poor delayed recall †	661 (26%)	329 (25%)	335 (8%)
Depression (CES-D≥16) †	327 (13%)	173 (13%)	265 (6%)
Anxiety (HADS-A≥8) †	505 (19%)	264 (20%)	834 (20%)
Polypharmacy‡	871 (33%)	305 (23%)	364 (9%)

Abbreviations: MMSE, mini–mental state examination; CES-D, Center for Epidemiologic Studies Depression Scale; HADS-A, Hospital Anxiety and Depression Scale – Anxiety subscale.

† Missing data: 8% missing income, 27% missing cognition, 2% missing delayed recall, 2% missing depression, 18% missing anxiety.

‡ Polypharmacy defined as reporting regular use of 5 or more prescription medications

3.4.1 Medication-level comparisons

In the survey 9,327 prescription medicines were self-reported, after excluding 385 non-prescription products. In the pharmacy records, 18,940 prescription medications were dispensed in the 6 months prior to the survey interview, with 9,217 of these dispensed regularly.

Of the prescription medications reported in the survey, 90% (n=8,348) were dispensed in the last 6 months in the pharmacy records. Of the medications dispensed regularly, 72% (n=6,625) were reported in the survey. This proportion was greater than 55% in all but three classes; dermatologicals (3%, n=2), antiinfectives for systemic use (39%, n=41), and sensory organ drugs (30%, n=54). In all classes at least 70% of survey medications were dispensed at least once in the last 6 months, except for dermatologicals (48%, n=11).

In the sensitivity analysis, the proportion of medications regularly dispensed that were self-reported only increased from 72% to 73% when either separately including likely non-prescription medications in the survey or when using the stricter definition of regular use in the pharmacy claims data.

3.4.2 Person-level agreement

The nineteen therapeutic classes examined include 88% of the self-reported and 87% of the regularly dispensed medications. Antithrombotic agents, agents acting on the renin-angiotensin system and lipid modifying agents were more often reported in the survey, but analgesics and psycholeptics were reported less often compared to the pharmacy records (table 3.2). Agreement was good or very good (kappa=0.64-0.86, $p<0.001$) for fifteen classes, but moderate for antiinflammatory and antirheumatic products (kappa=0.54), analgesics (kappa=0.50), and psycholeptics (kappa=0.59), and poor for ophthalmologicals (kappa=0.37).

Using the stricter definition of 'regular use' in the pharmacy data did not substantially alter these results (table 3.3).

Table 3.2. Agreement between regular prescription medicine use captured in the survey and pharmacy records, assessing the prevalence and agreement by common therapeutic groups

	Reported in the survey				Regularly dispensed in pharmacy records				
Therapeutic group (ATC class)	Prevalence	Total	Regularly dispensed	%	Prevalence	Total	Survey reported	%	kappa (95% CI)
Drugs for acid related disorders (A02)	23%	613	458	75%	23%	612	458	75%	0.67 (0.63 - 0.71)
Drugs used in diabetes (A10)	9%	240	193	80%	8%	205	193	94%	0.86 (0.82 - 0.89)
Mineral supplements (A12)	10%	254	179	70%	10%	262	179	68%	0.66 (0.62 - 0.70)
Antithrombotic agents (B01)	37%	982	757	77%	33%	871	757	87%	0.72 (0.68 - 0.76)
Cardiac therapy (C01)	6%	167	121	72%	6%	161	121	75%	0.72 (0.68 - 0.76)
Diuretics (C03)	15%	395	320	81%	15%	398	320	80%	0.77 (0.73 - 0.81)
Beta blocking agents (C07)	22%	577	456	79%	19%	508	456	90%	0.80 (0.76 - 0.84)
Calcium channel blockers (C08)	14%	376	294	78%	14%	356	294	83%	0.77 (0.73 - 0.81)
Agents acting on the renin-angiotensin system (C09)	35%	917	735	80%	31%	802	735	92%	0.78 (0.75 - 0.82)
Lipid modifying agents (C10)	41%	1,068	821	77%	35%	910	821	90%	0.73 (0.69 - 0.77)
Urologicals (G04)	6%	163	125	77%	7%	186	125	67%	0.70 (0.66 - 0.73)
Thyroid therapy (H03)	9%	245	185	76%	8%	201	185	92%	0.81 (0.78 - 0.85)
Antiinflamatory and antirheumatic products (M01)	11%	286	158	55%	10%	252	158	63%	0.54 (0.50 - 0.58)
Drugs for treatment of bone diseases (M05)	7%	194	142	73%	8%	213	142	67%	0.67 (0.63 - 0.71)
Analgesics (N02)	9%	235	154	66%	12%	324	154	48%	0.50 (0.46 - 0.54)
Psycholeptics (N05)	12%	306	229	75%	15%	403	229	57%	0.59 (0.55 - 0.63)
Psychoanaleptics (N06)	11%	291	217	75%	12%	308	217	70%	0.69 (0.65 - 0.73)
Drugs for obstructive airway diseases (R03)	10%	254	174	69%	10%	262	174	66%	0.64 (0.60 - 0.68)
Ophthalmologicals (S01)	3%	67	41	61%	5%	140	41	29%	0.37 (0.34 - 0.41)

Table 3.3 Agreement between regular* prescription medicine use captured in the survey and pharmacy records, assessing the prevalence and agreement by common therapeutic groups

	Reported in the survey				Regularly* dispensed in pharmacy records				
Therapeutic group (ATC class)	Prevalence	Total	Regularly dispensed	%	Prevalence	Total	Survey reported	%	kappa (95% CI)
Drugs for acid related disorders (A02)	23%	613	433	71%	22%	574	433	75%	0.65 (0.61 - 0.69)
Drugs used in diabetes (A10)	9%	240	186	78%	8%	198	186	94%	0.84 (0.80 - 0.87)
Mineral supplements (A12)	10%	254	167	66%	9%	244	167	68%	0.64 (0.60 - 0.67)
Antithrombotic agents (B01)	37%	982	732	75%	32%	843	732	87%	0.70 (0.66 - 0.74)
Cardiac therapy (C01)	6%	167	118	71%	6%	152	118	78%	0.72 (0.68 - 0.76)
Diuretics (C03)	15%	395	311	79%	15%	385	311	81%	0.76 (0.72 - 0.80)
Beta blocking agents (C07)	22%	577	443	77%	19%	493	443	90%	0.78 (0.75 - 0.82)
Calcium channel blockers (C08)	14%	376	283	75%	13%	342	283	83%	0.75 (0.72 - 0.79)
Agents acting on the renin-angiotensin system (C09)	35%	917	719	78%	30%	782	719	92%	0.77 (0.74 - 0.81)
Lipid modifying agents (C10)	41%	1,068	795	74%	34%	881	795	90%	0.71 (0.67 - 0.75)
Urologicals (G04)	6%	163	123	75%	7%	181	123	68%	0.70 (0.66 - 0.73)
Thyroid therapy (H03)	9%	245	182	74%	8%	197	182	92%	0.81 (0.77 - 0.85)
Antiinflamatory and antirheumatic products (M01)	11%	286	144	50%	8%	220	144	65%	0.52 (0.49 - 0.56)
Drugs for treatment of bone diseases (M05)	7%	194	137	71%	8%	206	137	67%	0.66 (0.62 - 0.70)
Analgesics (N02)	9%	235	145	62%	11%	283	145	51%	0.51 (0.47 - 0.55)
Psycholeptics (N05)	12%	306	222	73%	14%	377	222	59%	0.60 (0.56 - 0.64)
Psychoanaleptics (N06)	11%	291	207	71%	11%	294	207	70%	0.67 (0.63 - 0.71)
Drugs for obstructive airway diseases (R03)	10%	254	164	65%	9%	241	164	68%	0.63 (0.59 - 0.67)
Ophthalmologicals (S01)	3%	67	41	61%	5%	127	41	32%	0.40 (0.37 - 0.44)

* regularly dispensed defined as dispensed 4+ times in the last 6 months including the last month

3.4.3 Predictors of discordance

Sex, marital status, education, depression, anxiety, cognition and poor recall were not associated with under-reporting (table 3.4). After allowing for multiple testing, older age was associated with under-reporting of calcium channel blockers, drugs for the treatment of bone diseases and analgesics (table 3.5). In contrast older adults were more likely to report regularly dispensed urologicals. Less frequent dispensing was associated with under-reporting of five classes (cardiac therapy, antiinflamatory and antirheumatic products, analgesics, psycholeptics, and drugs for obstructive airway diseases). Those with a greater number of different medications regularly dispensed were less likely to report their lipid modifying agents and drugs for the treatment of bone diseases. The effect of interviewer was not statistically significant.

The strongest determinant of successfully reporting a regularly dispensed medication class was whether the participant had also reported being diagnosed with one of the main indications. For example, those reporting a doctor's diagnosis of diabetes were far more likely to report their regularly dispensed diabetes medication than those not reporting a diagnosis. This association was observed for 14 of the 19 therapeutic classes examined. Figure 3.2 shows the probability of reporting medications from each therapeutic class given one was regularly dispensed, stratified by whether a main indication was reported.

These associations remain significant after multivariate adjustment, except for the associations between indication and both analgesics and psychoanaleptics, and between dispensing frequency and drugs for obstructive airway diseases, which were both significantly attenuated.

Over-reporting of medication use was less common in comparison. Of 7,098 medication classes reported (from the 19), medications were never dispensed in the previous 6 months for 532 (7%) of these classes. No patient-level characteristics were associated with over-reporting after adjusting for multiple testing (see supplementary material for results).

Table 3.4. Odds ratios (with 95% confidence intervals) for the association between demographic factors, cognition, memory and mental health and failure to report regularly dispensed medications by therapeutic group

Therapeutic group (ATC class)	Female	Married	No/primary education	Poor cognition†	Poor recall†	Depression†	Anxiety†
Drugs for acid related disorders (A02)	1.1 (0.7-1.5)	1.1 (0.8-1.6)	0.9 (0.7-1.4)	1.0 (0.5-2.0)	0.9 (0.6-1.4)	0.8 (0.5-1.3)	1.1 (0.7-1.7)
Drugs used in diabetes (A10)	1.2 (0.4-3.9)	0.7 (0.2-2.4)	1.6 (0.5-5.4)	n/a	0.7 (0.2-2.8)	n/a	0.3 (0.0-2.7)
Mineral supplements (A12)	1.5 (0.7-3.2)	1.1 (0.7-1.9)	1.4 (0.8-2.3)	1.8 (0.7-4.7)	0.8 (0.4-1.5)	0.9 (0.4-1.8)	0.9 (0.4-1.8)
Antithrombotic agents (B01)	1.2 (0.8-1.8)	0.8 (0.5-1.1)	1.1 (0.8-1.7)	1.6 (0.8-3.1)	1.5 (1.0-2.3)	1.1 (0.6-2.0)	1.1 (0.7-1.9)
Cardiac therapy (C01)	1.5 (0.7-3.1)	0.9 (0.5-1.9)	1.7 (0.8-3.8)	2.5 (0.6-9.6)	1.1 (0.5-2.4)	1.4 (0.5-3.8)	2.3 (0.9-6.2)
Diuretics (C03)	1.4 (0.8-2.3)	0.9 (0.5-1.4)	1.3 (0.8-2.2)	0.6 (0.2-2.0)	0.9 (0.5-1.5)	1.6 (0.8-3.1)	1.9 (1.0-3.6)
Beta blocking agents (C07)	1.2 (0.7-2.1)	1.1 (0.6-1.9)	1.1 (0.6-1.9)	2.0 (0.7-5.6)	1.0 (0.5-1.9)	1.5 (0.7-3.3)	1.6 (0.8-3.3)
Calcium channel blockers (C08)	1.3 (0.7-2.3)	0.7 (0.4-1.1)	1.1 (0.7-2.0)	1.1 (0.4-3.0)	1.5 (0.8-2.7)	1.1 (0.5-2.6)	1.1 (0.5-2.4)
Agents acting on the renin-angiotensin system (C09)	0.9 (0.5-1.4)	0.9 (0.5-1.4)	0.8 (0.5-1.3)	1.6 (0.6-4.3)	0.8 (0.5-1.5)	1.7 (0.8-3.3)	1.9 (1.0-3.4)
Lipid modifying agents (C10)	1.0 (0.6-1.5)	1.4 (0.9-2.2)	0.9 (0.6-1.4)	0.6 (0.2-1.9)	1.4 (0.9-2.2)	0.6 (0.3-1.2)	1.0 (0.6-1.8)
Urologicals (G04)	0.8 (0.4-1.6)	0.7 (0.4-1.3)	1.4 (0.7-2.5)	0.3 (0.1-1.3)	0.6 (0.3-1.2)	1.1 (0.4-2.6)	1.3 (0.6-2.8)
Thyroid therapy (H03)	0.9 (0.2-3.4)	0.8 (0.3-2.3)	1.9 (0.6-5.7)	3.0 (0.6-5.9)	0.4 (0.1-1.9)	2.7 (0.8-9.1)	5.8 (1.8-9.1)
Antiinflamatory and antirheumatic products (M01)	0.8 (0.5-1.4)	1.3 (0.8-2.2)	0.8 (0.5-1.4)	1.1 (0.3-3.5)	1.2 (0.7-2.2)	1.0 (0.5-2.0)	1.1 (0.6-2.2)
Drugs for treatment of bone diseases (M05)	0.7 (0.3-1.7)	0.7 (0.4-1.2)	1.1 (0.6-2.0)	2.6 (0.9-7.5)	1.3 (0.7-2.5)	1.5 (0.6-3.6)	0.5 (0.2-1.4)
Analgesics (N02)	0.7 (0.5-1.1)	1.2 (0.8-1.8)	1.9 (1.2-3.0)	1.5 (0.6-3.7)	0.7 (0.4-1.1)	0.5 (0.3-0.9)	0.8 (0.5-1.4)
Psycholeptics (N05)	1.3 (0.8-2.0)	1.4 (1.0-2.1)	0.9 (0.6-1.3)	0.7 (0.3-1.6)	0.8 (0.5-1.2)	0.5 (0.3-0.8)	0.6 (0.4-0.9)
Psychoanaleptics (N06)	1.8 (1.1-3.2)	1.7 (1.0-2.8)	1.3 (0.8-2.1)	0.9 (0.4-2.2)	1.0 (0.6-1.7)	0.6 (0.4-1.1)	0.8 (0.5-1.4)
Drugs for obstructive airway diseases (R03)	1.2 (0.7-2.0)	0.8 (0.5-1.3)	1.0 (0.6-1.6)	1.2 (0.5-3.0)	1.0 (0.6-1.9)	0.9 (0.4-1.8)	0.8 (0.4-1.5)
Ophthalmologicals (S01)	0.9 (0.4-2.0)	1.2 (0.6-2.6)	0.9 (0.4-1.9)	0.5 (0.1-2.3)	0.9 (0.4-2.0)	0.4 (0.2-1.1)	0.5 (0.2-1.4)

† Missing data: 31% missing cognition, 2% missing delayed recall, 2% missing depression, 20% missing anxiety.
n/a = not applicable due to insufficient numbers

Table 3.5. Odds ratios (with 95% confidence intervals) for patient-level factors associated with failure to report regularly dispensed medications by therapeutic group

Therapeutic group (ATC class)	Age (per 10 years)	Low dispensing frequency	Number of medications regularly dispensed	Main indication(s) in survey	Any main indication reported
Drugs for acid related disorders (A02)	1.0 (0.9-1.3)	1.2 (0.7-2.0)	1.0 (0.9-1.0)	Stomach ulcer	0.6 (0.3-1.0)
Drugs used in diabetes (A10)	2.3 (1.1-4.6)	1.4 (0.2-1.5)	1.0 (0.9-1.2)	Diabetes	0.1* (0.0-0.5)
Mineral supplements (A12)	1.3 (1.0-1.7)	1.3 (0.7-2.6)	1.0 (1.0-1.1)	Osteoporosis	0.5* (0.3-0.9)
Antithrombotic agents (B01)	1.3 (1.0-1.6)	0.7 (0.3-1.6)	1.0 (0.9-1.1)	Heart attack, Stroke, TIA, Angina	0.6* (0.4-0.9)
Cardiac therapy (C01)	1.4 (0.8-2.3)	4.7* (1.6-3.7)	1.0 (0.9-1.1)	Abnormal Heart Rhythm, Heart failure	0.4* (0.2-0.9)
Diuretics (C03)	0.9 (0.7-1.2)	1.2 (0.5-2.7)	1.0 (0.9-1.1)	Hypertension, Heart failure	0.8 (0.5-1.4)
Beta blocking agents (C07)	0.9 (0.6-1.2)	0.5 (0.1-2.3)	1.1 (1.0-1.2)	Hypertension, Heart failure, Angina, Abnormal Heart Rhythm	0.7 (0.3-1.5)
Calcium channel blockers (C08)	1.7* (1.2-2.4)	1.1 (0.4-2.7)	1.1 (1.0-1.2)	Hypertension, Angina	0.3* (0.2-0.6)
Agents acting on the renin-angiotensin system (C09)	1.4 (1.0-1.8)	1.6 (0.7-3.9)	1.1 (1.0-1.2)	Hypertension, Heart attack	0.3* (0.2-0.6)
Lipid modifying agents (C10)	1.0 (0.8-1.3)	1.5 (0.8-3.0)	1.1* (1.0-1.2)	High Cholesterol, Heart attack, Stroke, TIA	0.5* (0.3-0.7)
Urologicals (G04)	0.6* (0.5-0.9)	1.4 (0.6-3.7)	1.0 (1.0-1.1)	Urinary incontinence (women only)	0.5 (0.1-1.9)
Thyroid therapy (H03)	1.1 (0.6-2.0)	2.3 (0.5-1.2)	1.1 (1.0-1.2)	n/a	n/a
Antiinflamatory and antirheumatic products (M01)	1.0 (0.7-1.3)	2.4* (1.3-4.3)	1.0 (1.0-1.1)	Arthritis, Pain	0.3* (0.2-0.6)
Drugs for treatment of bone diseases (M05)	1.6* (1.1-2.2)	0.8 (0.3-2.0)	1.1* (1.1-1.2)	Osteoporosis	0.4* (0.2-0.7)
Analgesics (N02)	1.4* (1.2-1.8)	2.9* (1.7-5.1)	1.0 (1.0-1.1)	Pain, Cancer, Arthritis	0.4* (0.2-0.8)
Psycholeptics (N05)	1.1 (0.9-1.3)	5.0* (2.6-9.6)	0.9 (0.9-1.0)	Any emotional problem†, sleep problems, alcohol/substance abuse	0.3* (0.2-0.5)
Psychoanaleptics (N06)	1.1 (0.9-1.4)	1.4 (0.6-3.0)	1.0 (0.9-1.1)	Any emotional problem†, serious memory impairment‡	0.3* (0.2-0.5)
Drugs for obstructive airway diseases (R03)	0.9 (0.7-1.2)	2.3* (1.2-4.4)	0.9 (0.9-1.0)	Chronic lung disease, asthma	0.3* (0.2-0.6)
Ophthalmologicals (S01)	0.8 (0.5-1.3)	5.3 (1.2-3.5)	0.9 (0.8-1.0)	Glaucoma, Other eye disease	0.4* (0.2-0.9)

*Associations significant after adjusting for multiple testing.

† Any emotional problem includes self-reported doctor's diagnosis of 'Any emotional, nervous or psychiatric problems, such as depression or anxiety'.

‡ Serious memory impairment includes self-reported doctor's diagnosis of dementia, Alzheimer's disease, or serious memory impairment

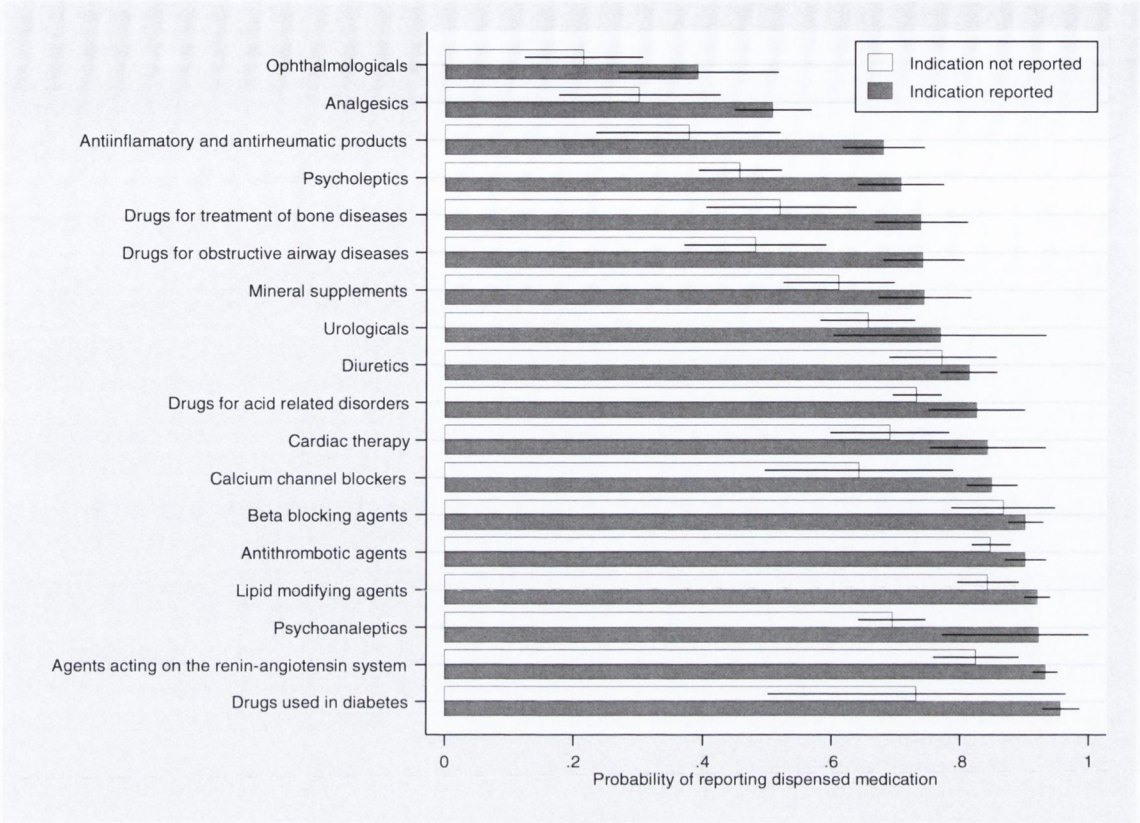


Figure 3.2. Proportion (with 95% confidence intervals) of participants self-reporting regularly dispensed medications by therapeutic class and reporting of a main indication

3.5 Discussion

Within a population-based study of ageing, we found good agreement between self-reports of regular prescription medication use and pharmacy records. Agreement was poorer for medications applied topically or used 'as-needed', and for psycholeptics. Not reporting an indicated health condition, less frequent dispensing and older age were generally associated with poorer self-reporting of regularly dispensed medications, however associations varied by class.

