FALLS IN OLDER PEOPLE AND THE ROLE OF COMMONLY PRESCRIBED ANTIDEPRESSANT AND ANTIHYPERTENSIVE MEDICATIONS

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Abstract

Background

Falls in older people result in harm for individuals and are a major public health problem, but there is little published data on the recording and incidence of falls seen in primary care, with which to consider the implications of recent policy initiatives. A range of factors contribute to falls risk. Amongst these, the role of some medications is well established, but the evidence base regarding the effects of some of the most commonly prescribed medications remains meagre and inconsistent.

Aims

The project aims to quantify the overall incidence and distribution of recorded falls among older people in primary care in the UK, and the associated risk of death. The falls risk profile of more recently introduced serotonin noradrenalin reuptake inhibitors (SNRIs) is explored to assess whether it is more favourable than that of selective serotonin reuptake inhibitors (SSRIs). Similarly, prescribing of subclasses of antihypertensive medication is explored to establish whether any of them modify risk of falling. Finally, other classes or sub-classes of medication prescribed in primary care are identified whose apparent falls risk warrants further investigation.

Methods

Analysis of falls and prescribing history in the electronic records of patients aged 60 years and over from The Health Improvement Network (THIN) using cohort, survival, case-control and case series study designs.

Results

Amongst people aged >60 years the overall crude incidence rate of recorded falls was 3.58/100 person-years (3.56–3.61), higher in older age groups, in women and least advantaged social groups, and was constant in the period 2003-2006. Fallers experienced a substantial increase in mortality (two-fold increase for recurrent fallers, and more than five-fold for those aged 60-74 years). This increase is independent of fractures recorded at the time of the

fall or subsequently. People who fall have an increased rate of subsequent fracture (approximately three-fold and, for recurrent fallers aged 60-74 years more than eight-fold).

There was an increased risk of current prescribing of SNRIs (adjusted OR 1.79, 1.42 - 2.25) in first fall cases compared with controls. This was similar in magnitude to that seen with tricyclic antidepressants and SSRIs. The increase in risk was apparent within the first 28 days after first prescription. The effects were also apparent in the self-controlled case series analysis: the incidence risk ratio for the period 1–28 days after initiation of treatment compared with unexposed periods was 1.49 (1.15 - 1.93).

There was an increased risk of current prescribing of thiazides (adjusted OR 1.28, 1.16–1.42). At 3 weeks after first prescribing the adjusted risk remained 4.28 (1.19–15.42). In the case series analysis the incidence risk ratio for the period 21 days after first prescription was 2.80 (1.7 – 4.57). We found a reduced risk for current prescribing of beta blockers (adjusted OR 0.90; 0.85–0.96), but a weakly positive effect in the case series analysis for the corresponding period IRR 1.23 (1.02–1.48).

Taken together, the case-control and case series analyses of other subclasses of antihypertensives provided weak or no evidence for an effect on falls.

In the hypothesis generating case-control analysis of other medication classes, unadjusted odds ratios of greater than 1.7 were found in a number of classes of medication including: laxatives, antifungals, corticosteroids, insulin, antibiotics for mild to moderate acne, and vaccines for influenza and other infections.

Conclusions

Older people with a recorded fall represent a group who are at increased risk of death, irrespective of whether they have a subsequent fracture. Nevertheless the incidence of falls recorded in primary care suggests that guidance about asking patients if they have fallen in the last year appears not to have been followed during the study period. The fact that the incidence rate of falls is strongly associated with social disadvantage suggests the need to target the design and delivery of interventions accordingly.

The falls risk profile of SNRIs, which is similar to that of SSRIs and TCAs, suggests that clinicians initiating prescribing of SNRIs should be alert to the increased risk of falls.

Similarly, clinicians initiating prescribing of thiazides in older people, which has generally been considered a 'safe' option for older patients, should be alert to the possibility of an increased risk of falls in the first three weeks of prescribing.

Case series analysis of recurrent periodic exposures can elucidate bias in classis case-control analysis of the same data, and will be useful in assessing the falls risk profile of other medications such as insulin.

Given the small size of sources of detailed data about older people who fall and the imprecision in their measurement of exposure to medications and potential confounders, case-control and case series analysis of first falls in THIN represents a valuable source of new evidence about medication risk factors.

Acknowledgements

I would like to take this opportunity to acknowledge the support of the East Midlands Strategic Health Authority in the form of a contribution to student fees.

Since before the start of this project I benefited from the generous approach of researchers in the Department of Epidemiology and Public Health, whose warm welcome and "open door" make for a great environment in which to learn. I knew that in the supervision of my project I would experience the same commitment to rigour, with support for the learner; and so it has proved. Therefore I wish to express my gratitude to Professors Lewis, Hubbard, and Gladman for their time and assistance. In particular I would like to thank Professor Lewis for her timely support and clear instruction, helpful challenge and correction, and warm encouragement throughout the project.

Closer to home I wish to thank Tom, Katie and Dan for the times when they have allowed me to hammer away at the keyboard. Closer still, I thank my wife Clare for trusting me to undertake a PhD without impacting family life and, when it inevitably did, for helping me forward.

List of tables

Abbreviations

GPRD	General Practice Research Database
IRR	incidence rate ratio
OR	odds ratio
RR	relative risk
SNRI	serotonin noradrenalin reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
TCA	tricyclic antidepressant
THIN	The Health Improvement Network

Confidence intervals for estimates of effect are in all cases 95% confidence intervals.

Personal statement

My interest in this project grew out of earlier studies I undertook using The Health Improvement Network (THIN) primary care database to investigate the epidemiology of idiopathic pulmonary fibrosis (IPF) in the UK. I had enjoyed the process of designing and executing a study, and of getting the work published. As a result I determined to develop my understanding of research methods and my familiarity with THIN, ideally as part of a PhD.

Initially I started to look at doing further work on IPF or other respiratory outcomes with which colleagues in the Department of Epidemiology and Public Health were already familiar. After further consideration, I decided to focus the project on an outcome which would have more immediate relevance to public health, in line with my career plans. Falls among older people was suggested to me as a possibility. An initial look at the literature suggested some apparent gaps in the literature, e.g. the impact of recent guidelines, and the effects of cardiovascular medication. This together with some interest from the Regional Director of Public Health for the East Midlands provided the impetus to make falls in older people the focus of my research project.

All the work contained in this thesis including the data management and statistical analysis is my own, except where specifically indicated to the contrary.

I am pleased to have had several of the studies published in four papers, which are included in Appendix C for reference:

Gribbin, J., et al., Incidence and mortality of falls amongst older people in primary care in the United Kingdom. QJM, 2009. **102**(7): p. 477-483.

Gribbin, J., et al., Risk of falls associated with antihypertensive medication: population-based case-control study. Age & Ageing, 2010. **39**(5).

Gribbin, J., et al., Risk of falls associated with antihypertensive medication: self-controlled case series. Pharmacoepidemiology and Drug Safety, 2011. **20**(8): p. 879-884.

Gribbin, J., et al., Serotonin-Norepinephrine Reuptake Inhibitor Antidepressants and the Risk of Falls in Older People: Case-Control and Case-Series Analysis of a Large UK Primary Care Database. Drugs & Aging, 2011. **28**(11): p. 895-902

1 Introduction

Falls represent a major public health problem and the leading cause of injury-related hospitalisation in older people, with significant consequences for the individual, carers and wider society. For countries like the United Kingdom whose populations are ageing, its scale is set to increase.

In this first chapter, some key definitions relating to the study of falls are outlined to provide a frame of reference within which to consider evidence of causation. The chapter goes on to set out what is known from the literature[a] about: the measurement, incidence and consequences of falls amongst community dwelling older people, the evidence of an association with various medications with particular reference to commonly prescribed cardiovascular and central acting medications, and contemporary approaches to the management of falls in the UK. It will highlight that:

- There is little published data on the recording and incidence of falls seen in primary care, with which to consider the implications of recent policy initiatives which envisage an important role for general practitioners and primary care within the care pathway for the prevention and treatment of falls
- The evidence base for the effect on falls in older people of some of the most commonly prescribed medications, including antihypertensive medications, is meagre and inconsistent
- There is a gap in the evidence concerning SNRIs, which some have suggested may be safer than SSRIs

Against this background, the chapter sets out the specific aims and objectives of the study, and the approval and funding secured. The chapter closes by mapping out the structure and flow of the thesis.

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[a] The search criteria for the literature review are set out in Appendix A

1.1 Definitions

1.1.1 Falls and recurrent falls

The World Health Organisation (WHO) defines a fall as "an event which results in a person coming to rest inadvertently on the ground or floor or other lower level" and specifically excludes falls from animals, burning buildings and transport vehicles, and falls into fire, water and machinery[1]. This WHO definition closely follows the consensus definition developed in 2005 by collaborators in the Prevention of Falls Network Europe (ProFaNE)[2]. These definitions are considered to be appropriate for studies addressing a broad range of risk factors for falls, including cardiovascular and neurological causes[3]. Other definitions appearing in the literature include that developed by the Kellogg International Working Group on the Prevention of Falls in the Elderly, which specifically excludes events which are the consequence of "sustaining a violent blow, loss of consciousness, sudden onset of paralysis as in stroke or epileptic seizure"[4].