The level of agreement was comparable to that reported in similar studies. The Three-City Study reported similar agreement across medication classes depending on the time-frame analysed in the pharmacy records (21). Slightly larger kappas were reported for psycholeptics and psychoanaleptics in the Finnish intervention study of over 75s (22), although kappa statistics may be influenced by the greater prevalence of medication use. The proportion of concordance within

cardiovascular medications was similar to that found in the Rotterdam study (20). In line with others studies (21,23,24), we found poorer concordance for medications applied topically and as-needed. Medications applied topically may not be perceived as medications (98), and those used as-needed may not be perceived as used regularly. Similar to a Danish study of medication use in the general population (23), we found only moderate agreement for psycholeptics suggesting a potential stigmatisation bias (99), as only 46% of the regularly dispensed anxiolytics (ATC N05B) were reported in the survey. Also medications kept by the bedside might have been forgotten when taking packages to the interviewer, for example only 56% of the regularly dispensed hypnotics and sedatives (ATC N05C) were reported in the survey.

Few demographic factors were associated with under-reporting, similar to findings from the Rotterdam study (20). We observed a weaker association between older age and poorer reporting than studies that did not use face-to-face interviews or medication inventories (26–29), suggesting that these may reduce age effects. Very few effects of cognition or mental health were found, in line with previous research (25,31,32), suggesting that recall bias in older populations is minimal when medications are ascertained in the home with the assistance of relatives.

The strongest predictor of reporting a regularly dispensed medication was reporting an indicated health condition, which to our knowledge has not been previously shown. It is not clear why those who fail to report a diagnosed health condition were more likely to fail to report an associated medication, but stigma, poor health awareness and poor adherence may be underlying factors. Previous studies have suggested that knowledge of their medications' indications may be poor among older people (25,100), and that the communication style between physician and patient can strongly predict verbal recall of prescription medications (31). Knowledge about indications has implications for adherence, patient-doctor communication, and knowledge about adverse effects (100). The factors underlying this finding need further exploration.

We found under-reporting of two medication classes among those regularly dispensed more medications. Recall also reduced for those prescribed more medications in a previous

cohort study (27). Studies have also shown better agreement for medications taken for longer periods (27,30). While we did not examine duration, we found medications dispensed more frequently were more likely to be reported in some classes. This may be due to the interpretation of 'regular' use by participants when considering medications used for a short period of time.

Previous concordance studies have highlighted the need to carefully consider the time window examined in the pharmacy records (21–23,101). Most studies use fixed-time periods (20–24,26,101), but often suggest the optimum period may vary by drug (21–23). Studies comparing use of a legend-time method to estimate the actual period of drug use based on daily defined doses (DDDs) (20,23,101), were often limited by DDDs being unavailable for some medications, and conclude they confer no real advantages over fixed-time periods. The way medication use is asked in the survey and the dispensing rules of the country also need to be taken into consideration (22,101). As the interview called for regular medication use, and most prescriptions are dispensed at least monthly under the scheme, we used two definitions; the main definition based on frequency of use (3 episodes within a 6 month period) and another based on any use in 6 months. We also performed a sensitivity analysis on the main definition and found little change to the results.

The main strength of our study was the use of a large population-based cohort who underwent a detailed assessment of their socio-economic characteristics, mental and cognitive health, allowing us to examine predictors of discordance individually for nineteen commonly used therapeutic classes. The linkage of the survey data to the pharmacy dispensing records was reliable.

However, pharmacy linkage was not available for all study participants, mainly due to pharmacy records only existing for those covered by public healthcare schemes. Participants with pharmacy records were older, had less education, lower incomes and fewer were employed than in the general population. They also reported more chronic diseases, medications, and depressive symptoms. Of those with a medical card, participants with linked pharmacy records were likely to

not be employed, not have symptoms of anxiety, and to have reported more medications taken regularly (see supplementary material in chapter 3.6). The agreement reported would therefore likely under-estimate the agreement among the over 50s. Associations with survey under-reporting are not likely to be affected by the participant selection, as results mostly remained unchanged in the multivariable analysis. The MMSE and anxiety questionnaires were only completed by a subsample of participants, however a missing MMSE score was not associated with under-reporting of any medication class and delayed recall, which was completed for 98% of the sample, showed no association with agreement. TILDA also excluded those with dementia; however individuals with dementia are unlikely to be asked to self-report their medications in an epidemiological context. Not completing the anxiety questionnaire was only associated with one class (Drugs for treatment of bone diseases), so the association between anxiety and this class should be interpreted with caution.

The pharmacy records are considered accurate, but may be incomplete for participants newly eligible for a Medical Card. However, the pharmacy database represents the vast majority Medical Card dispensing and indeed 90% of survey reported medications could be traced back to the pharmacy records. In the survey prescription status was not ascertained, but our classification seemed robust as including all medications did not add many matches to the regularly dispensed medications.

Discordance between self-report and pharmacy records could be caused by 1) poor adherence to prescribed medications, 2) inaccurate reporting through for example poor memory, lack of interest, poor health awareness, or stigma, or 3) methodological issues e.g. defining regular use, questionnaire design, interviewer error, or pharmacy database coverage. Most of our findings are consistent with poor adherence being partly responsible for discordance. Medication classes we found with only moderate agreement, e.g. hypnotics, analgesics, bronchodilators, benzodiazepines and symptomatic drugs, have been identified as being poorly adhered to in the elderly (25,102,103). Lack of insight into illness has also been identified as a major predictor of

poor adherence (104), and adherence decreases with more medications taken (105). However, we found no relationship between depression and cognition and discordance, which are often identified as major predictors of poor adherence (104), suggesting this does not fully explain the discordance in this study. Strong associations with reporting the indication suggest health awareness is important. Stigmatisation bias also potentially affects the reporting of psychotropics and urologicals. Interviewer variation had no effect on recall suggesting that interviewer were trained and performed uniformly.

Future studies ascertaining medication use should take adequate care over questionnaire design. A systematic review found that questionnaire design was an important factor in the recall of medications (106). Recall improved when using indication-oriented questions and pictures as memory aids (30,106). Best practice would be to also perform a medication inventory (107), with linkage to pharmacy records to supplement or assess agreement where possible. Interviewers should be encouraged to prompt participants to remember medications kept in other places, e.g. the bed side, and to tease out more information on topical medications and those used as-needed.

For researchers conducting pharmacoepidemiological analyses, the source of medication data requires careful consideration depending on the purpose of the analysis (21). Pharmacy data may better capture current use, use of medications taken topically and as-needed, and include information on dose and duration, but may not be available for the whole population. On the other hand interview data may better capture medications used chronically and adhered to and over-the-counter use. Differential misclassification appears minimal across socio-demographic and cognitive factors, although care should be taken when analysing the effects of medications whose reporting is known to be affected by stigmatisation bias.

In summary, ascertaining medication use via patient interview is valid in the over 50s. Agreement was moderate or poor for only a small proportion of therapeutic classes (those applied topically and as-needed) and associated with not reporting an indicated health condition,

and in some classes less frequent dispensing and older age. When performing pharmacoepidemiological studies, the source of medication data should be adequately considered.

3.6 Supplementary material

Table 3.6 provides further detail on the characteristics of those with linked pharmacy records compared to those with a medical card and compared to the rest of TILDA. Associations are provided as unadjusted odds ratios (with 95% CI) and as multivariable odds ratios adjusted for the characteristics in the table. Backwards stepwise logistic regression was used retaining $p<0.2$ to build the multivariable models (108). Compared to those in TILDA without linked pharmacy records, participants with linked records were older, had less education, lower incomes, fewer were employed, and they reported more chronic diseases, symptoms of depression and more medications taken regularly. Of those with a medical card, participants with linked pharmacy records were likely to not be employed, not have symptoms of anxiety, and to have reported more medications taken regularly.

Tables 3.7 and 3.8 display the associations between patient-level characteristics and survey over-reporting (medications reported in the survey when never dispensed in the last 6 months) in each therapeutic group. Only one association was statistically significant. Older age was associated with less over-reporting of lipid modifying agents (Odds ratio, 0.70 per 10 years; 95% CI 0.53-0.93), but this was not significant after adjustment for multiple testing.

Table 3.6. Odds ratios (with 95% confidence intervals) for the associations between characteristics of participants with and without linked pharmacy records

		Predictors of linkage in the medical card population						Predictors of linkage in the TILDA dataset					
		Univariate results			Multivariate results*			Univariate results			Multivariate results*		
Characteristic		OR	95% CI	P	OR	95% CI	p	OR	95% CI	p	OR	95% CI	P
Sex - women		0.93	0.82 - 1.06	0.30	n/a			1.11	1.01 - 1.22	0.03	n/a		
Age, mean (SD) years		1.01	1.01 - 1.02	<0.001	1.01	1.00 - 1.01	0.16	1.09	1.09 - 1.10	<0.001	1.06	1.05 - 1.07	<0.001
Education	Primary/none	1.00			1.00			1.00			1.00		
	Secondary	0.82	0.71 - 0.95	0.009	0.81	0.69 - 0.94	0.007	0.39	0.35 - 0.43	<0.001	0.68	0.60 - 0.77	<0.001
	Third/higher	0.92	0.76 - 1.10	0.36	0.86	0.70 - 1.05	0.15	0.22	0.19 - 0.25	<0.001	0.49	0.41 - 0.57	<0.001
Employment	Employed	1.00			1.00			1.00			1.00		
status	Retired	1.61	1.33 - 1.95	<0.001	1.28	1.02 - 1.60	0.03	7.00	6.10 - 8.03	<0.001	2.24	1.89 - 2.66	<0.001
	Other	1.47	1.20 - 1.79	<0.001	1.34	1.08 - 1.66	0.007	6.12	5.30 - 7.07	<0.001	2.92	2.48 - 3.43	<0.001
Marital status	Married	1.00			n/a			1.00			1.00		
	Never married	0.93	0.77 - 1.14	0.50				1.46	1.26 - 1.69	<0.001	1.14	0.96 - 1.36	0.14
	Separated/divorced	1.00	0.85 - 1.17	0.96				2.92	2.56 - 3.32	<0.001	0.93	0.79 - 1.10	0.40
	Widowed	0.83	0.65 - 1.06	0.13				1.46	1.21 - 1.76	<0.001	1.47	1.18 - 1.84	0.001
Annual household income													
	<€10k	1.00			1.00			1.00			1.00		
	€10 - €19k	1.05	0.84 - 1.30	0.69	1.04	0.83 - 1.31	0.71	1.43	1.20 - 1.71	<0.001	1.27	1.04 - 1.55	0.02
	€20k - €39k	1.15	0.93 - 1.43	0.21	1.12	0.90 - 1.41	0.31	0.74	0.63 - 0.88	<0.001	0.87	0.71 - 1.05	0.15
	€40k - €69k	1.09	0.81 - 1.46	0.59	1.09	0.80 - 1.48	0.57	0.20	0.17 - 0.25	<0.001	0.39	0.31 - 0.49	<0.001
	>€70k	0.69	0.40 - 1.20	0.19	0.72	0.41 - 1.28	0.26	0.06	0.04 - 0.09	<0.001	0.15	0.10 - 0.22	<0.001
Chronic health	0	1.00			1.00			1.00			1.00		
conditions	1	1.21	0.99 - 1.49	0.07	1.04	0.83 - 1.30	0.76	1.51	1.30 - 1.75	<0.001	1.07	0.89 - 1.28	0.48
	2	1.59	1.29 - 1.97	<0.001	1.23	0.97 - 1.57	0.09	2.28	1.96 - 2.65	<0.001	1.19	0.98 - 1.44	0.09
	3+	1.97	1.50 - 2.22	<0.001	1.21	0.95 - 1.55	0.12	4.00	3.47 - 4.63	<0.001	1.26	1.03 - 1.54	0.02
Mental health	Poor cognition	1.07	0.77 - 1.48	0.68	n/a			3.30	2.53 - 4.32	<0.001	n/a		
	Delayed recall	1.03	0.89 - 1.20	0.69	n/a			2.50	2.22 - 2.82	<0.001	1.15	0.99 - 1.33	0.06
	Depression	0.96	0.79 - 1.18	0.72	n/a			1.65	1.41 - 1.92	<0.001	1.29	1.07 - 1.57	0.008
	Anxiety	0.83	0.70 - 0.99	0.04	0.82	0.68 - 0.98	0.03	0.98	0.87 - 1.11	0.75	n/a		
Reported prescription medications													
	0 meds	1.00			1.00			1.00			1.00		
	1-4 meds	1.50	1.27 - 1.78	<0.001	1.27	1.04 - 1.55	0.02	2.57	2.27 - 2.91	<0.001	1.45	1.23 - 1.70	<0.001
	5+ meds	2.30	1.89 - 2.80	<0.001	1.78	1.39 - 2.27	<0.001	6.73	5.81 - 7.80	<0.001	2.29	1.87 - 2.80	<0.001

* Backwards stepwise retaining p<0.2

Table 3.7. Odds ratios (with 95% confidence intervals) for associations between patient-level sociodemographics and over-reporting (in survey relative to pharmacy records) by therapeutic group

	Pharmacy records (n)		Female		Age (per 10 years)		Married		No/primary education		Indication reported	
Therapeutic group (ATC class)	Yes	No	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI
Drugs for acid related disorders (A02)	577	36	1.58	0.78-3.23	0.94	0.67-1.33	0.86	0.44-1.68	0.65	0.33-1.30	0.58	0.20 - 1.68
Drugs used in diabetes (A10)	223	17	0.86	0.32-2.34	0.83	0.48-1.41	1.00	0.37-2.73	0.33	0.11-0.96	n/a	
Mineral supplements (A12)	234	20	n/a		0.67	0.41-1.08	1.11	0.44-2.76	0.43	0.15-1.23	0.59	0.24 - 1.48
Antithrombotic agents (B01)	914	68	1.24	0.75-2.03	0.92	0.70-1.21	1.04	0.63-1.72	0.88	0.54-1.45	0.76	0.45 - 1.28
Cardiac therapy (C01)	147	20	2.24	0.86-5.80	0.86	0.48-1.53	0.80	0.31-2.04	1.32	0.50-3.49	0.86	0.33 - 2.24
Diuretics (C03)	379	16	1.68	0.57-4.92	0.96	0.56-1.65	1.21	0.44-3.32	1.14	0.42-3.14	4.40	0.57 - 33.81
Beta blocking agents (C07)	535	42	1.13	0.60-2.12	0.85	0.59-1.22	0.83	0.44-1.56	0.88	0.47-1.64	0.95	0.39 - 2.33
Calcium channel blockers (C08)	356	20	1.28	0.51-3.21	0.87	0.54-1.40	1.08	0.43-2.71	0.22	0.07-0.68	1.01	0.23 - 4.54
Agents acting on the Renin-Angiotensin system (C09)	864	53	1.51	0.85-2.70	1.05	0.78-1.42	0.90	0.51-1.57	1.08	0.62-1.88	1.31	0.55 - 3.14
Lipid modifying agents (C10)	1005	63	0.92	0.55-1.53	0.70	0.53-0.93	1.03	0.61-1.73	0.73	0.44-1.22	0.71	0.40 - 1.26
Urologicals (G04)	153	10	2.02	0.54-7.53	0.76	0.38-1.52	2.12	0.43-10.34	0.99	0.27-3.55	0.65	0.21 - 1.99
Thyroid therapy (H03)	232	13	1.08	0.23-5.06	0.69	0.37-1.27	0.50	0.16-1.57	0.89	0.29-2.72	n/a	
Antiinflamatory and antirheumatic products (M01)	248	38	1.17	0.56-2.43	0.78	0.54-1.12	1.06	0.53-2.10	0.59	0.29-1.20	0.91	0.30 - 2.79
Drugs for treatment of bone diseases (M05)	180	14	1.44	0.18-11.69	0.81	0.44-1.48	1.30	0.43-3.91	2.18	0.70-6.76	0.48	0.16 - 1.47
Analgesics (N02)	207	28	0.70	0.31-1.55	0.83	0.57-1.21	1.26	0.57-2.78	0.62	0.28-1.38	1.55	0.34 - 6.96
Psycholeptics (N05)	282	24	0.78	0.33-1.85	0.84	0.57-1.24	1.02	0.44-2.35	1.57	0.67-3.72	0.91	0.40 - 2.11
Psychoanaleptics (N06)	268	23	2.78	0.92-8.41	0.87	0.58-1.29	0.88	0.37-2.06	1.25	0.53-2.93	n/a	
Drugs for obstructive airway diseases (R03)	234	20	1.77	0.66-4.77	0.91	0.58-1.44	1.12	0.44-2.84	1.07	0.43-2.67	0.79	0.28 - 2.29
Ophthalmologicals (S01)	60	7	0.30	0.06-1.47	0.71	0.29-1.69	6.41	0.73-56.55	1.25	0.26-6.06	0.11	0.01 - 0.98

Table 3.8. Odds ratios (with 95% confidence intervals) for associations between patient-level characteristics and over-reporting (in survey relative to pharmacy records) by therapeutic group

	Low dispensing frequency		Number of medications regularly dispensed[a]		Poor cognition		Poor recall		Depression		Anxiety	
Therapeutic group (ATC class)	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI
Drugs for acid related disorders (A02)	0.94	0.86-1.03	1.12	0.32-3.89	0.95	0.87-1.04	1.49	0.73-3.06	1.16	0.50-2.73	0.70	0.29-1.65
Drugs used in diabetes (A10)	0.88	0.76-1.02	n/a		1.00	0.89-1.12	0.98	0.33-2.94	1.26	0.34-4.63	0.60	0.13-2.82
Mineral supplements (A12)	0.94	0.84-1.06	1.44	0.30-6.86	0.84	0.68-1.05	0.85	0.29-2.44	0.92	0.26-3.30	0.52	0.15-1.89
Antithrombotic agents (B01)	0.94	0.88-1.01	0.65	0.19-2.14	1.00	0.94-1.06	0.95	0.54-1.68	1.83	0.96-3.46	1.18	0.62-2.26
Cardiac therapy (C01)	0.95	0.85-1.06	1.30	0.14-11.67	0.97	0.85-1.09	1.38	0.53-3.61	1.76	0.53-5.87	0.87	0.18-4.25
Diuretics (C03)	0.99	0.88-1.13	0.95	0.12-7.83	n/a		0.66	0.21-2.09	1.00	0.22-4.56	1.68	0.50-5.65
Beta blocking agents (C07)	1.02	0.94-1.11	0.99	0.22-4.42	1.02	0.94-1.09	1.48	0.75-2.93	1.38	0.56-3.42	0.98	0.41-2.33
Calcium channel blockers (C08)	1.00	0.88-1.13	n/a		1.01	0.91-1.13	0.65	0.21-2.01	1.46	0.41-5.21	0.94	0.26-3.37
Agents acting on the Renin-Angiotensin system (C09)	0.96	0.89-1.04	1.33	0.45-3.92	0.98	0.91-1.05	1.14	0.61-2.13	1.70	0.80-3.61	1.63	0.80-3.31
Lipid modifying agents (C10)	0.99	0.92-1.06	0.24	0.03-1.81	0.96	0.89-1.02	0.92	0.51-1.68	1.49	0.76-2.94	1.34	0.72-2.49
Urologicals (G04)	0.92	0.78-1.09	2.43	0.43-13.67	1.00	0.86-1.17	1.43	0.40-5.17	0.73	0.09-6.06	1.41	0.26-7.66
Thyroid therapy (H03)	0.93	0.79-1.10	n/a		0.91	0.76-1.08	0.27	0.03-2.09	0.65	0.08-5.21	n/a	
Antiinflamatory and antirheumatic products (M01)	0.93	0.84-1.03	1.40	0.37-5.26	0.91	0.81-1.01	1.12	0.51-2.45	1.16	0.50-2.71	1.86	0.84-4.09
Drugs for treatment of bone diseases (M05)	0.89	0.76-1.05	n/a		1.04	0.91-1.19	1.16	0.35-3.90	1.45	0.30-7.02	0.76	0.16-3.76
Analgesics (N02)	0.94	0.85-1.04	0.49	0.06-3.94	0.96	0.87-1.06	0.45	0.17-1.17	0.64	0.23-1.77	0.97	0.37-2.52
Psycholeptics (N05)	0.94	0.84-1.05	0.40	0.05-3.14	0.96	0.87-1.07	0.95	0.39-2.33	0.55	0.20-1.52	0.75	0.27-2.11
Psychoanaleptics (N06)	0.95	0.85-1.06	0.69	0.15-3.17	0.88	0.76-1.01	0.99	0.39-2.51	1.20	0.49-2.94	0.77	0.26-2.23
Drugs for obstructive airway diseases (R03)	0.96	0.86-1.07	0.48	0.06-3.83	0.92	0.80-1.07	0.61	0.17-2.15	1.39	0.48-4.02	1.16	0.40-3.34
Ophthalmologicals (S01)	1.01	0.86-1.19	n/a		1.01	0.83-1.22	1.34	0.22-8.06	0.69	0.07-6.46	0.47	0.05-4.41

a OR per additional medication regularly dispensed

4 Study II - The effect of free healthcare on polypharmacy: A comparison of Propensity Score Methods and Multivariable Regression to account for confounding

4.1 Abstract

Purpose Differing healthcare access has implications for public health. In Ireland, eligibility for free public healthcare is means tested. Here we examine the association between healthcare access and polypharmacy while accounting for underlying socioeconomic and health status differences.