These standards all define a fall in terms of an event which is the result of some other environmental or clinical factor. However, Grimley Evans[5] undertook secondary analysis of data from a contemporary falls study which demonstrated support for the hypothesis that people who fall comprise two distinct subgroups: one of people who are susceptible to falling (by virtue of exposure to a risk factor), and one of people whose fall can be more properly described a random event. On this basis, it is contested that there are some people who fall for whom it may be inaccurate (or at least premature) to consider the event as a symptom.

Amongst people who fall more than once, Grimley Evans found that the proportion whose fall event is a random event is much lower[5]. For this reason, a number of studies have been designed to measure recurrent rather than single falls events. More commonly now, a fall event is regarded as a product of risk factors and precipitating factors. This conceptualisation is set out in 1.2.

Definitions of recurrence vary, but many consider a second or subsequent fall within a 12 month period to be a recurrent event. Related to this is the consideration given by Cummings et al[6] to whether the relevant outcome measure in falls studies should be the instantaneous occurrence of a fall event (initial or recurrent), or the state of being a faller.

In some studies, the definition of fall is not specified. In many, including those based on routine data from surveillance and healthcare systems, the definition reflects whatever categories are available to those entering information to the source system (and the quality and consistency of the coding they apply).

1.1.2 Older person

The age at which studies consider an individual to be an 'older person' also varies. Many studies focus on falls subsequent to the date or year in which the subject is aged 65 years. Several studies of older people set a lower age threshold of 60 years and a few even lower than this. A number of studies stratify older people further into subgroups denoting the 'oldest old'. Reliable interpretation of such studies should take account of the subjectivity involved in applying these categories to the age of participants, which is a continuous (not categorical) variable.

1.2 Frame of reference for considering causation

Subsequent sections of this chapter will set out the evidence for the causal relationship between falls and medications. This is best considered within a wider frame of reference which identifies falls as the result of an interaction between a potential challenge to an individual's stability and their ability to mount an integrated reflex response to visual, vestibular and proprioceptive information[7]. This ability can be conceptualised as a "balance system". Ageing is associated with a degradation of the components of this system, which may render individuals progressively more susceptible to challenges to their stability. The system may allow an individual to compensate to some degree for a single deficit, but will become progressively more vulnerable to

multiple deficits. It is in the context of this complex system and the wide range of age-related and other factors impacting its performance that evidence about the aetiology of falls must be considered.

1.3 Design and methodology of studies measuring falls

1.3.1 Objectives and scope of studies in which the occurrence of falls is measured

In the three decades since Gryfe et al[8] published the first prospective study of falls based on standardised reporting and follow-up, there have been more than a hundred studies reporting the occurrence of falls as a primary outcome measure.

Many of these were trials and reviews[9 10] of the relative effectiveness of interventions, their significance to this review being the rates of occurrence they report in their control arms. Some of these trials were larger scale and were located in community settings[11], but most were based on small numbers, were located in institutionalised settings[12], or focused on subjects unlikely to be representative of the older population in general[13].

A smaller number of studies were designed with the primary objective of measuring the occurrence of falls or their risk factors in a population. Again, many of these studies were small-scale[14-29], or they studied settings or subjects unlikely to be representative of the general population[23 30-44] (because their focus was the institutionalised elderly or those attending a healthcare setting for reasons unrelated to their fall, for example).

Other studies focused on a subset of falls, e.g. those resulting in various degrees of injury[45-49] or hospitalisation[50-62]. Some studies based on surveillance or survey data focused on accidental injury in general (and often in all ages), of which injury attributed to falls or falls in older people is only one part[49 63-70].

1.3.2 Different approaches to detecting falls

Studies in the literature employ different approaches to detecting falls according to their design and logistical constraints. More recent studies have used prospective designs, employing self-completed questionnaires or interviews at regular intervals. The standard recommended by ProFaNE collaborators is prospective daily recording of fall events, with notification at least once a month backed up by telephone interviewing to secure missing returns[2]. Key constraints in this approach are the expense involved in securing daily recording from sufficient participants to achieve the necessary statistical power, and difficulties amongst participants who may have impaired recall. Currently, sensor technologies remain insufficiently developed to offer a reliable, practicable, non-intrusive means of measuring falls.[71]

In observational studies the occurrence of fall events is generally self-reported using some kind of questionnaire, which means the measurements may be affected by recall bias. Cummings et al found that amongst their 304 participants aged 60 years or over between 13-32% of prospectively recorded falls were not recalled subsequently. Rates of recall were lower for participants with lower score on the mini Mental State Examination[72]. In this sample, recall at 12 months was better than at 3 or 6 months, and was not associated with the actual number of fall events. One study in an Australian intermediate care setting found that systematic recording of falls by nurses increased the number of falls reported by one third[73].