Methods Self-reported regular medication use, history of diagnosed health conditions, disability, socio-demographics, and objective measures of depression and anxiety for adults aged 50-69 years (n=5,796) were ascertained from the population representative Irish Longitudinal study on Ageing (TILDA). Objective measures of frailty, cognition, hypertension, and body mass index were also assessed for 4,241 participants. The associations between free healthcare access and polypharmacy and use of fifteen medication classes were estimated using multivariable modified Poisson regression, adjustment for the propensity score and inverse probability of treatment weighting by the propensity score.

Results Polypharmacy was reported by 22% and 7% of the 1,932 and 3,864 participants with and without public healthcare coverage. Public patients had a 21-38% greater risk of polypharmacy depending on the method used to account for confounding. Results were less robust using propensity score weighting. There was evidence that classes of cardiovascular drugs, drugs for acid related disorders, and analgesics were used more commonly in public patients. Associations were mostly unaffected after also accounting for objective health measures, but were significantly attenuated after accounting for frequency of healthcare visits.

Conclusions Publically funded healthcare in Ireland leads to greater medication use in people aged 50 to 69 years. This may reflect overprescribing to public patients or restricted use among those who pay out-of-pocket.

4.2 Introduction

Differing access to healthcare has implications for public health (51). Studies in North America show that health insurance coverage affects mortality and health declines (50,51). Uninsured US citizens restrict medication use; particularly medications used to manage or prevent cardiovascular disease (52,53), and this cost-related restriction can lead to declines in health (54). Conversely, over-prescribing may occur among those with free healthcare, possibly enabled through free medical practitioner visits.

In the Republic of Ireland, eligibility for free public healthcare is means tested, and reports suggest free healthcare leads to increased use of primary care (45). Certain classes of medications are inappropriately prescribed in the Irish public healthcare system, or more frequently prescribed to those with lower incomes (46–48). Our aim is to assess whether free healthcare access is associated with greater polypharmacy while accounting for health and socioeconomic differences between those with and without access. Polypharmacy, often defined as the concurrent use of five or more medications, is a risk factor for inappropriate prescribing and adverse drug reactions (6,17), and is implicated with health outcomes including functional impairment, falls and fractures, hospitalization, and mortality (9,18). The Irish government has proposed plans to introduce universal health insurance for all Irish residents, which includes free physician visits (49). Understanding the effects of free healthcare on medication use is important for informing such policy debates. A finding of greater polypharmacy in the public system would have economic and public health implications.

When comparing medication use across groups defined by healthcare coverage, their underlying health and socioeconomic differences need to be accounted for. Multivariable regression is the traditional approach to control for confounders in epidemiology, but 'propensity scores' have become increasing popular (33). Approaches towards variable selection differ between these methods, and it is not clear which approach provides better control for confounding. Multivariable regression typically aims to seek a parsimonious model to avoid

multicollinearity between potential confounders (41), whereas recent studies using propensity score techniques have advocated using a greater number of potential confounders (42). Additionally, it is not known whether the ability to control for differences in health is substantially impaired by the usual reliance on self-reports of diagnosed conditions and health status, as opposed to objectively measured biomarkers or measures of frailty (110).

Here we use data from a nationally representative study of the middle aged and older population of Ireland to: (i) assess whether the rate of polypharmacy differs for adults with and without public healthcare coverage, (ii) to examine this further by assessing whether the use of major therapeutic classes differs by access to public healthcare, (iii) compare approaches to account for confounding and examine the degree of additional effect modification after controlling for objective measures of health, and (iv) assess whether access to free medical practitioner visits and hospital services is a mediating factor.

4.3 Methods

4.3.1 Study population

Data were retrieved from the Irish Longitudinal study on Ageing (TILDA) which is representative of the community-dwelling over 50s in Ireland. In its first wave (2009-2011), TILDA recruited 8,175 individuals with each participant undergoing an extensive in home face-to-face interview, invited to complete a self-completion questionnaire (SCQ) and a nurse conducted health assessment. Households were selected from a clustered sample of Irish residential addresses with an overall response rate of 62.0%. The sample is described in detail elsewhere (87). TILDA was approved by the Faculty of Health Sciences Research Ethics Committee of Trinity College Dublin.

Approximately 40% of the Irish population are entitled to free healthcare. Among the under 70's, eligibility is means tested and is available to those for whom medical expenses would cause undue hardship. For adults aged over 70 higher thresholds were introduced in January

2009. Most eligible individuals (93%) are issued a 'medical card', enabling free medical practitioner and hospital visits and prescription medications at minimal cost (free before Oct 2010; €0.50 per item from Oct 2010). The remaining 7% are eligible for a General Practitioner Visit Card, enabling free medical practitioner visits, but no benefits regarding other services or prescription medications. Personal prescription expenditure is capped for all individuals (€120 per month in 2010), but private insurance plans generally provide only limited benefits towards medical practitioner visit costs and none towards prescription medication costs.

Our exposure of interest was public healthcare coverage compared to the remaining population, as individuals covered by private insurance and the uninsured pay out-of-pocket for medical practitioner visits and for medications. As the majority of over 70s are covered by the Medical Card scheme, we only examined adults aged 50-69 years (*n*=5,866).

Interviewers asked participants for all medications taken on a regular basis, defined as "...like every day or every week", and viewed medication packages to enter the correct medication names. Medications were assigned WHO Anatomic Therapeutic Chemical (ATC) Classification codes (88). Polypharmacy was defined as regular use of five or more medicines (excluding dietary supplements) (6).

4.3.1.1 Interview ascertained health covariates

Doctor diagnosed health conditions were reported for the following: hypertension, angina, heart attack, heart failure, diabetes, transient ischaemic attack (TIA), high cholesterol, heart murmur, arrhythmia, stroke, other cardiovascular disease, cataracts, glaucoma, age related macular degeneration (ARMD), chronic lung disease, asthma, osteoporosis, cancer, arthritis, stomach ulcer, liver disease, varicose ulcer, Parkinson's disease, dementia, memory problems, anxiety, depression, or other emotional problem. Being troubled with Pain was self-reported as none, mild, moderate or severe.

Disability was reported as any limitations in Instrumental Activities of Daily Living (IADL) or Activities of Daily Living (ADLs) and the number of mobility impairments from a list of 11 (such as walking, climbing stairs, reaching, lifting). Frequency of healthcare visits were recorded by the number of medical practitioner visits, hospital outpatient and inpatient visits in the previous year. Depressive symptoms were assessed using the Centre for Epidemiologic Studies Depression Scale (89). Anxiety symptoms were assessed within the SCQ using the Hospital Anxiety and Depression Scale – Anxiety subscale (90).

4.3.1.2 Objectively measured health status

Health assessments were either performed in a dedicated university centre or in the participant's home if travel was impracticable (*n*=4,377, 75.5%). Timed Up-and-Go (TUG) whereby participants rose from a chair, walked 3m, and returned to sitting was used a measure of functional mobility (91). Handgrip strength was taken as the average for each hand measured using a Baseline dynamometer. Cognition was assessed using the mini–mental state examination (MMSE) (92). Uncontrolled hypertension was defined as a systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg from the average of two seated readings (irrespective of antihypertensive use). Height and weight were measured using standard procedures for body mass index (BMI).

4.3.2 Statistical methods

Differences in the characteristics of participants with and without public healthcare coverage were compared along with an assessment of the extent to which each characteristic confounds the relationship between healthcare coverage and polypharmacy (111). This was assessed by calculating the percentage difference between the unadjusted relative risk (RR) for polypharmacy and the RR adjusted for the characteristic.

The RR for the association between public health system use and polypharmacy was estimated using a modified Poisson regression with sandwich estimator to estimate a robust variance (112). The following three techniques were used to separately estimate an average treatment effect whilst account for confounding: (i) multivariable regression, (ii) regression adjusted for the (continuous) propensity score, and (iii) Inverse-Probability-of-Treatment-Weighted (IPTW) regression. Estimation of propensity score and variable selection strategies for each method are described below.

4.3.2.1 Propensity scores

Logistic regression was used to estimate the propensity score (PS) representing the probability of 'exposure' to public healthcare coverage given an individual's covariates. For IPTW regression, individuals with public coverage were then weighted by the reciprocal of their PS and individuals without public coverage were weighted by one minus the reciprocal of their PS. Weights were then stabilized by multiplying by the prevalence of public healthcare coverage for those with public healthcare coverage and one minus the prevalence for those without coverage (113). Once the weights were applied, balance was assessed by both examining standardised differences and the degree of confounding remaining as above (111).

Following usual recommendations for PS analyses, we excluded participants whose PS falls outside the overlapping range between the two sets of patients (33). The IPTW method can be sensitive to individuals with large weights (i.e. PS very close to 0 or 1), and there may be uncertainty over the coding of such individual's covariates and treatment at the extremes of the PS distribution. We therefore, as a sensitivity analysis, applied asymmetrical trimming and excluded those with PS lying outside the 1^{st} and 99^{th} percentiles of the PS distribution in those with and without public healthcare, respectively (110). To examine whether the association between public healthcare coverage and polypharmacy was modified by the PS, we estimated polypharmacy rate ratios in strata defined by the quintiles of the PS. We tested for heterogeneity

by performing a 4-df likelihood ratio testing for interaction between public healthcare coverage and indicators for each quintile in a modified Poisson model.

4.3.2.2 Variable selection

We compared two variable selection strategies: a priori selected covariates and a backwards stepwise approach. The a priori selected covariates were those that the researchers believed could confound the association between public healthcare and polypharmacy, informed by previous work (9). The backwards stepwise approach retained variables with $P<0.2$ from the set of a priori covariates in the multivariable outcome model. Both are common approaches to variable selection in multivariable regression and the more inclusive threshold of $P<0.2$ in backwards stepwise is often recommended (41).

A priori covariates included: sociodemographics (age, sex, marital status, urbanicity, education, employment status, annual household income, and house value), self-reported health conditions, pain, self-reported disability, depressive symptoms, anxiety symptoms and smoking. Except for age, continuous variables were categorised into quintiles to enable a non-linear relationship with the outcome (111). To test whether objectively measured health provides further confounding control, each analysis was repeated for participants completing the health assessment by including TUG, grip strength, BMI, cognition, and uncontrolled hypertension into the a priori list.

In the main analysis, participants who did not report their health coverage status (n=4), medication (n=41) or self-reported morbidity (n=25) data were excluded. Other variables with missing data were coded with a 'missing' category.

Data-driven strategies such as stepwise variable selection and PS methods where the PS is assumed to be estimated exactly are both known to underestimate true uncertainty (114,115). We therefore tested the sensitivity of our conclusions to this by additionally estimating

bootstrapped RRs and standard errors (SE) using 1,000 re-sampled datasets, performing the variable selection and PS estimation processes with each replicate.

4.3.2.3 Medication class

To understand whether any specific medication classes contributed to the differences in polypharmacy rates, analyses were repeated with each of the therapeutic classes (ATC 2nd level) used by 5% or more of the population used as the outcome instead. Backwards stepwise selection was performed separately for each class.

Finally, the mediating effect of healthcare visits (annual number of medical practitioner visits, hospital inpatient and outpatient visits) was tested by adding these variables to each model. All analyses were performed using Stata Version 12.0. Significance at $p<0.05$ is assumed.

4.4 Results

Polypharmacy was reported by 22% and 7% of the 1,932 and 3,864 participants with and without public healthcare coverage, respectively (table 4.1). Participants with public healthcare coverage were different with respect to most covariates, but employment status, mobility impairments, hypertension and pain had the greatest potential for confounding, as seen in the third column of Table 4.1, due to their large differences between the two sets of patients and strong associations with polypharmacy. Of those completing the health assessment, polypharmacy was again reported by 22% and 7% of the 1,322 and 3,055 participants with and without public healthcare coverage (table 4.2).

Table 4.1. Characteristics of 5,796 Irish adults aged 50-69 years according to public healthcare coverage, unweighted and after Inverse-Probability-of-Treatment-Weighting[a]

	Unweighted (n=5,796)			Inverse-Probability-of-Treatment-Weighted (n=5,494)			Inverse-Probability-of-Treatment-Weighted[b] (n=5,568)		
	Public healthcare		Change in	Public healthcare		Change	Public healthcare		Change
Variable	No	Yes	RR[c], %	No	Yes	in RR[c], %	No	Yes	in RR[c], %
Women	52.3	59.3	1	54.9	56.9	0	55.1	56.5	0
Age, years	58 (53-62)	60 (55-65)	-13	59 (54-64)	59 (54-64)	0	59 (54-64)	58 (53-64)	0
Married	78.9	60.3	0	73.2	73.1	0	78.0	65.7	0[d]
Third/higher education	41.1	15.9	-8	29.8	30.9	2	36.7	21.9	-7[d]
Urban	53.3	48.5	1	49.1	48.1	0	50.3	47.4	1
Employed full-time	35.4	9.4	-33	25.2	28.3	2	26.3	27.9	3
Household income < €20,000[e]	13.7	48.0	-10	25.7	25.9	-1	16.5	39.5	-9[d]
Renting[e]	3.1	21.0	1	8.1	8.7	0	7.2	7.1	0
Current smoker	16.0	29.3	-1	20.2	20.3	0	17.5	24.4	-1[d]
Health conditions									
Angina	2.1	6.2	-12	3.1	3.0	1	3.4	3.0	2
Arrhythmia	5.0	6.5	-3	5.4	4.5	1	5.5	4.6	2
Diabetes	4.9	9.6	-14	6.2	5.6	2	6.5	6.1	2
Heart attack	2.0	4.9	-8	3.0	2.5	2	3.0	2.5	2
High cholesterol	37.7	39.6	-2	37.4	36.6	1	38.2	36.7	2
Hypertension	28.1	39.4	-15	32.5	32.3	0	31.6	31.5	0
Other cardiovascular disease	2.5	3.5	-2	2.9	2.1	2	2.7	2.2	1
Arthritis	19.3	29.0	-8	23.2	22.8	1	23.0	22.5	1
Asthma	8.2	11.9	-4	9.0	8.4	1	9.2	8.1	2
Chronic lung disease	2.4	6.4	-4	3.7	3.6	0	3.4	3.3	0
Osteoporosis	7.5	10.4	-2	8.8	9.5	0	8.4	8.7	0
Stomach ulcer	6.2	9.5	-2	6.8	6.8	1	7.3	7.2	0

Variable	Unweighted (n=5,796)			Inverse-Probability-of-Treatment-Weighted (n=5,494)			Inverse-Probability-of-Treatment-Weighted[b] (n=5,568)		
	Public healthcare		Change in RR[c], %	Public healthcare		Change in RR[c], %	Public healthcare		Change in RR[c], %
	No	Yes		No	Yes		No	Yes	
Cataracts	3.9	6.1	-3	4.9	4.5	1	5.0	4.4	1[d]
Glaucoma	1.3	2.4	-1	2.1	1.8	0	1.8	1.9	0
Anxiety	4.5	7.3	-3	5.3	5.8	0	5.2	5.5	0
Depression	4.3	9.2	-4	6.3	5.9	1	5.1	8.0	-2[d]
Moderate/severe pain	19.8	34.1	-18	24.2	23.9	0	24.5	24.0	1
Disability (ADL or IADL)	5.5	14.2	-14	8.7	8.6	0	8.0	7.4	2[d]
Impairments	1 (0-2)	2 (0-4)	-30	1 (0-2)	1 (0-3)	0	1 (0-2)	1 (0-2)	1
Depressive symptoms[e]	3 (0-7)	5 (1-11)	-10	3 (1-8)	3 (1-8)	0	3 (1-8)	4 (1-9)	-3[d]
Anxiety symptoms[e]	5 (3-7)	6 (3-9)	-2	5 (3-8)	5 (3-8)	1	5 (3-8)	5 (3-8)	0[d]

a Values are expressed as percentage or median (interquartile range).

b Covariates were selected from the backwards stepwise procedure retaining $P<0.2$ from the a priori selected covariates.

c Calculated according to the formula RRA – RRC/RRC, where RRC is either the crude relative risk for polypharmacy or in the case of IPTW, the IPTW RR, and RRA is the relative risk after additional adjustment for the full covariate.

d Covariates not selected from the backwards stepwise procedure

e Missing data: 5% missing income, 9% missing housing, 1% missing depressive symptoms, 16% missing anxiety symptoms.

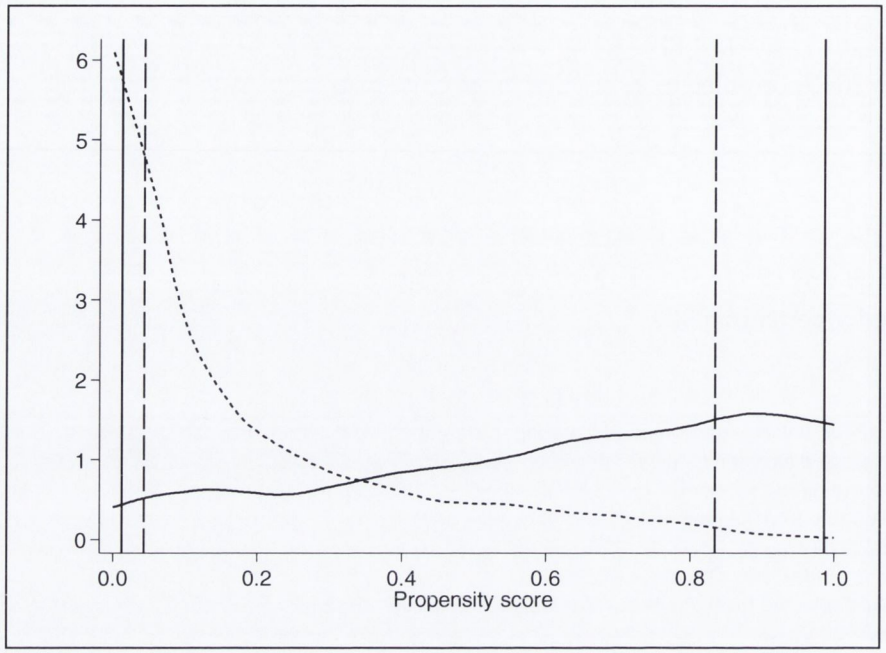
Table 4.2. Health characteristics of 4,377 Irish adults aged 50-69 years with objective health measured in 2010 according to public healthcare coverage

	Public healthcare[a]		Change in RR[b], %		
Variable[c]	No	Yes	Unweighted	IPTW	IPTW[d]
Grip strength	27.8 (9.8)	25.0 (9.0)	-2	-1	0
Timed Up-and-Go	8.1 (1.6)	9.1 (2.6)	-21	0	1[e]
Uncontrolled hypertension, %	36.5	38.4	-1	0	0
Body Mass Index	28.5 (4.8)	29.4 (5.9)	-7	-2	0[e]
MMSE	28.9 (1.5)	28.0 (2.2)	-6	0	1

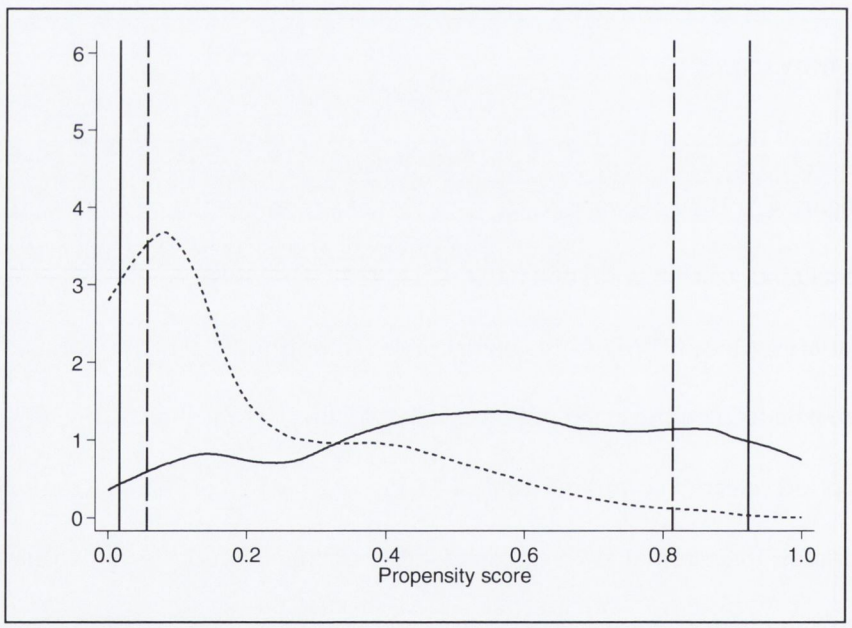
Abbreviations: IPTW, Inverse-Probability-of-Treatment-Weighted; MMSE, mini–mental state examination
a Values are expressed as mean (standard deviation), unless otherwise stated.
b Calculated according to the formula RRA – RRC/RRC, where RRC is either the crude relative risk for polypharmacy or in the case of IPTW, the IPTW RR, and RRA is the relative risk after additional adjustment for the full covariate.
c Missing data: 2% missing grip strength, <1% missing timed up-and-go, <1% missing uncontrolled hypertension, <1% missing body mass index, and <1% missing MMSE.
d Covariates were selected from the backwards stepwise procedure retaining $P<0.2$ from the a priori selected covariates.
e Covariates not selected using the backwards stepwise procedure.

4.4.1 Propensity scores

The distributions of the PSs in the full sample using a priori and stepwise selected covariates are displayed in figure 4.1. They overlapped for both sets of patients in the range 0.012-0.987 (302 participants excluded) using a priori and 0.016-0.923 (228 participants excluded) using backwards stepwise covariates. Once IPTW weights were applied, participants with and without public coverage were balanced on the covariates and little potential for residual confounding remained when using a priori selected covariates (table 4.1). However, when using backwards stepwise selected covariates, there remained imbalances in the excluded education and income variables. The mean (SD) and range of the stabilized IPTW weights using a priori and backwards stepwise selected covariates were 1.00 (1.21) and 0.4-28.5 and 1.01 (0.82) and 0.4-12.6, respectively. Applying asymmetrical trimming at the 1st and 99th percentiles, reduced the largest stabilized weight to 7.6 and 5.7 in each analysis, respectively.



(a) A priori selected covariates



(b) Backwards stepwise selected covariates

Figure 4.1. Probability density function of the propensity score for public healthcare coverage for 5,796 Irish adults aged 50-69 years. (a) A priori selected covariates (b) Backwards stepwise selected covariates. Dashed line, no public healthcare coverage. Solid line, public healthcare coverage. Solid vertical lines, cut-points for trimming areas of non-overlap. Dashed vertical line, cut-points for asymmetrical trimming at the 1st and 99th percentiles of the propensity score in those with and without public healthcare

4.4.2 Polypharmacy effect estimates

Table 4.3 summarises the bootstrapped associations between public healthcare coverage and polypharmacy using each method. The RR using conventional multivariable regression including all a priori covariates is 1.38 (95% confidence interval (CI): 1.14, 1.67), which would indicate a substantially higher risk of polypharmacy in the public system. Regression adjustment for the PS gave a similar result (RR 1.33, 95% CI: 1.13, 1.56), but the IPTW method yielded a smaller estimate (RR 1.25, 95% CI: 1.04, 1.50). The IPTW polypharmacy prevalence was 13.7% and 11.1% for those with and without public healthcare coverage, respectively. Table 4.4 shows no indication of a meaningful difference in polypharmacy rate ratios across strata defined by quintiles of the PS. However small numbers of exposed participants below the 40^{th} percentile mean we cannot rule out heterogeneity across groups. The RR increased slightly when asymmetrical trimming was applied, and the IPTW method was more sensitive to this. Point estimates were similar using covariates selected by the stepwise procedure. In addition, the bootstrapped SEs were no lower when using stepwise selected covariates, and were, in some instances slightly higher. The associations are provided with robust standard errors in table 4.5.

Adjustment for the a priori selected covariates led to the same point estimate of the RR in both the full sample and the health assessment subsample (RR 1.38, 95% CI: 1.13, 1.70), not shown. Additional adjustment for the objective health measures slightly reduced the RRs for multivariable regression and regression adjusted for the PS, but IPTW results changed more markedly, with larger SEs in some cases indicating instability in the method (table 4.4).

Table 4.3. Relative risks (with 95% CIs) between public healthcare coverage and polypharmacy using multivariable regression, regression adjustment for the propensity score and Inverse-Probability-of-Treatment-Weighting regression, for 5,796 Irish adults aged 50-69 Years

	Full sample (n=5,796)			Accounting for objective health (n=4,377)			Accounting for healthcare visits[a] (n=5,796)		
Model	RR	95% CI	SE	RR	95% CI	SE	RR	95% CI	SE
Crude	3.05	2.65, 3.50	0.22	3.19	2.71, 3.75	0.26	3.05	2.65, 3.50	0.22
Multivariable model									
A priori covariates[b]	1.38	1.14, 1.67	0.13	1.34	1.07, 1.66	0.15	1.18	0.97, 1.43	0.12
Backwards stepwise[c]	1.36	1.13, 1.63	0.13	1.32	1.03, 1.68	0.16	1.17	0.97, 1.42	0.12
Regression adjusted for propensity score									
A priori covariates[b]	1.33	1.13, 1.56	0.11	1.32	1.09, 1.59	0.13	1.25	1.06, 1.47	0.10
Trimmed[d]	1.36	1.14, 1.61	0.12	1.28	1.03, 1.59	0.14	1.31	1.09, 1.56	0.12
Backwards stepwise[c]	1.32	1.12, 1.55	0.11	1.32	1.07, 1.61	0.14	1.21	1.02, 1.43	0.10
Trimmed[d]	1.36	1.14, 1.63	0.12	1.28	1.02, 1.61	0.15	1.28	1.06, 1.54	0.12
IPTW model									
A priori covariates[b]	1.25	1.04, 1.50	0.12	1.29	1.02, 1.64	0.16	1.18	0.97, 1.44	0.12
Trimmed[d]	1.26	1.04, 1.53	0.12	1.19	0.93, 1.51	0.15	1.23	1.01, 1.51	0.13
Backwards stepwise[c]	1.21	0.99, 1.49	0.13	1.29	0.98, 1.70	0.18	1.16	0.95, 1.42	0.12
Trimmed[d]	1.30	1.06, 1.59	0.13	1.34	1.00, 1.78	0.20	1.22	0.99, 1.50	0.13

a Also accounted for differences in the annual number of medical practitioner, hospital inpatient and outpatient visits.

b A priori selected covariates accounted for: age, sex, marital status (married, single, widowed, divorced/separated), education (none/primary, junior certificate, leaving certificate, third/higher), location (Dublin, other city, rural), employment status (retired, part-time employed, full-time employed, self-employed, unemployed, incapacity, unpaid work), annual household income, house value (renting, <€100k, €100-199k, €200-399k, €400-699k, >€700k), hypertension, angina, arrhythmia, heart attack, diabetes, high cholesterol, heart murmur, heart failure, stroke, TIA, asthma, other cardiovascular disease, osteoporosis, cirrhosis, arthritis, cancer, varicose ulcer, stomach ulcer, ARMD, glaucoma, cataracts, anxiety, Parkinson's disease, dementia, serious memory impairment, depression, other emotional problem, pain, disability (none, ADL, IADL), number of impairments, smoking status (never, past, current), depressive symptoms, and anxiety symptoms. In the health assessment sample, a priori variables also include TUG, MMSE, BMI, grip strength, and uncontrolled hypertension.

c Covariates selected from the backwards stepwise procedure retaining $P<0.2$ from the a priori selected covariates.

d Exclusion of propensity scores lying beyond the 1st and 99th percentiles of the distribution in those with and without public healthcare coverage, respectively.

Table 4.4. Rates of polypharmacy among 5,494 Irish adults aged 50-69 years by access to public healthcare, according to percentiles of the propensity score[a]

		Public healthcare (n = 1,932)			No public healthcare (n = 3,864)			
			Polypharmacy			Polypharmacy		Rate
Percentile	Propensity score range	No.	No.	%	No.	No.	%	Ratio
<0	<0.01				278	10	3.6%	
0-1[b]	0.01-0.04	19	1	5.3%	794	28	3.5%	1.49
1[b]-20	0.04-0.06	14	1	7.1%	272	10	3.7%	1.94
20-40	0.06-0.16	139	7	5.0%	960	63	6.6%	0.77
40-60	0.16-0.37	251	35	13.9%	848	75	8.8%	1.58
60-80	0.37-0.67	580	93	16.0%	519	57	11.0%	1.46
80-99[b]	0.67-0.83	429	116	27.0%	157	29	18.5%	1.46
99[b]-100	0.83-0.99	477	163	34.2%	36	11	30.6%	1.12
>100	>0.99	23	15	65.2%				
Overall	0.01-0.99	1,909	416	21.8%	3,586	273	7.6%	2.86

a Propensity score using covariates selected a priori

b Asymmetric PS percentiles according to PS distribution in those with and without public healthcare separately. Percentiles between 0 and 1 are derived from the PS distribution in those with public healthcare, percentiles between 99 and 100 are derived from the PS distribution in those without public healthcare; all other percentiles are derived from the overall PS distribution.

Table 4.5. Relative risks (with 95% CIs) between public healthcare coverage and polypharmacy using multivariable regression, regression adjustment for the propensity score and Inverse-Probability-of-Treatment-Weighting regression, for 5,796 Irish adults aged 50-69 years*

	Full sample (n=5,796)			Accounting for objective health (n=4,377)			Accounting for healthcare visits[a] (n=5,796)		
Model	RR	95% CI	SE	RR	95% CI	SE	RR	95% CI	SE
Crude	3.05	2.65, 3.50	0.22	3.19	2.71, 3.75	0.26	3.05	2.65, 3.50	0.22
Multivariable model									
A priori covariates[b]	1.38	1.16, 1.64	0.12	1.34	1.08, 1.65	0.14	1.18	0.99, 1.40	0.10
Backwards stepwise[c]	1.36	1.16, 1.59	0.11	1.32	1.10, 1.58	0.12	1.17	1.00, 1.37	0.09
Regression adjusted for propensity score									
A priori covariates[b]	1.33	1.11, 1.60	0.12	1.32	1.06, 1.64	0.15	1.25	1.03, 1.50	0.12
Trimmed[d]	1.36	1.12, 1.64	0.13	1.28	1.01, 1.62	0.15	1.31	1.08, 1.59	0.13
Backwards stepwise[c]	1.32	1.11, 1.56	0.12	1.32	1.09, 1.59	0.13	1.21	1.02, 1.45	0.11
Trimmed[d]	1.36	1.14, 1.63	0.12	1.31	1.09, 1.57	0.13	1.28	1.06, 1.54	0.12
IPTW model									
A priori covariates[b]	1.25	0.99, 1.57	0.15	1.30	1.01, 1.68	0.17	1.19	0.94, 1.49	0.14
Trimmed[d]	1.26	1.02, 1.57	0.14	1.19	0.90, 1.55	0.16	1.24	0.99, 1.54	0.14
Backwards stepwise[c]	1.21	1.00, 1.47	0.12	1.29	1.04, 1.61	0.14	1.16	0.94, 1.42	0.12
Trimmed[d]	1.30	1.08, 1.57	0.13	1.28	1.05, 1.55	0.16	1.22	1.00, 1.50	0.13

* Standard errors estimated via robust sandwich estimator

a Also accounted for differences in the annual number of medical practitioner, hospital inpatient and outpatient visits.

b A priori selected covariates accounted for: age, sex, marital status (married, single, widowed, divorced/separated), education (none/primary, junior certificate, leaving certificate, third/higher), location (Dublin, other city, rural), employment status (retired, part-time employed, full-time employed, self-employed, unemployed, incapacity, unpaid work), annual household income, house value (renting, <€100k, €100-199k, €200-399k, €400-699k, >€700k), hypertension, angina, arrhythmia, heart attack, diabetes, high cholesterol, heart murmur, heart failure, stroke, TIA, asthma, other cardiovascular disease, osteoporosis, cirrhosis, arthritis, cancer, varicose ulcer, stomach ulcer, ARMD, glaucoma, cataracts, anxiety, Parkinson's disease, dementia, serious memory impairment, depression, other emotional problem, pain, disability (none, ADL, IADL), number of impairments, smoking status (never, past, current), depressive symptoms, and anxiety symptoms. In the health assessment sample, a priori variables also include TUG, MMSE, BMI, grip strength, and objective hypertension.

c Covariates selected from the backwards stepwise procedure retaining $P<0.2$ from the a priori selected covariates.

d Exclusion of propensity scores lying beyond the 1st and 99th percentiles of the distribution in those with and without public healthcare coverage, respectively.

4.4.3 Therapeutic class

The associations between public healthcare access and regular use of 15 therapeutic classes were examined in the full sample (table 4.6). Multivariable regression and adjustment for the PS identified public patients as significantly more likely to regularly use drugs for acid related disorders, agents acting on the renin-angiotensin system, lipid modifying agents, and analgesics.

4.4.4 Frequency of healthcare visits

Participants with and without public healthcare coverage reported a median (IQR) of 4 (2-6) and 2 (1-3) medical practitioner visits in the previous year, respectively. In the previous year, 32% of those with public coverage compared to 19% of those without had an outpatient hospital visit, and 17% and 9% had an inpatient visit, respectively. Accounting for differences in the frequency of healthcare visits significantly attenuated the associations with polypharmacy (table 4.4) and medication class (table 4.7).

Table 4.6. Relative risk estimates (with 95% CIs) between public healthcare coverage and regular use of medications using multivariable regression, regression adjustment for the propensity score, for 5,796 Irish adults aged 50-69 years, by ATC therapeutic group

	Multivariable regression				Adjusted for the propensity score				IPTW			
	A priori[a]		Backwards stepwise[b]		A priori[a]		Backwards stepwise[b]		A priori[a]		Backwards stepwise[b]	
Therapeutic group (ATC class)	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Drugs for acid related disorders (A02)	1.28	1.07, 1.54	1.29	1.08, 1.54	1.22	1.03, 1.45	1.24	1.04, 1.48	1.44	1.16, 1.80	1.19	0.94, 1.51
Drugs used in diabetes (A10)	1.16	0.91, 1.49	1.24	0.96, 1.60	1.23	1.03, 1.48	1.21	1.01, 1.44	1.08	0.86, 1.35	1.26	0.97, 1.65
Antithrombotic agents (B01)	1.16	0.99, 1.34	1.11	0.95, 1.30	1.13	1.00, 1.28	1.09	0.96, 1.23	1.12	0.94, 1.32	1.10	0.92, 1.32
Diuretics (C03)	1.31	0.99, 1.73	1.33	0.99, 1.78	1.40	1.06, 1.86	1.36	1.02, 1.83	1.28	0.92, 1.79	1.32	0.90, 1.93
Beta blocking agents (C07)	0.95	0.78, 1.18	0.99	0.80, 1.22	0.94	0.78, 1.12	0.98	0.83, 1.15	0.94	0.74, 1.19	0.94	0.76, 1.17
Calcium channel blockers (C08)	1.09	0.85, 1.39	1.14	1.03, 1.27	1.13	0.89, 1.44	1.14	0.88, 1.46	1.14	0.86, 1.49	1.16	0.86, 1.55
Agents acting on the Renin-Angiotensin system (C09)	1.15	1.04, 1.28	1.14	1.02, 1.27	1.16	1.04, 1.28	1.15	1.03, 1.29	1.13	0.98, 1.30	1.11	0.94, 1.30
Lipid modifying agents (C10)	1.12	1.01, 1.24	1.14	1.03, 1.27	1.12	1.02, 1.22	1.14	1.04, 1.25	1.10	0.97, 1.24	1.14	1.00, 1.29
Thyroid therapy (H03)	0.92	0.72, 1.18	0.94	0.74, 1.21	0.93	0.72, 1.20	0.96	0.74, 1.24	0.93	0.70, 1.25	0.85	0.62, 1.16
Antiinflamatory and antirheumatic products (M01)	1.21	0.91, 1.59	1.14	0.86, 1.50	1.10	0.85, 1.41	1.06	0.81, 1.37	1.11	0.81, 1.51	1.06	0.76, 1.47
Drugs for treatment of bone diseases (M05)	1.23	0.93, 1.63	1.17	0.89, 1.53	1.17	0.88, 1.56	1.11	0.83, 1.48	1.40	0.91, 2.16	1.07	0.74, 1.55
Analgesics (N02)	1.45	1.10, 1.91	1.40	1.05, 1.87	1.37	1.06, 1.77	1.30	0.97, 1.73	1.27	0.92, 1.75	1.33	0.96, 1.84
Psycholeptics (N05)	1.24	0.92, 1.68	1.23	0.92, 1.65	1.22	0.92, 1.62	1.22	0.92, 1.62	1.04	0.77, 1.40	1.10	0.80, 1.51
Psychoanaleptics (N06)	1.15	0.88, 1.51	1.16	0.89, 1.52	1.17	0.91, 1.49	1.13	0.88, 1.46	1.06	0.83, 1.36	0.96	0.71, 1.30
Drugs for obstructive airway diseases (R03)	1.18	0.90, 1.57	1.29	0.98, 1.70	1.12	0.89, 1.39	1.28	1.03, 1.60	1.12	0.81, 1.53	1.23	0.90, 1.67

IPTW = Inverse-Probability-of-Treatment-Weighted Regression

a A priori selected covariates accounted for: age, sex, marital status (married, single, widowed, divorced/separated), education (none/primary, junior certificate, leaving certificate, third/higher), location (Dublin, other city, rural), employment status (retired, part-time employed, full-time employed, self-employed, unemployed, incapacity, unpaid work), annual household income, house value (renting, <€100k, €100-199k, €200-399k, €400-699k, >€700k), hypertension, angina, arrhythmia, heart attack, diabetes, high cholesterol, heart murmur, heart failure, stroke, TIA, asthma, other cardiovascular disease, osteoporosis, cirrhosis, arthritis, cancer, varicose ulcer, stomach ulcer, ARMD, glaucoma, cataracts, anxiety, Parkinson's disease, dementia, serious memory impairment, depression, other emotional problem, pain, disability (none, ADL, IADL), number of impairments, smoking status (never, past, current), depressive symptoms, and anxiety symptoms.

b Covariates selected from the backwards stepwise procedure retaining $P<0.2$ from the a priori selected covariates.

Table 4.7. Relative risk estimates between public healthcare coverage and regular use of medications accounting for differences in the number of healthcare visits, for 5,796 Irish adults aged 50-69 years, by ATC therapeutic group

	Multivariable regression				Adjusted for the propensity score				IPTW			
	A priori[a]		Backwards stepwise[b]		A priori[a]		Backwards stepwise[b]		A priori[a]		Backwards stepwise[b]	
Therapeutic group (ATC class)	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Drugs for acid related disorders (A02)	1.11	0.91, 1.34	1.17	0.97, 1.41	1.08	0.90, 1.29	1.13	0.93, 1.37	1.25	0.98, 1.59	1.33	1.05, 1.69
Drugs used in diabetes (A10)	1.11	0.85, 1.46	1.23	0.94, 1.59	1.21	1.00, 1.46	1.22	1.01, 1.47	0.99	0.79, 1.23	1.21	0.91, 1.61
Antithrombotic agents (B01)	1.06	0.91, 1.24	1.01	0.87, 1.19	1.06	0.93, 1.21	1.03	0.90, 1.17	1.05	0.87, 1.28	1.03	0.84, 1.26
Diuretics (C03)	1.22	0.92, 1.63	1.21	0.90, 1.62	1.31	0.97, 1.75	1.26	0.91, 1.76	1.27	0.90, 1.81	1.17	0.77, 1.77
Beta blocking agents (C07)	0.88	0.71, 1.09	0.93	0.75, 1.14	0.88	0.73, 1.06	0.92	0.76, 1.12	0.82	0.64, 1.06	0.87	0.67, 1.12
Calcium channel blockers (C08)	1.01	0.80, 1.29	1.10	0.86, 1.40	1.05	0.83, 1.34	1.15	0.89, 1.48	1.04	0.77, 1.41	1.09	0.78, 1.53
Agents acting on the Renin-Angiotensin system (C09)	1.07	0.96, 1.20	1.08	0.97, 1.22	1.09	0.98, 1.22	1.12	1.00, 1.26	1.08	0.92, 1.26	1.21	1.03, 1.42
Lipid modifying agents (C10)	1.05	0.95, 1.17	1.09	0.98, 1.21	1.06	0.96, 1.17	1.09	0.99, 1.21	1.06	0.92, 1.22	1.06	0.92, 1.23
Thyroid therapy (H03)	0.78	0.59, 1.02	0.82	0.63, 1.06	0.79	0.60, 1.03	0.83	0.64, 1.08	0.86	0.60, 1.24	0.80	0.58, 1.11
Antiinflamatory and antirheumatic products (M01)	1.09	0.81, 1.47	1.04	0.79, 1.37	0.98	0.76, 1.27	1.02	0.78, 1.34	1.11	0.79, 1.54	1.05	0.73, 1.50
Drugs for treatment of bone diseases (M05)	1.08	0.81, 1.44	1.03	0.77, 1.39	1.08	0.82, 1.44	1.05	0.78, 1.43	1.37	0.85, 2.19	1.02	0.67, 1.55
Analgesics (N02)	1.28	0.95, 1.72	1.22	0.93, 1.61	1.23	0.94, 1.62	1.14	0.86, 1.52	1.17	0.83, 1.65	1.14	0.82, 1.59
Psycholeptics (N05)	1.04	0.76, 1.44	1.03	0.76, 1.40	1.10	0.81, 1.49	1.08	0.81, 1.44	0.94	0.69, 1.27	0.88	0.64, 1.22
Psychoanaleptics (N06)	1.02	0.79, 1.32	1.00	0.78, 1.30	1.01	0.79, 1.29	0.99	0.76, 1.29	0.82	0.64, 1.04	0.84	0.62, 1.14
Drugs for obstructive airway diseases (R03)	1.07	0.80, 1.44	1.11	0.84, 1.46	1.06	0.85, 1.33	1.10	0.87, 1.39	0.98	0.70, 1.38	1.14	0.83, 1.55

IPTW = Inverse-Probability-of-Treatment-Weighted Regression

a A priori selected covariates accounted for: age, sex, marital status, education, location, employment status, annual household income, house value, hypertension, angina, arrhythmia, heart attack, diabetes, high cholesterol, heart murmur, heart failure, stroke, TIA, asthma, other cardiovascular disease, osteoporosis, cirrhosis, arthritis, cancer, varicose ulcer, stomach ulcer, ARMD, glaucoma, cataracts, anxiety, Parkinson's disease, dementia, serious memory impairment, depression, other emotional problem, pain, disability, number of impairments, smoking status, depressive symptoms, anxiety symptoms and number of annual medical practitioner, hospital inpatient and outpatient visits.

b Covariates selected from the backwards stepwise procedure retaining $P<0.2$ from the a priori selected covariates and number of annual medical practitioner, hospital inpatient and outpatient visits.

4.5 Discussion

Middle-aged adults in the public healthcare system in Ireland were at greater risk of polypharmacy than those not in the public system after accounting for differences in underlying socioeconomic factors and health. However, this association was attenuated by 21-53% after accounting for differences in frequency of healthcare visits. There was evidence that some cardiovascular medications and drugs for acid related disorders were used more often by public patients, again partly explained by differences in the frequency of medical practitioner and hospital visits. Associations were mostly unaffected by adjusting for objective health measures in addition to self-reported health conditions, suggesting that self-report is adequate for this purpose.