Recognising the problems of recall bias and the expense of securing daily recording, Lachenbruch et al sought to quantify the role of recall bias in the under-reporting of falls, and proposed an approach to adjust for it using proportional hazards modelling[74]. Several studies[75-77] have investigated the extent to which different follow-up intervals optimise the level of recall amongst elderly participants, and the extent to which a "better" estimate of actual falls can be derived by compensating for length of recall[78]. Nevertheless, these approaches remain dependent on inferences made from

a subset or comparator for whom prospectively collected falls data is available. Furthermore, there may be other factors related to recall and reporting which need to be compensated for (e.g. socio-economic status and health beliefs in different groups: "only old people fall – I'm not old"[74]) for which it is problematic to collate data for a subset large enough to support valid inferences.

Other studies detect fall events resulting in healthcare activity, e.g. admissions or attendances. Such measures are variable in terms of their completeness (e.g. not all falls result in attendance) or consistency (thresholds for admission may vary between institutions and over time, independently of any underlying variation in incidence).

1.3.3 Measures of occurrence of fall

A variety of measures are used to quantify the occurrence of falls. Population studies generally measure occurrence of falls in terms of incidence and incidence rate. Some studies report these rates as a crude rate, but usually it is age- or age-sex specific. In a number of studies, occurrence is stated in terms of a proportion who experience a fall or, to be precise, who have experienced a fall during a defined period (usually one year)[79]. In studies based in institutional settings, the denominator for the rate may be given in terms of bed-time, e.g. fall events per bed-month.

1.3.4 Differences in setting

Most studies reporting the occurrence of falls are set outside of the UK. Many of them are set in the industrialised economies of Western Europe, North America, Australia and the wealthier parts of Asia. The literature also comprises studies based in countries with diverse economies or less developed healthcare infrastructures including Egypt, Iran, Pakistan, Thailand, China, Latin America and the Caribbean. The validity of generalisations from these countries to the UK depends, in part, on the degree of similarity in contextual factors, including health and social care arrangements, climate, and culture as well as more obvious differences in the respective demographics of study participants.

1.3.5 *Summary of the strength of evidence*

In summary, the data on the occurrence of falls in community dwelling older people in the UK is sparse. It is derived from surveys of self-reported falls[14] [79-81], small-scale studies[17 18], or relates to institutional[40] and acute healthcare settings[57 58]. It is supplemented by a more substantial body of literature relating to other countries.

1.4 What is known about the incidence of falls in older people

1.4.1 *Development of the literature*

Current knowledge about the epidemiology of falls in older people builds on a body of literature that dates back to the middle of the last century. Although falls in older people were recognised as a frequent occurrence and as a cause of significant morbidity, research into falls had been, prior to 1977, restricted to a few studies of falls resulting in serious injury (for example,[82-85]). Gryfe et al claimed that their five year longitudinal study of older people living in an institutionalised setting[8] was the first prospective study of falls of any severity, with standardised reporting and follow-up. Since the late 1970s, retrospective and prospective studies have reported the incidence of falls in a range of settings and populations. Increasingly over time, publications reporting incidence of falls have been based on intervention studies, as opposed to observational studies of basic epidemiology.