Increased polypharmacy among public patients could represent both over-prescribing to public patients due to additional medical practitioner visits and under use of medications due to cost barriers for patients without public healthcare coverage. Public patients in Ireland are known to access services more frequently (45), and if prescribing behaviour is influenced by patient demand and expectations of a prescription as noted in the UK healthcare system (116), this may lead to over-prescribing. We found that agents acting on the renin-angiotensin system, proton pump inhibitors (PPIs) and non-steroidal anti-inflammatories were used more frequently by public patients, and these classes have previously been associated with over- or inappropriate prescribing in Ireland (46,47). We also found greater use of analgesics in public patients, however chronic pain is more frequently reported by those with lower socioeconomic status (117), so unmeasured socioeconomic confounding could be a factor.

Similar to other studies, we found that effect estimates were similar using multivariable regression and regression adjusted for the PS (33,43,44). Effect estimates using the IPTW method were generally closer to the null, less precise and more sensitive to trimming than adjusting for the PS. Sensitivity to large weights is a limitation of IPTW to which there is no perfect solution

(118). Larger weights could have resulted from the inclusion of a larger number of covariates thus leading to the possibility of non-positivity (119), whereby there are patients with certain combinations of characteristics that mean they are almost certain to have or not have polypharmacy. However, as there were few large weights, we cannot rule out that the differences in trimmed estimates could also be due to treatment effect heterogeneity at the tails of the PS distribution. Asymmetrical trimming generally improved model stability at the expense of altering the study population. After trimming, our population of public patients had a lower prevalence of polypharmacy (18% rather than 22%), thus reducing the range of patients to which our findings are applicable. A range of percentile cut points were considered for the various models, and 1% to 99% chosen as a compromise between excluding extreme weights, but with minimal restriction to the population considering the relatively uniform effects observed.

Little research has been devoted to variable selection for propensity scores (114,120,121). Recent studies suggest that selecting variables associated with the outcome reduces bias and improves precision, but give little guidance on effective methods to do this (114,120,122). Although backwards stepwise selection is commonly used to select variables associated with the outcome in regression modeling, and to our knowledge it has not been compared for use in PS methods, it led to very similar effect estimates to a priori variable selection here. However, the exclusion of income and education from the propensity score led to remaining imbalances in these variables implying some residual confounding remained. Further research is needed comparing practical data-driven variable selection methods for PSs, particularly when using IPTW where there is a need to balance confounding control against the risk of non-positivity and extreme weights (119). The backwards stepwise procedure appeared to improve precision using the robust SEs, but this improvement disappeared when examining the bootstrapped SEs. Hence, we recommend bootstrapping estimates when using data-driven variable selection due to the underestimation of true uncertainty in both the variable selection procedure and PS estimation (115).

This study involved considerable confounding. Our crude estimates reduced considerably after adjustment for sociodemographics and self-reported health. Pharmacoepidemiological analyses are often conducted using routinely collected datasets that do not include objective measures of health status, and it has been suggested that this could cause substantial unmeasured confounding (109,110). However, further adjustment for objective health measures in this study, resulted in minimal reductions in the RRs, suggesting that unmeasured health confounding is limited. Some residual confounding may nevertheless remain, particularly with respect to disease severity and socioeconomic factors which are difficult to precisely measure in an epidemiological context.

The main strength of our study was the availability of a large population-representative cohort who underwent a detailed assessment of their socioeconomic characteristics, cognitive and physical health, allowing us to examine potential confounders usually unavailable to pharmacoepidemiological studies. The data was fairly complete. For example, only 1% of participants were excluded from the main analysis due to missing data. Missing data indicators were also used for 4 covariates in the main analysis, none of which were strong confounders in the multivariable model. Combining multiple imputation for missing data with our bootstrapping procedure was not computationally feasible, but using multiple imputation instead of missing data categories did not alter the results when estimating robust standard errors.

Medication reporting was based on self-report within the home, which has the advantage that we are measuring medicines taken by the participant as opposed to those prescribed or dispensed. On the other hand we cannot be certain whether participants were adhering to their prescriptions or were failing to report some medications. We previously compared the self-reported medications to pharmacy dispensing claims for public patients and good agreement was generally found (123). Most health variables were self-reported, but objective measures added only limited additional information beyond the self-report measures. Those completing the health measures were not fully representative of the whole population; non-attendees were

more likely to have public healthcare coverage, less education, be single and smoke. However, conclusions were similar when restricting our primary analysis to only those who underwent a health assessment.

The cross-sectional nature of this study is a limitation. It is possible that observed health status and public healthcare coverage status at the time of interview may not fully reflect health status and coverage at the time of prescribing. However, administrative data suggests that at least 97% of those with public healthcare coverage had been eligible for the 3 months prior to data collection, and that very few individuals under 70 years in the cohort become newly eligible each year, suggesting that healthcare coverage was largely constant among this cohort. Therefore, although it is possible that worsening health leads to increases in medical practitioner visits as well as decreasing household income thus enabling public healthcare coverage eligibility, this is unlikely to have occurred in significant numbers. Among those without public healthcare, we did not distinguish between those with private health insurance and the uninsured as these groups incur similar out-of-pocket expenses for both primary care consultations and medications. Furthermore, the rate of polypharmacy was 7% in both those with private insurance (n=3,059) and no insurance (n=805) and there were no statistically significant differences between the two groups when adjusted for the covariates. Analysing individual medication classes suggests that the effect of public healthcare varied by therapeutic class, however we did not attempt to distinguish use of indicated preventive therapies from overprescribing and so these findings should be interpreted with caution.

Free healthcare may have positive and negative consequences for an individual's health. We have demonstrated a higher risk of polypharmacy among those with public healthcare coverage in Ireland, which may reflect both restricted use of medications by patients without public coverage and inappropriate prescribing among patients with public coverage. Further evidence is needed to inform policy decisions around the public provision of healthcare,

specifically to ascertain the effect on healthcare utilisation and population health if public healthcare coverage were available to all.

5 Study III - Polypharmacy including falls risk-increasing medications and subsequent falls in community-dwelling middle and older aged adults

5.1 Abstract

Background Polypharmacy is an important risk factor for falls, but recent studies suggest only when including medications associated with increasing risk of falls.

Design Prospective, population-based cohort study

Subjects 6666 adults aged ≥50 years from The Irish Longitudinal study on Ageing.

Methods Participants reported regular medication use at baseline. Any subsequent falls, the number of falls, and any injurious falls, were reported two years later. Associations between polypharmacy (>4 medications) and fall risk-increasing medications and any falls or injurious falls were assessed using modified Poisson regression. Negative binomial regression was used to model the number of falls.

Results During follow-up, 231 falls per 1000 person-years were reported. Polypharmacy including antidepressants was associated with a greater risk of any fall (adjusted relative risk (aRR) 1.28, 95% CI 1.06 to 1.54), of injurious falls (aRR 1.51, 95% CI 1.10 to 2.07), and a greater number of falls (adjusted incident rate ratio (aIRR) 1.60, 95% CI 1.19 to 2.15), but antidepressant use without polypharmacy, and polypharmacy without antidepressants were not. Benzodiazepine use was associated with a greater number of falls (aIRR 1.32, 95% CI 1.05 to 1.65), independent of polypharmacy. However, injurious falls were more likely with benzodiazepines coupled with polypharmacy (aRR 1.40, 95% CI 1.04 to 1.87). The other fall risk-increasing medications of antihypertensives, diuretics, and antipsychotics were not associated with outcomes.

Conclusion In middle and older aged adults, polypharmacy including antidepressant or benzodiazepine use, was associated with injurious falls and a greater number of falls.

5.2 Introduction

Falls are common in the elderly with around 30% of community-dwelling older adults falling every year and around half of these experiencing multiple falls (56,57). Most falls in this age group result in injury ranging from more severe fractures and dislocations to less severe cuts and bruises (57,58). Falls are associated with increased rates of hospitalisation, institutionalisation, disability, fear of falling, decreased activity and poorer quality of life (55).

Risk factors for falling are complex and involve intrinsic and extrinsic factors (64). Medications are modifiable extrinsic risk factors. Certain medication classes, including benzodiazepines, antidepressants, antipsychotics, antihypertensives, and diuretics have been consistently associated with increased falling risks in population-based studies (68,69). Polypharmacy is also an important risk factor for falling (18). However, recent studies suggest that the association may not be significant when indications for the medicines are considered (65), and that polypharmacy only poses a risk if it includes falls risk-increasing medications (76).

In a large prospective cohort study of adults aged ≥50 years in Ireland, we investigated the interaction between polypharmacy and established medications associated with falling on the subsequent risk of any fall, of a greater number of falls, and of injurious falls over two years after adjusting for sociodemographics and comorbidity.

5.3 Methods

5.3.1 Participants

Data were retrieved from the Irish Longitudinal study on Ageing (TILDA) which is representative of the community-dwelling ≥50 year olds in Ireland. The sample is described in detail elsewhere (87). In its first wave (September 2009 - February 2011), TILDA recruited 8,175 individuals with participants completing an extensive in home face-to-face computer based interview, self-

completion questionnaire and nurse conducted health assessment. Households were selected from a clustered sample of Irish residential addresses with an overall response rate of 62.0%. TILDA was approved by the Faculty of Health Sciences Research Ethics Committee of Trinity College Dublin. Participants with dementia or with a cognitive impairment severe enough to prevent consent (determined at the discretion of the interviewer) were not included in the study.

5.3.1.1 Falls outcomes

In TILDA's second wave (April - December 2012), 6831 participants (201 had died, 1,111 dropped out) were re-interviewed in the home. They were asked whether they had fallen since the first interview, how many times they had fallen and whether they injured themselves seriously enough to need medical treatment (injurious fall). To improve falls data accuracy, we excluded participants with dementia (n=46), institutionalised (n=20), with missing baseline medication data (n=82), or whose falls data was missing or provided by a proxy (n=49), leaving 6666 participants for analysis (figure 5.1).

5.3.1.2 Baseline medications

Interviewers recorded all medications taken on a regular basis by viewing medication packages. Medications were assigned WHO Anatomic Therapeutic Chemical (ATC) classification codes (88). Polypharmacy was defined as regular use of five or more medicines (excluding dietary supplements) (6). Falls risk-increasing medications were identified from previous systematic reviews and meta-analysis as antihypertensives (ATC C02, C07A, C08, C09A, or C09C), diuretics (C03), antipsychotics (N05A), benzodiazepines (N05BA, N05CD, or N05CF), and antidepressants (N06A) (68,69).

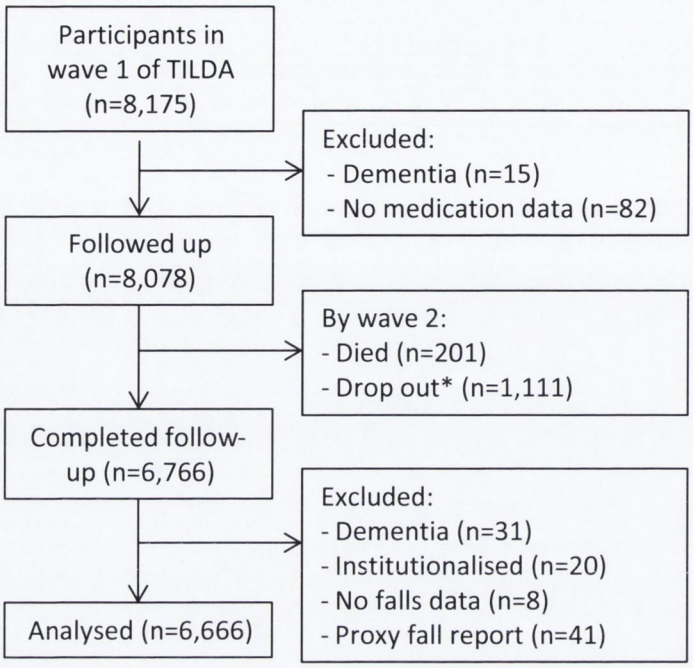


Figure 5.1. Selection of participants with longitudinal falls data for analysis

* For the 1,111 dropping out by wave 2, the main reasons were refusal (87%), non-contact (10%), and moving abroad (3%).

5.3.1.3 Baseline health status

History of a diagnosis were reported for: hypertension, angina, heart attack, heart failure, diabetes, transient ischaemic attack, high cholesterol, heart murmur, arrhythmia, stroke, other cardiovascular disease, cataracts, glaucoma, age related macular degeneration, chronic lung disease, asthma, osteoporosis, cancer, arthritis, stomach ulcer, liver disease, varicose ulcer, Parkinson's disease, anxiety, depression, or other psychological disorder (emotional problem, mood swings, hallucinations, schizophrenia, or other). The number of health conditions reported from this list was recorded.

Disability was reported as any limitations in Instrumental Activities of Daily Living (IADL) or Activities of Daily Living (ADLs). Participants self-reported pain (none, mild, moderate or severe), urinary incontinence in the past 12 months, sleep problems (trouble falling asleep most of the time), vision and hearing (excellent, very good, good, fair, or poor), and any hospital

admission in the last year. Falls related history included falls in the last year, fractures (hip or wrist), blackouts or fainting. Cognition was assessed using the animal naming test, where participants were asked to name as many different animals as possible in one minute. Depressive symptoms were assessed using the Centre for Epidemiologic Studies Depression Scale (89).

Approximately 40% of the Irish population are entitled to free healthcare through the public General Medical Services scheme. Eligibility is means tested and is available to those for whom medical expenses would cause undue hardship. Most of those aged over 70 years are eligible. The remaining population purchase private insurance plans, whilst many remain uninsured but caps exist on medical expenses.

5.3.2 Statistical analysis

Separate regression models were used to estimate the effect of (i) each falls risk-increasing medication class and (ii) polypharmacy on each fall-rated outcome. We used modified Poisson regression to calculate the relative risks (RR) for both any falls and injurious falls outcomes (112). A sandwich estimator was used to estimate a robust variance for the 95% confidence intervals (CI) (112). We used negative binomial regression to calculate incident rate ratios (IRR) and 95% CIs for the number of falls due to over-dispersion. The number of falls was capped at 5 due to concerns on the accuracy of reporting beyond this. Associations are provided unadjusted and adjusted for sociodemographics, days between interviews, health-related variables, and fall-related variables.

For each of the regression models above, the interaction between polypharmacy and the falls risk-increasing medication class was tested. For medication classes with a statistically significant interaction for any falls outcome, the results of this interaction were reported for all falls outcomes. We also estimated the adjusted falls risks for polypharmacy including all statistically significant falls-risk increasing medication classes.

To examine differential attrition, we used modified Poisson regression to estimate the association between baseline polypharmacy and falls risk-increasing medication use and loss to follow-up (i.e. study dropout, or proxy-reported or no falls data) by wave 2 after adjusting for the potential covariates. Analyses were performed using Stata Version 12.0. Significance at $p<0.05$ is assumed.

5.4 Results

Of the 6,666 eligible participants completing the falls questions at follow-up, 1,140 (17%) participants reported polypharmacy at baseline. The mean (SD) time between the baseline and second interview was 24.3 (2.8) months, range 15.9 - 36.8 months. A total of 1,455 (22%) participants reported falling during follow-up, reporting 3,113 falls in total (rate of 231 falls per 1000 person-years) and 642 (10%) reported an injurious fall. Those who fell were more likely to be female, older, have more chronic diseases, disability, report moderate/severe pain, and a history of falls and/or fractures (table 5.1). For example, 36% of those falling during follow-up had also fallen in the previous year.

5.4.1 Medication class and falls

Table 5.2 details the identified falls-risk increasing medications reported at baseline. Neither polypharmacy, nor the use of antihypertensives, diuretics, or antipsychotics were associated with any falls outcomes after adjusting for the covariates (table 5.3). Benzodiazepine use was associated with a greater number of falls in the next two years (adjusted incidence rate ratio (aIRR) 1.32, 95% confidence interval 1.05 to 1.65), but the association did not reach statistical significance for the 'any falls' or 'injurious falls' outcomes. Antidepressant use was associated with a greater number of falls (aIRR 1.28, 95% CI 1.03 to 1.60) and risk of an injurious fall (adjusted rate ratio (aRR) 1.37, 95% CI 1.06 to 1.75). There was evidence of an association with the risk of any fall, but this did not quite reach statistical significance (aRR 1.16, 95% CI 0.99 - 1.35).

Table 5.1. Baseline characteristics of participants reporting a fall by the second interview

	No falls (n=5,211)		At least one fall (n=1,455)		
Baseline characteristics	n	%	n	%	p†
Sociodemographics					
Sex – women	2,732	52.4	884	60.8	<0.001
Age, mean (SD)	62.7 (9.2)		65.0 (9.6)		<0.001
Third/higher education	1,602	30.7	473	32.5	0.18
Employed	2,099	40.3	450	30.9	<0.001
Household income < €20,000*	1,388	28.9	452	34.2	0.002
Lives alone	1,024	19.7	378	26.0	<0.001
Current smoker	892	17.1	243	16.7	0.71
Chronic disease					
Number of health conditions					<0.001
0	1,083	20.8	210	14.4	
1	1,446	27.7	292	20.1	
2	1,134	21.8	331	22.7	
3	739	14.2	231	15.9	
4	432	8.3	164	11.3	
5+	377	7.2	227	15.6	
Moderate/severe pain	1,148	22.0	512	35.2	<0.001
Urinary incontinence	579	11.1	246	16.9	<0.001
Trouble falling asleep	1,715	32.9	610	41.9	<0.001
Depressive symptoms, median (IQR)*	3 (1-7)		4 (1-10)		<0.001
Disability (ADL or IADL)	447	8.6	262	18.0	<0.001
Fair/poor self-rated vision	425	8.2	157	10.8	0.002
Fair/poor self-rated hearing	694	13.3	238	16.4	0.003
Cognition, animal naming mean (SD)*	21.0 (7.0)		20.4 (7.1)		0.008
Healthcare utilisation					
Public healthcare coverage	2,341	44.9	780	53.6	<0.001
Hospital admission in past year	589	11.3	237	16.3	<0.001
Fall-related history					
Fall in the last year	752	14.4	520	35.7	<0.001
History of hip or wrist fracture	636	12.2	269	18.5	<0.001
History of fainting/blackouts	889	17.1	348	23.9	<0.001

† Chi-square test for binary and ordinal variables, t-test for continuous variables, Mann-Whitney U-test for depressive symptoms.

* Missing data (number of participants): Income (529), Depressive symptoms (89), Cognition (26)

Table 5.2. Falls-risk increasing medications reported by participants at baseline

Medication class	ATC	Medication subclass	n
Antihypertensives			2112
	C02	Antihypertensives	124
	C07A	Beta blocking agents	869
	C08	Calcium channel blockers	918
	C09A	ACE inhibitors, plain	784
	C09C	Angiotensin II antagonists, plain	533
Diuretics			538
	C03A	Low-ceiling diuretics, thiazides	233
	C03B	Low-ceiling diuretics, excluding thiazides	69
	C03C	High-ceiling diuretics	178
	C03D	Potassium-sparing agents	22
	C03E	Diuretics and potassium-sparing agents in combination	61
Antipsychotics			81
	N05A	Antipsychotics	81
Benzodiazepines			366
	N05BA	Anxiolytics - benzodiazepine derivatives	135
	N05CD	Hypnotics and sedatives - benzodiazepine derivatives	100
	N05CF	Benzodiazepine related drugs	159
Antidepressants			422
	N06AA	Non-selective monoamine reuptake inhibitors	85
	N06AB	Selective serotonin reuptake inhibitors	232
	N06AF/G/X	Other antidepressants	122

Table 5.3. Associations (with 95% CI) between polypharmacy, the regular use of high-risk medications and incident falls

		Any fall		Number of falls		Injurious fall	
Medication class	n	Crude RR	Adjusted RR*	Crude IRR	Adjusted IRR*	Crude RR	Adjusted RR*
Polypharmacy	1140	1.54 (1.39 - 1.71)	1.01 (0.90 - 1.14)	1.94 (1.69 - 2.23)	1.10 (0.93 - 1.30)	1.70 (1.45 - 2.01)	1.02 (0.84 - 1.24)
Antihypertensives	2112	1.16 (1.06 - 1.28)	0.91 (0.81 - 1.02)	1.24 (1.09 - 1.40)	0.92 (0.78 - 1.08)	1.19 (1.02 - 1.38)	0.89 (0.73 - 1.07)
Diuretics	538	1.40 (1.22 - 1.61)	1.06 (0.92 - 1.23)	1.45 (1.19 - 1.77)	1.07 (0.87 - 1.31)	1.42 (1.12 - 1.78)	0.96 (0.75 - 1.23)
Antipsychotics	81	1.02 (0.68 - 1.53)	0.71 (0.49 - 1.02)	1.15 (0.69 - 1.94)	0.58 (0.34 - 1.01)	1.42 (0.81 - 2.47)	0.88 (0.51 - 1.47)
Benzodiazepines	366	1.72 (1.49 - 1.98)	1.14 (0.98 - 1.34)	2.10 (1.68 - 2.64)	1.32 (1.05 - 1.65)	2.01 (1.59 - 2.52)	1.24 (0.97 - 1.58)
Antidepressants	422	1.66 (1.45 - 1.91)	1.16 (0.99 - 1.35)	2.18 (1.77 - 2.69)	1.28 (1.03 - 1.60)	1.96 (1.57 - 2.44)	1.37 (1.06 - 1.75)

RR=relative risk; IRR=incident rate ratio

* Adjusted for baseline covariates: age, sex, living alone, education, employment status, income, smoking status, time between interviews, comorbidities (listed in text), incontinence, pain, sleep problems, depressive symptoms, cognition, self-rated vision, self-rated hearing, disability, public healthcare coverage, history of falls, fracture, fainting, and hospitalisation.