1.4.2 *Overall occurrence in populations*

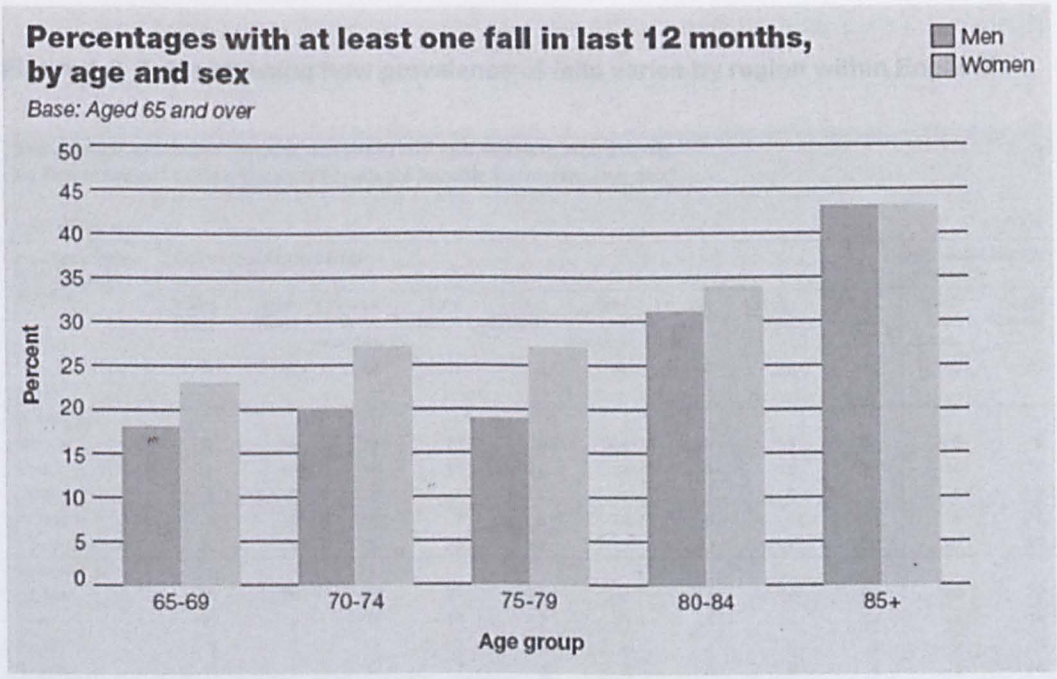
Findings from studies of the annual prevalence rate of falls in older people in the UK vary from 15% to over 40%. For example, amongst people aged 65 years or over, the Health Survey for England 2005 found that 23% of men and 29% of women recalled having fallen one or more times in the previous 12 months[81]. Amongst the 2793 respondents aged over 65 years in an early community-based study in the UK, the annual prevalence rate of one or more falls was 28%[79]. Amongst 1042 older people surveyed by Blake et al[80] there was an annual prevalence rate of 34%. A smaller study in Manchester of 203 people aged over 75 years found that 42% had suffered at least one fall

in the previous 12 months[17]. Amongst 100 self-selected participants in Birmingham aged over 65 years, 15% had sustained at least one fall in the previous year[18]. A longitudinal study of older people in Nottingham found that 26.5% had experienced one or more falls in the previous year[14] (N.B. the overall incidence described in the abstract for this paper includes recurrent falls).

Almost all of the studies in various urban and rural, institutionalised and non-institutionalised settings across all continents reported findings across a similar range to studies in UK settings. A number of studies in Japanese[16 86-89], other Asian settings[90-93] and one Spanish study[94] report prevalence rates towards the lower end of this range (i.e. rates ranging from 14-20%).

A few studies also report rates for recurrent falls. A longitudinal study of 1517 ambulatory older people in Hong Kong found an overall annual prevalence of recurrent falling of 5% (compared to 19% for once-only fallers) [91 92]. A survey of 921 older people in Switzerland found that 10% had fallen more than once in the previous year (compared to 17% for once-only fallers)[95]. A Finnish longitudinal study of 1159 people aged 70 years or over found that 11% fell more than once (compared to 30% who fell once-only)[96]. In an Australian study of 704 community dwelling women aged 65 years or over[97], 20% were found to have fallen once in the previous year and a further 14% to have fallen on two or more occasions.

Figure 1-1 Chart showing how proportion of older people reporting a fall increases with age



1.4.3 Variations in occurrence by sex and age

There is consistent evidence from most studies in the UK[79 80] and other countries that the rate of incidence of falls among women is higher than in men (see Figure 1-1 for example). With very few exceptions[8 16 20], the literature also shows an increase in the incidence rate of falls or fall-related injuries with increasing age, until the very oldest age groups amongst whom incidence rates are constant. There is consistent evidence that this age-related increase in incidence is steeper amongst men[79 80]. In England, rates of self-reported falls amongst those aged 85 and over are the same for men and women[81]. Gryfe et al[8] found some clustering of falls prior to death.

1.4.4 Variations in occurrence by country/region

Evidence of regional variations in the occurrence of falls within the UK is limited. The best regional comparisons available are those published in the Health Survey for England 2005 which shows that the East Midlands region had the highest age-standardised prevalence of reported falls for older

people (approximately 30%) and East of England the lowest (approximately 20%) – see Figure 1-2. This apparent variation remains unexplained.