5.4.2 Polypharmacy including and excluding fall risk-increasing medications

There was a significant interaction effect between antidepressant use and polypharmacy with respect to any fall (p=0.03) and the number of falls (p=0.02) (table 5.4). There was also a significant interaction between benzodiazepine use and polypharmacy with respect to injurious falls (p=0.03). Polypharmacy including antidepressant use was associated with a greater risk of any fall (aRR 1.28, 95% CI 1.06 to 1.54) and a greater number of falls (aIRR 1.60, 95% CI 1.19 to 2.15) compared to those without polypharmacy or using antidepressants, but both antidepressant use without polypharmacy, and polypharmacy without antidepressants were not (table 5.5). In addition there was an elevated risk of an injurious fall for those with polypharmacy including benzodiazepines (aRR 1.40, 95% CI 1.04 to 1.87). Seventy participants reported polypharmacy and both antidepressant and benzodiazepine use. This was associated with a greater risk of an injurious fall (aRR 2.02, 95% CI 1.32 to 3.08), and a greater number of falls (aIRR 1.70, 95% CI 1.08 to 2.67), but not any fall (aRR 1.25, 95% CI 0.94 to 1.65).

Table 5.4. P-values for the interaction between medication class and polypharmacy according to fall outcome

Medication class	Any fall	Number of falls	Injurious fall
Antihypertensives	0.78	0.31	0.32
Diuretics	0.93	0.50	0.75
Antipsychotics	0.10	0.26	0.78
Benzodiazepines	0.52	0.43	0.03
Antidepressants	0.03	0.02	0.12

Table 5.5. Multivariate* associations (95% CI) between polypharmacy, including and excluding benzodiazepines or antidepressants, and incident falls

		Any fall	Number of falls	Injurious fall
Medications	n	RR (95% CI)	IRR (95% CI)	RR (95% CI)
No BZD, no polypharmacy	5368	1.00	1.00	1.00
No BZD, polypharmacy	932	1.00 (0.88 - 1.14)	1.09 (0.91 - 1.30)	0.91 (0.73 - 1.13)
BZD, no polypharmacy	158	1.22 (0.96 - 1.55)	1.43 (1.03 - 1.99)	0.84 (0.53 - 1.35)
BZD, polypharmacy	208	1.11 (0.91 - 1.35)	1.30 (0.97 - 1.75)	1.40 (1.04 - 1.87)
p for interaction†		*0.52*	*0.43*	*0.03*
No AD, no polypharmacy	5295	1.00	1.00	1.00
No AD, polypharmacy	949	0.95 (0.83 - 1.08)	0.99 (0.82 - 1.18)	0.92 (0.74 - 1.14)
AD, no polypharmacy	231	0.98 (0.78 - 1.24)	0.97 (0.71 - 1.32)	1.13 (0.79 - 1.63)
AD, polypharmacy	191	1.28 (1.06 - 1.54)	1.60 (1.19 - 2.15)	1.51 (1.10 - 2.07)
p for interaction†		*0.03*	*0.02*	*0.12*

RR=relative risk; IRR=incident rate ratio; BZD=benzodiazepine; AD=antidepressant

* Adjusted for baseline covariates: age, sex, living alone, education, employment status, income, smoking status, time between interviews, comorbidities (listed in text), incontinence, pain, sleep problems, depressive symptoms, cognition, self-rated vision, self-rated hearing, disability, public healthcare coverage, history of falls, fracture, fainting, and hospitalisation.

† P-value for the interaction between polypharmacy and use of the specific medication class.

5.4.3 Attrition

In total 1,160 participants dropped out during follow-up, or had no or proxy-reported falls data. They were more likely to be smokers, have less education and lower cognition than those assessed at follow-up (see supplementary material in chapter 5.6). However, they were not more likely to have fallen at baseline nor report greater use of any medication class studied once adjusted for the other factors.

5.5 Discussion

In this prospective, population-based study of community-dwelling adults aged 50 years and older, polypharmacy was not associated with an increased risk of falls after adjustment for comorbidity. However, polypharmacy including antidepressant use was associated with a greater number of falls and of injurious falls. Benzodiazepine use was also only associated with an increased risk of injurious falls when combined with polypharmacy. However, benzodiazepine use was associated with a greater number of falls irrespective of polypharmacy.

Our findings are consistent with another population-based study of Dutch adults aged ≥55 years, who also found that polypharmacy was only associated with a greater risk of falling if it

included falls risk-increasing medications (76). However, this study was cross-sectional and although their definition of falls risk-increasing medications included a broader range of classes dominated by benzodiazepines, it did not include antidepressants. As studies differ in medication classes they find associated with falls, we only examined established fall risk-increasing medications identified from systematic reviews (68,69).

Polypharmacy entails frequent changes in medications, which could lead to confusion and a greater chance of drug interactions (124). The identified falling risks may be attributed to potential drug interactions between antidepressants and other medications, or the concomitant use of other psychotropic medications, as, for example, 67% of those with polypharmacy including antidepressants were also taking another psychotropic medication (benzodiazepine for 37%). For community-dwelling older men, studies have found multiple central nervous system (CNS) active medications have further increased the risk of falls (125), and fractures (126). They suggest that the effects of concomitant use of several CNS active medications on postural balance may be additive (126). Also the multiple underlying diseases causing the concomitant use of these medications may have negative effects on physical functioning (126).

The association between antidepressant use and falls has been replicated many times (68), and effects attributed to sedation and postural hypotension (127). Unfortunately, we had insufficient power to examine the effects of specific antidepressant sub-classes. Selective serotonin reuptake inhibitors negatively affect bone metabolism (128), whereas syncope can occur with tri-cyclic antidepressant use (129). All classes of antidepressants can cause cardiovascular depressant effects by inhibiting cardiovascular ion channels (130).

Benzodiazepine use has also commonly been implicated with increased falls risks (68), and attributed to dizziness, sedation, impaired motor coordination, and postural disturbances (127). Our findings for injurious falls are in line with recent studies examining concomitant benzodiazepine use with injury and hip fracture risk (131,132), which suggest that

pharmacodynamic drug interactions (e.g. with CNS active medications, muscle relaxants, opioids, and H1-antihistamines) with benzodiazepines contribute to the excess risk.

Our findings of no association for polypharmacy, antihypertensives, and diuretics, further highlight the importance of thorough adjustment for confounders (65). However, we do not believe our findings reflect over-adjusting, as, although each of these exposures was significantly related to falls outcomes, this was not so when adjusted for age, sex and only the self-reported health conditions. The exclusion of those institutionalised or with dementia from our cohort could be responsible for our lack of association for antipsychotics, and may lead to underestimation of the association with benzodiazepines, antidepressants and falling.

Our study has a number of strengths. The use of a large randomly sampled population-representative cohort with longitudinal follow-up ensured medication exposure preceded the falls outcomes. Participants underwent a detailed assessment of their socioeconomic characteristics, cognitive and physical health, allowing us to examine potential confounders usually unavailable to pharmacoepidemiological studies. It was important to fully adjust for comorbidity (65). We modeled all health conditions simultaneously allowing each condition to exert its own weight for predicting falls, rather than using a pre-weighted comorbidity index which provides only limited confounding control (133). Most health variables were self-reported, but results were unchanged when additionally adjusted for objectively measured health status and frailty for a subset of participants who attended a health assessment (see supplementary material in chapter 5.6). Nevertheless, despite this extensive adjustment for health-related major risk factors for falling, the possibility of some residual confounding by indication cannot be excluded.

Medication reporting based on self-report was improved by interviewers viewing medication packages. Self-report allows the collection of non-prescription medication use and potentially better reflects adherence than prescribing or dispensing records (123). We previously compared the self-reported medications to pharmacy dispensing claims for public patients and good agreement was generally found (123). Performing pharmacoepidemiology in cohort studies

is limited by medication use only being ascertained at the time of interview. Although falling was recorded subsequent to medication exposure, we lack the ability to observe the full temporal relationship between the use of medications and the falls. However, medication use remained fairly constant with 66-87% of those taking each medication class at baseline continued to at follow-up (see supplementary material in chapter 5.6). We also only considered established falls risk-increasing medication classes; hence we may be missing more specific drug classes that are risk factors for falling. We were also unable to examine the effect of dose or duration.

The data was mostly complete. Only 1% of participants were excluded from the main analysis due to missing falls or medication data. Study attrition was not associated with either a baseline falls history, or use of any medication class studied. Refusal at baseline was associated with lower education (87). Use of study inverse probability weights to weight the analysis for differential refusal at baseline or loss to follow-up led to very similar findings (results not shown). The association between medication class and baseline falls also did not vary completion rates at wave 2 (results not shown), hence we have no reason to believe the associations with incident falls would be differential.

There may be misclassification of the falling outcomes. Concerns over the accuracy of falls recall in the elderly have been discussed extensively, with studies finding that injurious falls are recalled more accurately (134). Falls may be under-reported due to the fairly long follow-up and the misclassification of the any fall outcome may explain why we failed to identify any statistical significant associations for that outcome. The effect of under reporting of falls was minimised by excluding institutionalised participants and those with apparent cognitive impairment and dementia.However, we have no reason to believe the recall would be differential, and the rate of falling among our sample was comparable to that found in similar populations (65,135).

In this prospective study of community-dwelling middle and older-aged adults, polypharmacy was associated with increased falls risks if including regular antidepressant or

benzodiazepine use. Medication reviews have been shown to be successful at reducing falls in the older population (136), and these findings give more specific medication classes to target interventions towards. The risks and benefits need to fully considered when initiating these medications in those at risk of falls. The findings also further support the idea that it is the type of polypharmacy that is important for adverse events (69,76).

5.6 Supplementary material

In study II (in chapter 4), we found different patterns of medication use according to access to public healthcare coverage, leading to the possibility of confounding by healthcare system use when examining health outcomes. For the falling outcomes, however, there was no evidence of a confounding effect by access to public healthcare coverage. For example, the adjusted RR for the association between access to public healthcare coverage and injurious falls was 1.04 (95% CI 0.86 to 1.26). This could be due to the short follow-up, so further research is still needed to examine whether differences in access to public healthcare in Ireland has longer term health consequences, potentially using subsequent TILDA waves.

Results were similar when additionally adjusted for objectively measured health (i.e. gait speed, Timed Up-and-Go, grip strength, BMI, orthostatic hypotension, osteoporosis) for a subset of participants who attended a health assessment (table 5.6). However, the only statistically significant association remaining was between antidepressant use and injurious falls (aRR 1.49, 95% CI 1.05 - 2.11).

Table 5.7 describes the reported medication use at baseline and at 2-year follow-up. Most (87%) of those with polypharmacy at baseline, also reported polypharmacy at follow-up. Antihypertensive use remained the most constant, with 89% of those reporting use at baseline, still reported regular use at follow-up. For the other medication classes studied, 66-78% of users still reported regular use at follow-up.

A total of 1,111 participants were excluded from the falling analysis due to dropping out of TILDA during follow-up. The characteristics of those that did and did not dropout are detailed in table 5.8. Those dropping out of the study were independently more likely to be smokers, not married, have less education and lower cognition than those assessed at follow-up.

Table 5.6. Associations (with 95% CI) between polypharmacy, the regular use of high-risk medications and incident falls for participants completing a health assessment (N=4,535)*

		Any fall	Falling rate	Injurious fall
Medication class	N	Adjusted RR*	Adjusted IRR*	Adjusted RR*
Polypharmacy	657	0.93 (0.79 - 1.09)	1.04 (0.83 - 1.29)	1.04 (0.80 - 1.37)
Antihypertensives	1294	0.87 (0.74 - 1.01)	0.89 (0.73 - 1.09)	0.74 (0.57 - 0.97)
Diuretics	288	1.12 (0.93 - 1.36)	1.01 (0.77 - 1.32)	1.04 (0.75 - 1.44)
Antipsychotics	50	0.68 (0.41 - 1.12)	0.59 (0.28 - 1.28)	0.74 (0.31 - 1.72)
Benzodiazepines	216	1.17 (0.95 - 1.45)	1.32 (0.98 - 1.78)	1.05 (0.72 - 1.55)
Antidepressants	253	1.18 (0.98 - 1.43)	1.31 (0.97 - 1.76)	1.49 (1.05 - 2.11)

RR=relative risk; IRR=incident rate ratio

* Adjusted for baseline covariates: age, sex, living alone, education, employment status, income, smoking status, time between interviews, comorbidities (listed in text), incontinence, pain, sleep problems, depressive symptoms, cognition, self-rated vision, self-rated hearing, disability, public healthcare coverage, history of falls, fracture, fainting, hospitalisation, gait speed (quintiles), Timed Up-and-Go (quintiles), grip strength (quintiles), BMI (quintiles), orthostatic hypotension (normal, no recovery after 40s, no recovery after 110s), osteoporosis heel ultrasound (normal, osteopenia, osteoporosis).

Table 5.7. Medication use at baseline and at 2-year follow-up

	Regular use	Regular use at 2-year follow-up		P(use at 2-years
Medication	at baseline	Yes	No	given baseline use)
Antihypertensives	Yes	1875	237	0.89
	No	514	4040	
Diuretics	Yes	377	161	0.70
	No	199	5929	
Antipsychotics	Yes	57	24	0.70
	No	51	6534	
Benzodiazepines	Yes	241	125	0.66
	No	193	6107	
Antidepressants	Yes	330	92	0.78
	No	225	6019	
Polypharmacy	Yes	993	147	0.87
	No	869	4657	

Table 5.8. Characteristics of participants who completed the wave 2 interview or dropped out between wave 1 and 2, and multivariate predictors of dropout

		Completers (N=6,766)		Dropout (N=1,111)			Multivariate predictors of dropout*		
Characteristic		n	%	N	%	p	RR	95% CI	p
Sex – women		3,672	54.3	615	55.4	0.50	n/a		
Age, mean (SD) years		63.4	9.5	64.2	10.1	0.008	n/a		
Education	Primary/none	1,922	28.4	427	38.5	<0.001	1.00		0.008
	Secondary	2,750	40.7	419	37.8		0.83	0.73 - 0.94	
	Third/higher	2,093	30.9	263	23.7		0.82	0.70 - 0.97	
Employment	Employed	2,558	37.8	366	32.9	0.008	n/a		
Status	Retired	2,454	36.3	416	37.4				
	Other	1,730	25.6	323	29.1				
Marital status	Married	4,738	70	768	69.1	0.03	1.00		0.03
	Never married	646	9.5	109	9.8		0.90	0.74 - 1.09	
	Separated/divorced	474	7	58	5.2		0.68	0.53 - 0.88	
	Widowed	908	13.4	176	15.8		0.93	0.79 - 1.09	
Annual household income									
	<€10k	572	8.5	105	9.5	<0.001	1.00		0.10
	€10 - €19k	1,315	19.4	260	23.4		1.01	0.82 - 1.25	
	€20k - €39k	2,262	33.4	372	33.5		0.90	0.74 - 1.10	
	€40k - €69k	1,433	21.2	185	16.7		0.82	0.65 - 1.03	
	>€70k	646	9.5	79	7.1		0.84	0.63 - 1.11	
Smoking status	Never	3,007	44.4	456	41.0	<0.001	1.00		<0.001
	Past	2,606	38.5	399	35.9		1.00	0.89 - 1.14	
	Current	1,153	17.0	256	23.0		1.32	1.14 - 1.52	
Cognition**, mean (SD)		20.8	7.0	18.4	6.7	<0.001	0.96	0.95 - 0.97	<0.001
CES-D, median (IQR)		3	1 – 8	4	1 - 9	<0.001	n/a		

CES-D = Center for Epidemiologic Studies Depression Scale

*Variables selected using backwards stepwise retaining p<0.15. ** Cognition assessed using the animal naming test

6 Study IV - Use of medications with anti-cholinergic activity and injurious falls in community-dwelling adults aged 50 years and older

6.1 Abstract

Objective To assess the association between the use of medications with anti-cholinergic activity and the subsequent risk of falls in middle and older aged adults.

Design Prospective, population-based study, using data from The Irish Longitudinal study on Ageing (TILDA).

Setting Irish population

Participants 6666 community-dwelling dementia-free adults aged 50 years and older.

Main outcome measure Injurious falls over two years follow-up.

Results Between the baseline and second interviews, the rate of reported falls was 231 per 1000 person-years. The regular use of medications with definite anti-cholinergic activity at baseline was not associated with an increased risk of having any fall over the next two years (adjusted risks 21.7 vs 23.8%; relative risk (RR) 1.12, 95% CI 0.93 to 1.33), but was associated with an increased risk of injurious falls (adjusted risks 13.6 vs 9.4%; adjusted RR 1.45, 95% CI 1.09 to 1.94) and a greater number of falls (adjusted rate 184 vs 246 per 1000 person-years; adjusted incident rate ratio 1.34, 95% CI 1.03 to 1.75). The use of additional medications with anti-cholinergic activity increased these risks further. Associations did not vary by age, sex, cognition, or falls history. Findings were replicated in those with linked pharmacy dispensing records (n=2402). The adjusted relative risk for baseline use of medications with definite anti-cholinergic activity and injurious falls over the next two years was 1.52 (95% confidence interval 1.05 to 2.19). Findings were also robust to adjustment for baseline objective health measures.

Conclusion The regular and recent use of medications with anti-cholinergic activity is associated with subsequent injurious falls and a greater number of falls.

6.2 Introduction

Fall-related injuries are of major public health concern (55). Around 30% of community-dwelling persons aged over 65 years fall annually (56,57), and more than half result in injury (57,58). Injuries can range from serious fractures, head injury and joint dislocations, to less serious soft-tissue bruises, cuts, and abrasions (59). Many injurious falls require lengthy hospitalisation and often result in institutionalisation (60,61). Less serious injuries can still lead to disability and fear of falling, decreased activity and poorer quality of life (56,59,60,63).

Risk factors for falls are multifactorial and involve a complex interplay between many intrinsic and extrinsic factors. Intrinsic health status has commonly been associated with falling; the most important examples of which include depression, comorbidity, urinary incontinence, pain, impaired vision, and cognitive impairment (64,65). The use of certain medications are risk factors for falling, particularly antipsychotics, antidepressants and benzodiazepines (68). Possible explanations include sedative, autonomic and extrapyramidal effects, and the effects on alpha-adrenergic receptors of psychotropics increase the risk of falling (70–74). A further factor could be their anti-cholinergic activity. Anti-cholinergic medications block muscarinic cholinergic receptors in the brain thereby inhibiting the parasympathetic nervous system (77). Common anti-cholinergic side-effects in the elderly, such as constipation, dry mouth, urinary disorders, and memory loss, often develop gradually and may get overlooked as they mimic the aging process (79). Other side-effects that may influence falls risk include blurred vision, increased heart rate, and Central Nervous System effects such as sedation, confusion, behavioural excitation and hallucinations (79,80). The use of medicines with anti-cholinergic activity is common in older adults(81), who are more susceptible to their effects, given age-related deficits in drug metabolism, elimination, and in cholinergic neurotransmission (77,79). These medications are prescribed for a variety of conditions including incontinence (e.g. Oxybutin), depression (e.g. Amitriptyline) and psychosis (e.g. Olanzapine) (78–80). Furthermore, older people are often prescribed a "cocktail" of

medicines with anti-cholinergic activity resulting in accumulative burden increasing the risk of side-effects(81).

Medications with anti-cholinergic activity have been implicated with cognitive decline in community-dwelling older populations, but little research has been devoted to examining the risks of functional decline and falls (83). We aimed to assess the association between the use of medications with anti-cholinergic activity and subsequent falls and injurious falls over two years in community-dwelling adults aged 50 years and older in Ireland. We examined the associations using both self-reported regular medication use data and linked pharmacy dispensing records in a subset.

6.3 Methods

6.3.1 Participants

Data were retrieved from the Irish Longitudinal study on Ageing (TILDA), a prospective study representative of the community-dwelling over 50s in Ireland. At baseline (September 2009 - February 2011), TILDA recruited 8,175 individuals with each participant undergoing an extensive in home face-to-face interview, invited to complete a self-reported questionnaire (SCQ) and undertake a nurse conducted health assessment. Households were selected from a clustered sample of Irish residential addresses with an overall response rate of 62.0%. The sample is described in detail elsewhere (87,93). TILDA was approved by the Faculty of Health Sciences Research Ethics Committee of Trinity College Dublin. Participants with dementia or with a cognitive impairment severe enough to prevent being able to personally consent to the study (determined at the discretion of the interviewer) were excluded.

6.3.2 Falls outcomes

In TILDA's second wave (April - December 2012), 6831 participants were re-interviewed in their home. They were asked whether they had had a fall since the first interview, how many times they had fallen and whether they injured themselves seriously enough to need medical treatment including surgery (injurious fall). To improve the accuracy of the falls data, we excluded participants with dementia, who had been institutionalised, or whose falls data was provided by a proxy, leaving 6666 participants in the analysis (figure 5.1).

6.3.3 Baseline medications – self report

Medication use was assessed both by interviewers in the home and by linkage to pharmacy dispensing records on a subset of patients. Interviewers asked participants for all medications taken on a regular basis, defined as "...like every day or every week", and viewed medication packages to enter the correct medication names. Medications were assigned World Health Organisation (WHO) Anatomic Therapeutic Chemical (ATC) Classification codes(88).

6.3.3.1 Baseline medications – pharmacy dispensing records

Linkage to pharmacy dispensing records was available for those enrolled in the General Medical Services (GMS) Scheme, who gave consent for their records to be linked and for whom linkage was successful (n=2402, 36%). Details of the linkage can be found elsewhere (123). Individuals enrolled in the GMS scheme are entitled to free health care and prescription medications at minimal cost. Eligibility is based on a gross income means assessment. Women and those over the age of 70 years are over represented in the scheme. The Irish Health Service Executive Primary Care Reimbursement Service (HSE–PCRS) pharmacy claims database collates information on dispensed prescribed medication for all individuals in the GMS Scheme. Medications are coded using the WHO ATC classification system (88). In addition to dispensing data, the database also

contains basic demographic information, such as gender, age and region of residence. Dispensing records were extracted for the 30 days prior to the TILDA baseline interview.

6.3.3.2 Anti-cholinergic assessment

The anti-cholinergic burden of self-reported regularly used medications and recently dispensed medications was assessed using the Anti-cholinergic Cognitive Burden (ACB) scale (78,137). Further information is available from www.agingbraincare.org/tools/abc-anti-cholinergic-cognitive-burden-scale. This is a published and recently updated scale that classifies, through expert consensus and literature review, the evidence for anti-cholinergic activity of medications. Content validity was tested by presenting the list to an expert interdisciplinary panel of geriatricians, pharmacists, geriatric psychiatrists, general physicians, specialist geriatric nurses, and aging brain researchers. Any disagreements were resolved by consensus. Medications with serum anti-cholinergic activity or in vitro affinity to muscarinic receptors but with no known clinically relevant negative cognitive effects were rated one on the ACB scale, and drugs with established and clinically relevant anti-cholinergic effects were scored 2 or 3 based on blood-brain penetration and any reported association with delirium.

Among each participant, total anti-cholinergic burden was defined as the sum of ACB scores for all medications taken. As an alternate measure, the ratings were categorised according to the most severely rated medication taken as none (score 0), possibly (1) or definitely (2-3) anti-cholinergic.

6.3.4 Baseline covariates

Baseline covariates were selected that have either been associated with falling previously (64), or are indications for the anti-cholinergic medications. Sociodemographic factors included gender,

age, residential status (living alone), socioeconomic status (household income, education and employment status), and smoking status.

Doctor diagnosed health conditions were reported for the following: hypertension, angina, heart attack, heart failure, diabetes, transient ischaemic attack (TIA), high cholesterol, heart murmur, arrhythmia, stroke, other cardiovascular disease, cataracts, glaucoma, age related macular degeneration (ARMD), chronic lung disease, asthma, osteoporosis, cancer, arthritis, stomach ulcer, liver disease, varicose ulcer, Parkinson's disease, anxiety, depression, or other psychological disorder (emotional problem, mood swings, hallucinations, schizophrenia, or other). The number of health conditions reported from this list was recorded.

Participants self-reported pain (none, mild, moderate or severe), urinary incontinence in the past 12 months, sleep problems (trouble falling asleep most of the time), their vision and hearing (both excellent, very good, good, fair, or poor), and any hospital admissions in the last year. Disability was reported as any limitations in Instrumental Activities of Daily Living (IADL) or Activities of Daily Living (ADLs). Falls related history included falls in the last year, fractures (hip or wrist) or blackouts or fainting. Depressive symptoms were assessed using the Centre for Epidemiologic Studies Depression Scale (89). Cognition was assessed using the animal naming test, where participants were asked to name as many different animals as possible in one minute.

6.3.5 Health assessment measures

Comprehensive health assessments were performed in one of two dedicated university centres (*n*=4,431, 66%). Functional mobility was measured via Timed Up-and-Go (TUG) and gait speed. The TUG measures the time for participants to rise from a chair, walk 3m, and return to sitting (91). A 4.88m gait mat was used to assess gait speed (cm/s) at usual walking pace. Handgrip strength was taken as the average for each hand measured using a dynamometer. Height and weight were measured using standard procedures for body mass index (BMI). The bone mass of a

participant's non-dominant foot was measured using quantitative heel ultrasound to provide an index of bone stiffness (SI). Osteoporosis was defined as SI ≤ 65%, osteopenia for SI between 65% and 86%, and normal bone density for SI >86% (43). Orthostatic blood pressure was measured using continuous beat-to-beat plethysmography (Finometer) during active stand. Orthostatic hypotension severity was graded by sustained failure to return to at least 90% of baseline systolic blood pressure at 40 seconds post stand, and at 110 seconds post stand (94). Further details about the health assessment procedures can be found elsewhere (93).

6.3.6 Statistical analysis

We used modified Poisson regression to calculate the relative risk (RR) for the association between baseline use of medications with anti-cholinergic activity and the presence of both falls and injurious falls between baseline and follow-up (112). A sandwich estimator was used to estimate a robust variance for the 95% confidence intervals (CI). We used negative binomial regression to calculate the incidence rate ratio (IRR) relating baseline use of medications with anti-cholinergic activity and the number of falls between baseline and follow-up due to over dispersion. The number of falls was capped at five due to concerns over the accuracy of reporting beyond this. Associations are provided unadjusted and adjusted for the sociodemographics, health and fall-related covariates listed above, as well as public healthcare coverage, duration between interviews, and number of non-anti-cholinergic medications. Analyses were repeated for participants attending a health assessment and among this group were additionally adjusted for the objective health measures. Continuous health measures were categorised into quintiles to enable non-linear relationships with the fall outcomes to be taken into account. Covariates with missing data were coded with a 'missing' category. Analyses were repeated for participants with linked pharmacy records, with baseline anti-cholinergic exposure defined by the medications dispensed in the 30 days before the TILDA interview and scored as previously defined.

Due to known associations between both Epilepsy and Parkinson's disease and falling, we performed a sensitivity analysis excluding participants taking medications for Epilepsy (ATC N03, excluding gabapentin and pregabalin which may also prescribed for neuropathic pain) or Parkinson's disease (ATC N04). We performed a sensitivity analysis using inverse probability weights to determine whether differential refusal at baseline or loss to follow-up (i.e. study dropout, or proxy-reported or no falls data) affected the validity of our main findings (138). Attrition weights were computed using a logistic regression model for non-response based on age, gender, education, marital status, smoking status, medication use, and cognition, as well as their two-way interactions. All analyses were performed using Stata Version 12.0. Two-sided significance at $p<0.05$ is assumed.

6.4 Results

There were 6,666 eligible participants reporting falls data at follow-up. The mean (SD) time between baseline and second interview was 24.3 (2.8) months, range 15.9 - 36.8 months. A total of 249 (4%) participants reported regularly using at least one medication with definite anti-cholinergic activity, whilst 1717 (26%) participants regularly using only medications with possible anti-cholinergic activity. The most commonly reported classes of medication with definite anti-cholinergic activity were antidepressants (n=85), urologicals (n=81), and antipsychotics (n=36), with the most commonly reported medications being the antidepressants amitriptyline (n=51) and paroxetine (n=27), and the urological tolterodine (n=39). See table 6.1 for a full list of medications with anti-cholinergic activity reported. Medications with possible anti-cholinergic activity were reported from a range of therapeutic classes, but most commonly cardiovascular (n=1409), nervous system (n=659), or respiratory (n=221). The most frequently reported medications with possible anti-cholinergic activity were the cardiac medicines hydrochlorothiazide (n=269), atenolol (n=255), and bendroflumethiazide (n=233).

Table 6.1. Medications with anti-cholinergic activity recorded at baseline in TILDA by Anti-cholinergic Cognitive Burden (ACB) score

Drug class	Drug name
Definite anti-cholinergic activity (ACB score 3)	
Antispasmodics	Butylscopolamine
Urologicals	Fesoterodine
	Flavoxate
	Oxybutynin
	Solifenacin
	Tolterodine
	Trospium
Anti-cholinergics used for Parkinson's disease and drug-induced movement disorder	Biperiden
	Procyclidine
Antipsychotics	Chlorpromazine
	Olanzapine
	Quetiapine
	Trifluoperazine
Antidepressants	Amitriptyline
	Clomipramine
	Paroxetine
	Trimipramine
Antihistamines	Chlorphenamine
	Diphenhydramine
	Promethazine
	Hydroxyzine
Definite anti-cholinergic activity (ACB score 2)	
Cardiovascular	Captopril and hydrochlorothiazide
Analgesics	Nefopam
Antiepileptics	Carbamazepine
Antiparkinsonians	Amantadine
Antipsychotics	Zuclopenthixol
	Pimozide
Possible anti-cholinergic activity (ACB score 1)	
H2 antagonists	Cimetidine
	Famotidine
	Ranitidine
Antispasmodics	Alverine
	Mebeverine
	Fybogel mebeverine
Antidiarrheals	Diphenoxylate
	Loperamide
Antithrombotics	Dipyridamole
	Warfarin
Cardiovascular	Aldactide
	Atenolol
	Bendroflumethiazide
	Captopril
	Clonidine
	Digoxin
	Disopyramide
	Doxazosin
	Furosemide
	Hydrochlorothiazide
	Indoramin
	Isosorbide Dinitrate

Drug class	Drug name
Possible anti-cholinergic activity (ACB score 1)	
Cardiovascular	Isosorbide Mononitrate
	Methyldopa
	Metolazone
	Metoprolol
	Nifedipine
	Propafenone
	Quinidine
	Torasemide
Corticosteroids	Hydrocortisone
	Triamcinolone Nasal Preparation
Musculoskeletal drugs	Baclofen
	Colchicine
Analgesics	Buprenorphine
	Codeine
	Dextropropoxyphene
	Dihydrocodeine
	Fentanyl
	Hydromorphone
	Meptazinol
	Morphine
	Oxycodone
	Tramadol
Antipsychotics	Amisulpride
	Aripiprazole
	Flupentixol
	Fluphenazine
	Haloperidol
	Prochlorperazine
	Risperidone
	Sulpiride
Benzodiazepines	Alprazolam
	Diazepam
Antidepressants	Citalopram
	Escitalopram
	Mirtazapine
	Tranylcypromine
	Trazodone
	Venlafaxine
Antihistamines	Cinnarizine
	Flunarizine
Drugs for obstructive airway diseases	Aminophylline
	Fenoterol
	Ipratropium bromide
	Salbutamol
	Theophylline
	Tiotropium bromide
Antihistamines	Cetirizine
	Desloratadine
	Levocetirizine
	Loratadine

6.4.1 Falls

A total of 1,455 (22%) participants fell by the second interview, reporting 3113 falls in total (rate of 231 falls per 1000 person-years) and 642 (10%) reported an injurious fall. Those reporting an injurious fall were more likely to be female, older, disabled, to report pain, and to have a history of falls, fractures and/or fainting and hospital admission (table 6.2). In those attending the health assessment, injurious falls were more common in those with worse objective health (table 6.3).

6.4.2 Self-reported anti-cholinergic medication use and falls

The regular use of medications with definite anti-cholinergic activity was not significantly associated with any fall by the second interview (adjusted risks 21.7 vs 23.8%; relative risk (RR) 1.12, 95% CI 0.93 to 1.33), although it was associated with injurious falls (adjusted risks 13.6 vs 9.4%; RR 1.45, 95% CI 1.09 to 1.94) and a greater number of falls (adjusted rates 184 vs 246 per 1000 person-years; incident rate ratio (IRR) 1.34, 95% CI 1.03 to 1.75) after adjusting for covariates (table 6.4). The regular use of medications with possible anti-cholinergic activity alone was not associated with any of the falling outcomes. The associations also did not vary across age, sex, cognition or history of a previous fall in the last year. A dose-response relationship was observed between greater total ACB score and injurious falls, with those who scored 5 or greater on the ACB scale having a RR of 1.65 (95% CI 1.11 to 2.45) increased risk of an injurious fall compared to those not taking any medications with anti-cholinergic activity.

Among the 4535 participants attending the health assessment centres, the association between the use of medications with definite anti-cholinergic activity and injurious falls was not attenuated when also adjusted for objective health measures (table 6.5). The association between the use of medications with definite anti-cholinergic activity and the number of falls was slightly attenuated. Associations were only slightly attenuated when excluding participants with Parkinson's Disease or Epilepsy (table 6.6).

Table 6.2. Baseline characteristics of participants reporting an injurious fall by the second interview

	No injurious fall (n=6,024)		Injurious fall (n=642)		
Baseline characteristics	**N**	**%**	**n**	**%**	**p†**
Sociodemographics					
Gender – women	3,178	52.8	438	68.2	<0.001
Age, mean (SD)	62.9 (9.2)		66.0 (10.1)		<0.001
Third/higher education	1,880	31.2	195	30.4	0.14
Employed	2,379	39.5	170	26.5	<0.001
Household income < €20,000*	1,604	26.6	236	36.8	<0.001
Lives alone	1,207	20.0	195	30.4	<0.001
Current smoker	1,036	17.2	99	15.4	0.26
Health					
Number of health conditions					<0.001
0	1,211	20.1	82	12.8	
1	1,611	26.7	127	19.8	
2	1,321	21.9	144	22.4	
3	868	14.4	102	15.9	
4	520	8.6	76	11.8	
5+	493	8.2	111	17.3	
Moderate/severe pain	1,433	23.8	227	35.4	<0.001
Urinary incontinence	709	11.7	116	18.1	<0.001
Trouble falling asleep	2,018	33.5	307	47.8	<0.001
Depressive symptoms, median (IQR)*	3 (1-8)		5 (1-10)		<0.001
Disability (ADL or IADL)	582	9.7	127	19.7	<0.001
Fair/poor self-rated vision	505	8.4	77	12.0	0.002
Fair/poor self-rated hearing	827	13.8	105	16.3	0.07
Cognition, animal naming mean (SD)*	21.0 (7.0)		19.9 (7.1)		<0.001
Healthcare utilization					
Public healthcare coverage	2,748	45.6	373	58.1	<0.001
Hospital admission in past year	704	11.7	122	19.0	<0.001
Fall-related history					
Fall in the last year	1,031	17.1	241	37.5	<0.001
History of hip or wrist fracture	766	12.7	139	21.7	<0.001
History of fainting/blackouts	1,078	17.9	159	24.8	<0.001

† Chi-square test for binary and ordinal variables, t-test for continuous variables, Mann-Whitney U-test for depressive symptoms.

* Missing data (number of participants): Income (529), Depressive symptoms (89), Cognition (26)

Table 6.3. Baseline health assessment measures of participants by injurious fall by the second interview occurrence (N=4,528)

	No injurious fall (n=4,116)		Injurious fall (n=412)		
Health assessment measure*	**N**	**%**	**n**	**%**	**p†**
Osteoporosis (heel ultrasound)					
Normal	2,184	53.1	180	43.7	0.001
Osteopenia	1,569	38.1	178	43.2	
Osteoporosis	341	8.3	49	11.9	
Orthostatic hypotension					
Normal	3,631	88.2	338	82.0	0.001
No recovery after 40s	236	5.7	29	7.0	
No recovery after 110s	174	4.2	32	7.8	
Grip strength, mean (SD)	26.3 (9.5)		23.1 (8.8)		<0.001
Timed Up-and-Go, mean (SD)	8.5 (1.9)		9.1 (2.5)		<0.001
Gait speed, mean (SD)	136.8 (20.0)		130.2 (22.1)		<0.001
BMI, mean (SD)	28.6 (4.9)		28.5 (5.2)		0.63

* Missing data (number of participants): Grip strength (21), Timed Up-and-Go (31), Gait speed (68), BMI (9), Orthostatic hypotension (89), Osteoporosis (27)

† Chi-square test for binary and ordinal variables, t-test for continuous variables.

Table 6.4. Associations (with 95% CIs) between the use of medications with anti-cholinergic activity and incident falls (N=6,666)

ACB		Any fall		Number of falls		Injurious fall	
measure	N	Crude RR	Adjusted*	Crude IRR	Adjusted*	Crude RR	Adjusted*
Max ACB							
None	4709	1.00	1.00	1.00	1.00	1.00	1.00
Possible	1708	1.35 (1.23 to 1.49)	1.00 (0.89 to 1.11)	1.55 (1.36 to 1.76)	1.03 (0.89 to 1.19)	1.47 (1.25 to 1.73)	1.00 (0.84 to 1.19)
Definite	249	1.84 (1.54 to 2.19)	1.12 (0.93 to 1.33)	2.75 (2.11 to 3.58)	1.34 (1.03 to 1.75)	2.45 (1.88 to 3.19)	1.45 (1.09 to 1.94)
ACB sum							
0	4709	1.00	1.00	1.00	1.00	1.00	1.00
1	1209	1.29 (1.15 to 1.44)	1.02 (0.91 to 1.15)	1.40 (1.21 to 1.62)	1.06 (0.91 to 1.23)	1.36 (1.13 to 1.64)	1.01 (0.83 to 1.22)
2	379	1.49 (1.26 to 1.76)	0.97 (0.81 to 1.15)	1.95 (1.55 to 2.45)	1.05 (0.83 to 1.34)	1.55 (1.17 to 2.05)	0.99 (0.74 to 1.33)
3	195	1.42 (1.13 to 1.80)	0.89 (0.71 to 1.12)	1.70 (1.24 to 2.33)	0.93 (0.68 to 1.27)	1.81 (1.28 to 2.57)	1.10 (0.78 to 1.56)
4	95	1.84 (1.40 to 2.42)	1.15 (0.87 to 1.52)	2.76 (1.82 to 4.19)	1.44 (0.97 to 2.13)	2.70 (1.83 to 3.98)	1.52 (1.01 to 2.28)
5+	79	2.47 (1.95 to 3.13)	1.29 (1.01 to 1.63)	3.85 (2.49 to 5.96)	1.40 (0.91 to 2.15)	3.55 (2.49 to 5.08)	1.65 (1.11 to 2.45)

* Adjusted for baseline covariates: age, sex, living alone, education, employment status, income, smoking status (never, past, current), time between interviews, comorbidities, incontinence, pain, sleep problems, depressive symptoms (quintiles), cognition (quintiles), self-rated vision, self-rated hearing, disability (none, iADL, ADL), public healthcare coverage, history of falls, fracture, fainting, and hospitalisation, and number of other medications.

Table 6.5. Multivariable associations (with 95% CIs) between the use of medications with anti-cholinergic activity and incident falls for participants completing a health assessment (N=4,535)

ACB		Any fall		Falling rate		Injurious fall	
exposure	N	Adjusted RR*	Fully adjusted*†	Adjusted IRR*	Fully adjusted*†	Adjusted RR*	Fully adjusted*†
Max ACB							
None	3297	1.00	1.00	1.00	1.00	1.00	1.00
Possible	985	0.93 (0.80 to 1.07)	0.94 (0.82 to 1.09)	0.97 (0.81 to 1.16)	0.94 (0.78 to 1.12)	1.00 (0.79 to 1.26)	0.97 (0.76 to 1.23)
Definite	149	1.09 (0.86 to 1.38)	1.11 (0.87 to 1.40)	1.46 (1.03 to 2.05)	1.37 (0.98 to 1.94)	1.57 (1.07 to 2.31)	1.56 (1.06 to 2.30)
ACB sum							
0	3364	1.00	1.00	1.00	1.00	1.00	1.00
1	770	0.95 (0.82 to 1.11)	0.94 (0.80 to 1.09)	1.00 (0.83 to 1.22)	0.97 (0.80 to 1.18)	1.01 (0.78 to 1.30)	1.00 (0.77 to 1.29)
2	194	0.95 (0.74 to 1.21)	0.91 (0.72 to 1.17)	0.89 (0.64 to 1.25)	0.86 (0.62 to 1.21)	1.11 (0.76 to 1.64)	1.03 (0.71 to 1.52)
3	116	0.92 (0.70 to 1.24)	0.90 (0.67 to 1.21)	0.97 (0.65 to 1.45)	0.93 (0.62 to 1.40)	1.14 (0.72 to 1.80)	1.11 (0.70 to 1.76)
4	53	1.15 (0.79 to 1.68)	1.11 (0.77 to 1.62)	1.83 (1.10 to 3.07)	1.63 (0.97 to 2.72)	1.43 (0.75 to 2.75)	1.41 (0.76 to 2.61)
5+	31	1.23 (0.85 to 1.78)	1.21 (0.82 to 1.78)	1.52 (0.76 to 3.03)	1.55 (0.78 to 3.09)	1.89 (1.02 to 3.49)	1.62 (0.80 to 3.30)

* Adjusted for baseline covariates: age, sex, living alone, education, employment status, income, smoking status (never, past, current), time between interviews, comorbidities (listed in text), incontinence, pain, sleep problems, depressive symptoms (quintiles), cognition (quintiles), self-rated vision, self-rated hearing, disability (none, iADL, ADL), public healthcare coverage, history of falls, fracture, fainting, and hospitalisation, and number of other medications.

† Also adjusted for gait speed (quintiles), Timed Up-and-Go (quintiles), grip strength (quintiles), BMI (quintiles), orthostatic hypotension (normal, no recovery after 40s, no recovery after 110s), osteoporosis heel ultrasound (normal, osteopenia, osteoporosis).

Table 6.6. Multivariable* associations (with 95% CIs) between the use of medications with anti-cholinergic activity and incident falls excluding participants with Epilepsy or Parkinson's disease (N=6,540)

ACB exposure	n	Any fall Adjusted RR*	Falling rate Adjusted IRR*	Injurious fall Adjusted RR*
Max ACB				
None	4662	1.00	1.00	1.00
Possible	1678	0.98 (0.88 to 1.10)	1.01 (0.88 to 1.17)	0.99 (0.83 to 1.18)
Definite	200	1.02 (0.83 to 1.25)	1.26 (0.94 to 1.70)	1.42 (1.03 to 1.94)
ACB sum				
0	4662	1.00	1.00	1.00
1	1190	1.01 (0.89 to 1.14)	1.04 (0.89 to 1.22)	1.00 (0.82 to 1.21)
2	362	0.93 (0.78 to 1.12)	0.95 (0.74 to 1.22)	0.99 (0.73 to 1.34)
3	181	0.90 (0.71 to 1.14)	0.93 (0.67 to 1.29)	1.04 (0.72 to 1.50)
4	84	1.06 (0.78 to 1.44)	1.45 (0.95 to 2.20)	1.52 (0.99 to 2.33)
5+	61	1.05 (0.79 to 1.39)	1.23 (0.75 to 2.00)	1.53 (0.99 to 2.38)

* Adjusted for baseline covariates: age, sex, living alone, education, employment status, income, smoking status (never, past, current), time between interviews, comorbidities (listed in text), incontinence, pain, sleep problems, depressive symptoms (quintiles), cognition (quintiles), self-rated vision, self-rated hearing, disability (none, iADL, ADL), public healthcare coverage, history of falls, fracture, fainting, and hospitalisation, and number of other medications.

6.4.3 Dispensed anti-cholinergic medications and falls

Pharmacy dispensing records were available for 2402 (36%) participants. Of these, 177 (7%) were dispensed medications with definite anti-cholinergic activity in the 30 days prior to the baseline interview, whilst 971 (40%) were dispensed only medications with possible anti-cholinergic activity (table 6.7). Baseline use of medications with definite anti-cholinergic activity was again not significantly associated with falling by the next interview (RR 1.19, 95% CI 0.94 to 1.51), but was significantly associated with an increased risk of injurious falls (RR 1.52, 95% CI 1.05 to 2.19) and a greater number of falls (IRR 1.47, 95% CI 1.07 to 2.03) after adjusting for covariates.