Figure 1-2 Table showing how prevalence of falls varies by region within England

Prevalence and number of falls (observed and age-standardised), by Government Office Region/Strategic Health Authority and sex[a]

Aged 65 and over — *2005*

Number of falls in previous 12 months	Government Office Region									Strategic Health Authority	
	North East	North West	Yorkshire & the Humber	East Midlands	West Midlands	East of England	London	South West	South East	South East Coast	South Central
	%	%	%	%	%	%	%	%	%	%	%
Men											
Observed											
No falls	77	76	77	70	79	83	78	76	80	80	79
1 fall	15	15	15	15	15	15	15	15	15	14	14
2 falls	5	7	6	7	4	2	2	5	3	3	3
3+ falls	4	5	7	8	5	4	6	4	4	4	4
One or more fall	*23*	*24*	*23*	*30*	*21*	*17*	*22*	*24*	*20*	*20*	*21*
Standardised											
No falls	76	76	76	71	78	83	78	76	80	80	79
1 fall	15	12	11	15	12	10	14	16	14	14	14
2 falls	5	7	7	7	4	3	2	5	3	3	3
3+ falls	4	5	7	7	5	4	6	4	4	3	4
One or more fall	*24*	*24*	*24*	*29*	*22*	*17*	*22*	*24*	*20*	*20*	*21*
Women											
Observed											
No falls	70	72	69	69	70	75	71	68	72	73	71
1 fall	16	16	18	16	17	14	16	20	15	16	14
2 falls	6	7	7	7	7	7	6	5	7	6	9
3+ falls	9	5	5	8	6	5	6	6	5	5	6
One or more fall	*30*	*28*	*31*	*31*	*30*	*25*	*29*	*32*	*28*	*27*	*29*
Standardised											
No falls	68	73	69	68	71	75	71	68	72	74	69
1 fall	17	15	18	16	17	13	17	20	15	15	15
2 falls	6	7	8	7	7	7	6	6	7	6	9
3+ falls	9	5	5	8	6	4	6	6	5	5	6
One or more fall	*32*	*27*	*31*	*32*	*29*	*25*	*29*	*32*	*28*	*26*	*31*
Bases (unweighted)											
Men	*116*	*256*	*184*	*176*	*190*	*231*	*193*	*246*	*301*	*158*	*143*
Women	*139*	*369*	*235*	*202*	*255*	*265*	*223*	*292*	*386*	*224*	*162*
Bases (weighted)											
Men	*102*	*233*	*187*	*169*	*193*	*227*	*218*	*226*	*307*	*161*	*146*
Women	*125*	*348*	*247*	*199*	*269*	*266*	*259*	*276*	*406*	*235*	*171*

1.4.5 Variations in occurrence by deprivation

A Finnish study of falls resulting in medical attention found higher incidence rates of fall-related injuries in women and in people with only basic level education[98]. This association with education was not significant in the men, the numbers in this strata being too small to demonstrate an effect.

Analysis of a survey of urban-living older people in British Columbia found that risk of falling for lower socio-economic status disappeared after adjusting for chronic illness, age and sex[99], which suggests that the association in this population between falls and socio-economic status may be a function of higher rates of fall-related chronic illness in this group.

An ecological study of admissions data for falls-related injuries and hip fractures in people aged 70 years and over in England found evidence that relative deprivation is associated with higher fall rates, but not with rates of hip fracture[58]. On the other hand, Health Survey for England found no association between fall rates and PCT Spearhead-status[b], nor with quintile of household income[81].

In summary, the evidence for an association with deprivation is mixed, and may reflect the measures of deprivation used.

1.4.6 Variations in occurrence by ethnicity

There is some evidence from other countries that incidence rates vary by ethnicity. For example, Japanese living in Hawaii experience lower rates of falls than their white American counterparts, although the risk of serious injury between fallers in the two groups was not significantly different[100]. Another study comparing fall rates amongst these groups found that fall rates of older people in Japan were similar to Japanese-Americans in Hawaii, but about twice that of Caucasian groups[87].

In the US, elderly Mexican-Americans have a similar risk of falling as Caucasians[101]. Another US-based study comparing incidence of falling in

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[b] Spearhead status is the label assigned by HM Government departments to denote high levels of deprivation and need

elderly women found no significant differences between the rate in African- and Caucasian-American women[102].

It remains unclear the extent to which specific differences may be attributed to lifestyle and environmental factors, or intrinsic factors (systematic differences in sensorimotor function, say), or to their interactions.

1.4.7 Variations in occurrence by marital status

Ryynanen et al found higher rates of incidence of fall-related injury in unmarried, divorced or widowed people compared to those who were married, but in estimating the odds of falling amongst these groups no adjustment was made for age, sex, or other potential confounders such as the prevalence of co-morbidities[98].

1.4.8 Variations in occurrence by residence setting

Luukinen et al[96] found incidence rates of 2021 per 1000 person years in men and 1423 per 1000 person years in women living in institutions (compared to 368 and 611 per 1000 person years in home-dwelling). In a further study[45] they found similar rate ratios between home- and institutional-dwelling older people. Another study in institutional care settings in Finland found an incidence rate of 1398 falls per 1000 person years[103].

A Swiss study[95] found that people aged 65 and over in nursing homes had a significantly higher risk of falling compared to home-dwelling people (adjusted OR 2.46, 1.04 - 5.78)[c]. Similarly, a comparison of fall rates in different residential settings in Sweden found that rates in an institutional setting (which cared for older people with dementia) were twice that found in a residential home and in apartments set aside for older people[104].

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[c] Confidence intervals for estimates of effect are in all cases 95% confidence intervals

There is consistent evidence from studies such as these that the incidence of falls amongst people in institutional living arrangements is higher than amongst home-dwelling people, and that this is not explained by differences in age[95]. Since the prevalence of morbidities and frailty is higher amongst older people living in institutional care than amongst community dwellers, it is thought that this accounts for much of the difference, including the differences in type of injury sustained[45]. However, we cannot be certain of the extent to which observed differences in type of injury sustained and in diurnal distribution of falls are explained by extrinsic factors.

1.4.9 Long term variations in occurrence

There is some evidence that the incidence of falls has increased over time. Some of this evidence is relatively weak and may be due to changes in ascertainment and recording[50].

Evidence from Finland based on surveillance of hospital discharges for the whole Finnish population suggests that age-adjusted incidence rates of fall-related injuries increased by about one quarter in the 24 years to 1995, but that there was no corresponding increase in fall-induced death[53]. The same period also saw increases in falls-induced, fracture-associated spinal cord injuries[54], but this may be due to factors relating to bone health rather than to falls. The observed trend in rates of injury resulting from falls in older people has persisted to 2004[60 61]. The findings of a longitudinal study also found an increase in the incidence of major soft tissue injury from falls from start to end of the study period lasting 9 years (adjusted OR 1.08, 1.03 - 1.12), but no increase in the rate of incidence of hip fractures[105]. Neither did the study find an increase in the rate of falls. These findings suggest that observed increases in injuries are not due to an increased tendency to fall, but could be due to an increase in severity, which the authors hypothesize to be a result of increasing environmental, situational or behavioural hazards. However, elsewhere, analysis of rates of fatal and non-fatal falls in the US between 1993-2003 shows that the rate of non-fatal injury has not changed[48].

In England, a large study using hospital episode statistics found that age-specific rates of admission for fractures of the hip had stabilised by 2001[106]. Hip fracture is often taken to be a marker of falls in older people, but the extent to which the association between falls and hip fracture has remained constant over time is not clear. Therefore inferences made about trends in rate of falls must be tentative.

Demographic changes in the UK and industrialised countries mean that unless there is a reduction in age specific rates, the actual number of falls is likely to increase.

1.4.10 Short term variations in occurrence

The evidence for seasonal variations in falls is mixed. A study of 761 people in New Zealand aged 70 years and over found that winter was associated with an excess of falls amongst women[107], but a survey of 1321 people aged 65 and over from a rural Japanese community found no difference in the rates of falls by season[108]. Similarly, a 10 year longitudinal study of Finns aged 75 or 80 years at outset found no variation in fall incidence by season[29]. Analysis of national surveillance of falls in people aged 65 and over in the US found that neither fatal nor non-fatal falls showed any seasonal pattern, but that the frequency of fatal falls was on average 9% higher in colder climates[109].

1.4.11 Summary

The literature is rich in evidence for the public health significance of falls amongst older people in terms of its overall frequency, and its demographic, socio-economic and temporal distribution.

Many peer-reviewed studies, review articles and standard textbooks about healthcare of the elderly state that up to a third of older people fall each year. Evidence underpinning these estimates arises from the analysis of cross-sectional and longitudinal data generated in the course of observational studies (and some trials), and the analysis of routinely collected health data. Evidence of the frequency of attendance in primary care for falls in

community-dwelling adults is sparse. In a UK setting it is limited to self-reported data.

1.5 Health consequences of falls in the community

1.5.1 Falls associated mortality

The literature quantifying mortality following a fall in a community setting is small compared to that for the frequency of falls.

Amongst 339 older people attending an A&E department following a fall, Morfitt[15] found an excess in one-year mortality which could not be attributed to the injuries sustained in the fall. Another early UK study of 125 fallers aged 65 years and over living at home found a one year all-cause mortality five times that in their age-sex matched controls[110]. This evidence underlines the fact that fallers represent an important group of people in terms of mortality, irrespective of the severity of injury sustained during the fall.