Table 6.7. Multivariable* associations (with 95% CIs) between the baseline use of medications with anti-cholinergic activity and incident falls for participants with pharmacy record linkage (N=2,402)

ACB		Any fall		Number of falls		Injurious fall	
exposure	N	Crude RR	Adjusted*	Crude IRR	Adjusted*	Crude RR	Adjusted*
Max ACB							
None	1254	1.00	1.00	1.00	1.00	1.00	1.00
Possible	971	1.20 (1.04 to 1.39)	1.01 (0.86 to 1.19)	1.34 (1.12 to 1.62)	1.07 (0.88 to 1.32)	1.43 (1.14 to 1.80)	1.16 (0.90 to 1.49)
Definite	177	1.63 (1.32 to 2.03)	1.19 (0.94 to 1.51)	2.16 (1.57 to 3.00)	1.47 (1.07 to 2.03)	2.13 (1.53 to 2.97)	1.52 (1.05 to 2.19)
ACB sum							
0	1254	1.00	1.00	1.00	1.00	1.00	1.00
1	627	1.13 (0.96 to 1.34)	1.00 (0.84 to 1.19)	1.26 (1.02 to 1.56)	1.09 (0.88 to 1.36)	1.41 (1.09 to 1.83)	1.24 (0.94 to 1.63)
2	308	1.27 (1.03 to 1.55)	1.09 (0.88 to 1.35)	1.38 (1.05 to 1.80)	1.16 (0.88 to 1.54)	1.29 (0.92 to 1.81)	1.07 (0.74 to 1.53)
3	138	1.40 (1.07 to 1.82)	1.08 (0.83 to 1.41)	1.68 (1.16 to 2.42)	1.13 (0.78 to 1.65)	1.85 (1.25 to 2.73)	1.33 (0.88 to 2.01)
4	46	1.81 (1.26 to 2.59)	1.24 (0.84 to 1.85)	3.12 (1.80 to 5.43)	1.91 (1.11 to 3.28)	1.78 (0.92 to 3.40)	1.14 (0.59 to 2.23)
5+	29	2.72 (2.01 to 3.68)	1.68 (1.15 to 2.46)	3.26 (2.49 to 6.49)	1.92 (0.98 to 3.78)	4.92 (3.26 to 7.43)	2.41 (1.41 to 4.11)

* Adjusted for baseline covariates: age, sex, living alone, education, employment status, income, smoking status (never, past, current), time between interviews, comorbidities (listed in text), incontinence, pain, sleep problems, depressive symptoms (quintiles), cognition (quintiles), self-rated vision, self-rated hearing, disability (none, iADL, ADL), public healthcare coverage, history of falls, fracture, fainting, and hospitalisation, and number of other medications dispensed in the previous 30 days.

6.5 Discussion

In this large prospective study of community-dwelling Irish adults aged 50 years and older, the regular use of medications with anti-cholinergic activity was associated with injurious falls and a greater number of falls in the subsequent two years. The findings were robust to adjustment for objective health measures and when assessing recent medication use using pharmacy dispensing records.

The main strength of our study was the use of a large randomly sampled population-representative cohort with detailed pharmacy records. Longitudinal follow-up ensured medication exposure preceded the measurement of falls outcomes. Participants underwent a detailed assessment of their socioeconomic characteristics, cognitive and physical health, allowing us to examine potential confounders usually unavailable to pharmacoepidemiological studies. We were able to limit confounding by indication by adjusting for many of the main indications for anti-cholinergic medications, e.g. diagnosed depression and anxiety, depressive symptoms, sleep problems, psychosis, and urinary incontinence. We fully adjusted for baseline disability and multimorbidity, modeling all health conditions simultaneously and thereby allowing each health condition to exert its own weight for predicting falls, instead of using a pre-weighted comorbidity index as these provide only a limited ability to control for confounding (133). Most health variables were self-reported, but objective measures added only limited additional information beyond the self-report measures. Those completing the health assessment (66%) were not fully representative of the whole population; non-attendees were more likely to have public healthcare coverage, less education, be single and smoke. However, associations were similar when restricting our primary analysis to only those who underwent a health assessment. Despite extensive adjustment for health-related major risk factors for falling, the possibility of some residual confounding by indication cannot be excluded. However, due to the fact that objective health measures did not reduce the association and the comprehensive nature of the TILDA health assessment, we feel that significant residual confounding is unlikely.

To better ascertain medications adhered to, participants recorded medications taken regularly, and reporting was improved by interviewers viewing medication packages. However, we cannot be sure that the participants accurately adhered to the medication regimen. Furthermore, adherence decreases with increasing regimen complexity and therefore the impact of a large anti-cholinergic burden on the prevalence of falls would potentially be under-estimated (139).

Although self-reported medication use may be subject to recall bias, we found little evidence for this in a previous study comparing the self-report data to pharmacy dispensing records (123). We did, however, find that some regularly dispensed medications with definite anti-cholinergic activity (in particular psycholeptics) were less likely to be reported as being used regularly than other classes (123). To examine whether a different source of mediation data affected our risk estimates, we also performed the analyses using the pharmacy dispensing records, although such records may less accurately reflect adherence. Pharmacy linkage only exists for those covered by public healthcare schemes. Hence participants with pharmacy records were older, less educated, had lower incomes and less likely to be employed than in those without record linkage. They also reported more chronic diseases, medications, and depressive symptoms. However, conclusions were similar when restricting our primary analysis to only those who had linked pharmacy records. Although falling was recorded subsequent to medication exposure, we do not know the precise timing of the injurious fall event and therefore what medications were being taken at that time. However, 68% of participants regularly using medications with definite anti-cholinergic activity at baseline were still regularly using them at the second interview.

The ACB has not been validated against in vitro measures of anti-cholinergic activity, although it is uncertain whether assays reflect anti-cholinergic activity in the human brain, and not all relevant drugs have been assayed in vitro (140,141).

The data was mostly complete. Only 1% of participants were excluded from the main analysis due to missing falls or medication data. Missing data indicators were used for income, depressive symptoms and cognition in the main analysis, but use of multiple imputation to impute missing data did not alter our findings. Fourteen percent of participants dropped out of the study between the first and second interview and these were more likely to be smokers, not married, have less education and lower cognition than those assessed at follow-up (see supplementary material in chapter 5.6). Use of study inverse probability weights to weight the analysis lead to very similar findings (see supplementary material in chapter 6.5) and our results are unlikely to be affected by differential drop-out.

There may be misclassification of the falling outcomes. Concerns over the accuracy of falls recall in the elderly have been discussed extensively, but studies suggest that, as more significant events, injurious falls are more accurately recalled (134). Also in terms of health care costs, injurious falls are the most relevant. However, we have no reason to believe the recall would be differential, and the rate of falling among our sample was comparable to that found in similar populations (65,135). Moreover, the effect of under reporting of falls was minimised by excluding institutionalised participants and those with dementia.

Few studies have examined the relationship between anti-cholinergic medication use and falling (71,84,85), and to the best of our knowledge, none have examined injurious falls. A lack of association between baseline use of medication with anti-cholinergic activity and falling was also reported in community-dwelling older adults in France (84). They however reported a positive association for regular anti-cholinergic medication use, but this definition included use post-falling. Contrary to our findings, two studies report associations with anti-cholinergic medication use and any incident fall, albeit in higher risk populations of psychiatric inpatients and residential care facility residents (71,85). Also in one case these findings were presented in combination with sedatives (85), and in the other only as crude associations (71).

Although there is little research into anti-cholinergic medication use and falls, prospective studies support an association with functional decline. Prescription of anti-cholinergic medications were associated with decline in instrumental activities of daily living over 2 years (142). Increased burden of anti-cholinergics and sedatives has been associated with incident frailty (143), and declines in gait speed and grip strength in one study (144), but not in another study of older residential care facility residents with higher rates of cognitive impairment (145). Studies also support an effect of anti-cholinergic medications on delirium and cognitive decline (83). The association between injurious falls and anti-cholinergic burden could be a factor contributing to the potential link between anti-cholinergic burden and mortality (81).

Intervention studies are needed to determine whether reducing anti-cholinergic burden can prevent injurious falls. Over 44 weeks of follow-up a randomised controlled trial found the gradual withdrawal of psychotropic medications was effective at reducing the number of falls and injurious falls, but not any fall (146). The trial enrolled 93 men and women aged 65 years, mainly taking benzodiazepines and antidepressants, who could potentially benefit from psychotropic withdrawal. However, permanent withdrawal was found very difficult to achieve. Educational visits to doctors and pharmacists were effective at reducing the prescribing of highly anti-cholinergic antidepressants (147), and subsequently were successful at reducing anti-cholinergic side-effects over the next year (148).

Our main finding was that the use of medications with definite anti-cholinergic activity was associated with a 46% increased risk of an injurious fall over the subsequent two years. This association did not vary across age, sex, cognition, or falls history. Hence this represents a substantial absolute risk increase for those at high risk of falling, e.g. in those reporting a fall in the year before baseline the difference in the adjusted risk of an injurious fall between those taking medications with no anti-cholinergic activity and medications with definite anti-cholinergic activity was 19% compared to 27%, respectively. Our finding of relative risks for injurious falls of around 1.4 represents a substantial increased risk, in line with that for antipsychotics and

antidepressants (65,149,150). The consequences of injurious falls are costly both economically and to patients' health (55,151). Therefore, medication risks need to be fully evaluated in these vulnerable patients to limit costly outcomes. Many different possess anti-cholinergic activity and clinicians should consider the cumulative anti-cholinergic burden when prescribing to older adults as this exposure may increase the risk of an injurious fall. Regular medication reviews in patients at risk of falls should aim to limit the overall anti-cholinergic burden.

Future studies are needed to examine whether falls risks vary by the dose and by the therapeutic class of anti-cholinergic medications used. Prescribing decisions would be improved with further understanding of the extent and type of injuries experienced when taking anti-cholinergic medications, and further characterisation of the underlying pathways for psychotropic medications' association with falls.

6.6 Supplementary material

Study attrition weights are provided, which accounted for baseline non-response and longitudinal attrition, based on age, gender, education, marital status, smoking status, medication use, and cognition, as well as their two-way interactions. Use of these study inverse probability weights to weight the analysis led to very similar findings (table 6.8).

Table 6.8. Multivariable* associations (with 95% CIs) for the use of medications with anti-cholinergic activity and incident falls, inverse-probability of attrition weighted (N=6,666)

ACB Exposure	N	Any fall Adjusted RR*	Falling rate Adjusted IRR*	Injurious fall Adjusted RR*
Max ACB				
None	4709	1.00	1.00	1.00
Possible	1708	1.00 (0.89 to 1.11)	1.03 (0.89 to 1.18)	0.99 (0.83 to 1.18)
Definite	249	1.08 (0.90 to 1.29)	1.30 (1.00 to 1.69)	1.43 (1.07 to 1.90)
ACB sum				
0	4709	1.00	1.00	1.00
1	1209	1.02 (0.90 to 1.15)	1.05 (0.91 to 1.23)	0.99 (0.82 to 1.21)
2	379	0.98 (0.82 to 1.17)	1.06 (0.84 to 1.33)	0.99 (0.74 to 1.33)
3	195	0.91 (0.72 to 1.14)	0.90 (0.68 to 1.19)	1.08 (0.76 to 1.53)
4	95	1.09 (0.83 to 1.44)	1.37 (0.92 to 2.04)	1.47 (0.98 to 2.21)
5+	79	1.19 (0.92 to 1.52)	1.39 (0.98 to 1.99)	1.64 (1.11 to 2.43)

* Adjusted for baseline covariates: age, sex, living alone, education, employment status, income, smoking status (never, past, current), time between interviews, comorbidities (listed in text), incontinence, pain, sleep problems, depressive symptoms (quintiles), cognition (quintiles), self-rated vision, self-rated hearing, disability (none, iADL, ADL), public healthcare coverage, history of falls, fracture, fainting, and hospitalisation, and number of other medications.

7 Overall Discussion

The aim of this research was to demonstrate the value of performing pharmacoepidemiology in cohort studies and to explore its limitations through an applied example of medication use as a risk factor for falling. Within the discussion, firstly a brief summary of the research findings will be presented, followed by a review of the methodological considerations and study limitations. Next, both methodological and public health implications and future directions will be highlighted.

7.1 Summary of study findings

7.1.1 Measuring medication use

The first study explored the accuracy of data on medication use. When comparing self-reported regular prescription medication use in a cohort study to pharmacy claims records for older adults, we generally found good agreement. Agreement was poorer for medications applied topically or used 'as-needed', and for psycholeptics. Not reporting an indicated health condition, less frequent dispensing and older age were generally associated with poorer self-reporting of regularly dispensed medications, however, associations varied by class. This suggests that while self-reported medication use is generally adequate for pharmacoepidemiological investigations in the older population, pharmacy dispensing records should also be used where available in particular when considering the effects of specific medication classes in vulnerable groups.

7.1.2 Confounding by healthcare system use

Healthcare coverage is a potentially significant determinant of medication use and is linked to many health outcomes and so it is important to understand this potentially confounding relationship. Middle-aged adults with public healthcare coverage were at greater risk of

polypharmacy than those without coverage, after accounting for differences in underlying socioeconomic factors and health. These associations are strongly mediated by the frequency of healthcare visits, suggesting free visits are a pathway to differential medication use. There was evidence that some cardiovascular medications, drugs for acid related disorders, and analgesics were used more often by public patients, again partly explained by differences in the frequency of medical practitioner and hospital visits. It is therefore essential to consider healthcare coverage as a potential confounder in pharmacoepidemiological studies in Ireland, and in other settings with differential healthcare coverage.

Propensity score methods provided an alternative approach to account for confounding, but generally lead to similar results to multivariable regression. Whether covariates were selected a priori or via a backwards stepwise procedure made little difference to the findings. Beyond accounting for self-reported covariates, associations were mostly unaffected by also accounting for objective health confounders including measures of frailty, suggesting that self-report is adequate to correct for confounding caused by underlying health status.

7.1.3 Multiple medication use and increased falls risk

Fall-related injuries in the older population are of major public health concern (55). Certain medications including antipsychotics, antihypertensives, benzodiazepines, antidepressants, and polypharmacy, have been commonly implicated with increased falling risk (68,69). In TILDA, polypharmacy was not found to be associated with subsequent falling risk after adjustment for comorbidity. However, polypharmacy including either antidepressant or benzodiazepine use, was associated with both a greater number of falls and risk of injurious falls.

The regular or recent use of medications with definite anti-cholinergic activity was associated with an increased risk of injurious falls and a greater number of falls in the subsequent two years. The use of additional medications with anti-cholinergic activity increased these risks

further. Associations did not vary by age, sex, cognition, or falls history. The findings were robust to adjustment for objective health measures.

As the findings from study I (in chapter 3) indicated only moderate agreement for some of the anti-cholinergic medications, the analysis was repeated using pharmacy dispensing records, and similar results were found. Given the different patterns of medication use between those with and without free healthcare highlighted in study II (in chapter 4), healthcare access was investigated as a confounder, but there was no evidence of a confounding effect over the 2-year follow-up. As both studies III and IV (chapters 5 and 6) highlight medications associated with falls, we aimed to compare these and examine the anti-cholinergic properties by medication class, but had insufficient numbers within this study.

7.2 Methodological considerations

Possible limitations of the present study have been addressed in individual chapters, but the most important considerations with respect to the validity of our observations are (re)considered below.

7.2.1 Representativeness of the TILDA cohort

The main strength of this research was the use of a large randomly sampled population-representative cohort. The initial response rate was good, and comparing responders to the 2006 Irish census and the 2010 Quarterly National Household Survey revealed the cohort was representative, although slightly under-represented by those with lower education (87). For example when using the study weights, each participant with third level education represents around 70-100 members of the Irish population depending on their age and sex, however those with primary education represent around 150-250 individuals.

7.2.2 Attrition between waves

The rate of attrition in TILDA over 2-years was low. Those dropping out of the study were more likely to be smokers, not married, have less education and lower cognition. Use of study inverse probability weights to weight the fallings analyses lead to very similar findings, hence the results are unlikely to be affected by differential drop-out.

7.2.3 Confounding

Confounding is one of the greatest threats to observational studies. TILDA participants underwent a detailed assessment of their socioeconomic characteristics, cognitive and physical health, allowing us to examine potential confounders usually unavailable to pharmacoepidemiological studies. In the falling analyses, we were able to limit confounding by indication by adjusting for many of the main indications for the medications. We fully adjusted for baseline disability and multimorbidity, modeling all health conditions simultaneously and thereby allowing each health condition to exert its own weight for predicting falls, instead of using a pre-weighted comorbidity index, which provide only a limited ability to control for confounding (133). Some residual confounding may nevertheless remain, particularly with respect to disease severity and socioeconomic factors which are difficult to precisely measure in an epidemiological context.

7.2.4 Missing data

The TILDA data was mainly complete (e.g. 98% completed medication, sociodemographic and comorbidity data) and few participants were excluded from the analyses due to missing data. Missing data indicators were used for some covariates in the falling analysis, but use of multiple imputation did not alter the study findings.

7.2.5 Self-reported covariate data

Misclassification of confounders could lead to residual confounding. Most health covariates were self-reported, but objective measures added only limited additional confounding control beyond the self-report measures suggesting that this was not a significant issue.

7.2.5.1 Self-reported medications

Misclassification of exposures can lead to biased effect estimates. Medication reporting in TILDA based on self-report benefited from interviewers viewing medication packages. Self-report allows the collection of non-prescription medication use and potentially better reflects adherence than prescribing or dispensing records. To examine whether a different source of mediation data affected our risk estimates, we also performed the analyses using the pharmacy dispensing records, although such records may less accurately reflect adherence.

7.2.5.2 Self-reported falls

There may be misclassification of the falling outcomes leading to potentially reduced power for analyses. Concerns over the accuracy of falls recall in the elderly have been discussed extensively, but studies suggest that, as more significant events, injurious falls are more accurately recalled. For example, a study of 252 seniors found that 87% of those having an injurious fall over 12 months of follow-up subsequently recalled falling during a self-completed questionnaire (134). Also in terms of health care costs, injurious falls are the most relevant. Falls may be under-reported due to the fairly long follow-up and the misclassification of the any fall outcome may explain why we failed to identify any statistical significant associations for that outcome. The effect of under reporting of falls was minimised by excluding institutionalised participants and those with dementia. However, we have no reason to believe the recall would be differential, and the rate of falling among our sample was comparable to that found in similar populations (65,135).

7.2.6 Study design

The cross-sectional nature of study II (in chapter 4) was a limitation. It is possible that observed health status and public healthcare coverage status at the time of interview may not fully reflect health status and coverage at the time of prescribing. However, public healthcare coverage remained fairly constant over the year before the TILDA baseline interview, so the possibility of reverse-causation is thought minimal.

Longitudinal follow-up ensured medication exposure preceded the measurement of falls outcomes in studies III & IV. Performing pharmacoepidemiology in cohort studies is limited by medication use only being ascertained at the time of interview. Although falling was recorded subsequent to medication exposure, we lack the ability to observe the full temporal relationship between the use of medications and the falls. However, medication use remained fairly constant over the 2-year follow-up.

7.3 Implications and future directions

7.3.1 Implications for conducting pharmacoepidemiological studies

The source of medication data should be taken into account when performing pharmacoepidemiological studies (21). Pharmacy data may better capture current use, use of medications taken topically and as-needed, and include information on dose and duration, but may not be available for the whole population and may not represent medications accurately adhered to. Alternatively, interview data may better capture medications used chronically and adhered to and over-the-counter use. Differential misclassification appears minimal across socio-demographic and cognitive factors, although care should be taken when analysing the effects of medications where reporting was thought to be affected by stigmatisation bias (e.g. the psycholeptics). Further research is required to examine the association between medication recall and reporting of the indicated health condition.

Little research has been devoted to variable selection for propensity scores. Further research is needed comparing practical data-driven variable selection methods for propensity scores, particularly when using IPTW where there is a need to balance confounding control against the risk of non-positivity and extreme weights.

7.3.2 Public health implications

Free healthcare may have positive and negative consequences for an individual's health. We demonstrated a higher risk of polypharmacy among those with public healthcare coverage in Ireland, which may reflect both restricted use of medications by patients without public coverage and inappropriate prescribing among patients with public coverage. Further evidence is needed to inform policy decisions around the public provision of healthcare, specifically to ascertain the effect on healthcare utilisation and population health if public healthcare coverage were available to all.

Our findings of polypharmacy including antidepressants or benzodiazepines as a risk factor for falls needs replicating and further examination. Possible explanations for the additive pharmacodynamic drug interactions need exploring. The findings also further support the idea that it is the type of polypharmacy that is important for adverse events (69,76).

Future studies are needed to examine whether falls risks vary by the dose and by the therapeutic class of anti-cholinergic medications used. These medications need further examination and their use limited in vulnerable patients. Prescribing decisions would be improved with further understanding of the extent and type of injuries experienced when taking anti-cholinergic medications, and further characterisation of the underlying pathways for psychotropic medications' association with falls.

Medication reviews have been shown to be successful at reducing falls in the older population (136), and our findings potentially give more specific medication classes to target interventions towards. Intervention studies are needed to determine whether reducing anti-

cholinergic burden can prevent injurious falls. With global population ageing teamed with the financial and societal costs of falls, further research into their prevention is needed.

7.4 Conclusions

This research has illustrated the value and limitations of performing pharmacoepidemiology using cohort studies. One of the biggest concerns is the reliance on self-reported data. Self-reported medication use was shown to agree well with pharmacy dispensing records. Self-reported comorbidity and health were shown to account well for health confounding, as additional adjustment for objective measures made little or no difference to effect estimates. However, cohort studies may be under powered for specific medication comparisons. The analysis of falling data demonstrated that clinically meaningful research can be performed, accounting for substantial confounding and potentially overcoming any biases. Future waves of TILDA will provide much needed data on the safety of medication use and the possible mechanisms of their adverse effects.

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