1.5.2 Variations in mortality by age and sex

In their 1990 study, Sattin et al[51] found that for males in the US the risk of death following a fall-related injury was double that for females. This is consistent with the findings of a Canadian study of falls in people aged 65 and older, which found higher mortality rates and lower accident-related admission rates for men compared to women. Riley postulated that this was due to the possibility that while more women fall than men, more men incur serious injury[52]. This in turn might be because the normal ageing process in men has advanced further than in women by the time a fall is experienced, or because men experience more extreme challenges to their postural stability. In either case, falls are a stronger indicator of mortality risk in men than in women.

1.5.3 Variations in mortality by fall history

In their small longitudinal UK study, Bath and Morgan found that mortality for people experiencing 3 or more falls during 4 years of follow-up was about twice that of people who reported no falls (HR 2.22, 1.37 - 3.61)[14]. Similarly,

analysis of people aged 70 or more from the US Longitudinal Study of Aging[111] showed that risk of death within 2 years was greater for people falling once (OR 1.5, 1.1 - 2.0) and for multiple fallers (OR 2.2, 1.7 - 2.8), compared to non-fallers.

In the UK, a prospective cohort study in the UK of people aged over 75 years also found an increased risk of death for recurrent fallers at one year (OR 2.6, 1.4 - 4.7) and three years (OR 1.9, 1.2 - 3.0), but found no such associations for single fallers[112].

1.5.4 Variations in mortality over time

Analysis of mortality rates of fatal and non-fatal falls in the US between 1993-2003 shows that the rate of non-fatal injury has not changed whilst the risk of death as an immediate result of falling has increased[48]. On the other hand, analysis of surveillance data from European countries suggests that recent years may have seen a small decline in fall-related injury mortality[70].

1.5.5 Physical injury and medical treatment following a fall

There is evidence that for community dwelling older people in England the proportion of falls that require medical treatment is different for men and women. The Household Survey for England found that the proportion of women requiring medical treatment following a fall varied from 29% for those aged 65-69 years to 42% for those aged 85 and over. Men accessed treatment in only 23% of falls, and this proportion did not vary with age[81]. A UK study based in a residential care setting found that 82.5% of falls involved nil or negligible injury; only 17.5% were severe enough to be brought to immediate medical attention[8]. A large Finnish study found that the incidence rate of people requiring medical attention following a fall was 3.8 per 100 person years (and 5.5 when recurrent events were included)[98]. Another Finnish study[45] followed up 1169 people aged 70 or over and found a rate of fall-related injury requiring medical attention of 57 per 1000 person years for men and 113 per 1000 person years for women. A large population study in Singapore found a one year prevalence for falls of 17%, just under half of whom had sought medical attention[90]. It is clear that the number of falls

requiring medical treatment is smaller than the total number of self-reported falls, but the relationship between these varies by sex and setting and, for women, by age.

1.5.6 Other health consequences of falls

Another significant outcome following a fall is admission to a nursing home. Analysis of surveillance data in Florida found that 50% of the people with falls-related injuries which were sustained at home and required admission to hospital were subsequently discharged to a nursing home. Similarly, a UK-based study[112] found that one year risk of admission to long-term care was increased for once-only (OR 3.8, 1.8 - 8.3) and recurrent fallers (OR 4.4, 1.7-12) compared to non-fallers.

There is also consistent evidence of restriction in activities of daily living, reduced quality of life, and loss of independence following a fall[3]. For example, Tinetti and Williams found a decline in activities of daily living in the 3 years following a fall, for both non-injurious and injurious falls[113]. Amongst those suffering a fall without injury, they found reported declines in social activities.

The fear of falling accompanied by a loss of mobility and independence has been described as 'post-fall syndrome'[114]. In many cases this fear may reflect a realistic appraisal of the individual's risk of falling. In others, it may be unrealistic, but is nevertheless associated with functional decline, reduced quality of life, and social isolation[115]. In a small qualitative study Faes et al[116] noted the consequential emotional impact on the individual responsible for providing care to an older person who has fallen.

Taken together these studies underline the fact that for many people, a fall is subsequently associated with changes to health and social relationships which endure long after the healing of any physical injury which may have been incurred.

1.5.7 *Economic cost of falls*

The economic costs associated with falls in people aged over 60 years in the UK in 1999 was estimated to be £981m, based on unit costs in 2000[57]. This estimate is derived from accident and emergency department attendance for injuries resulting from falls. It includes costs arising in healthcare including hospital and GP referrals, and some social care costs relating to long-stay nursing home care. However, it excludes costs of falls resulting in a visit to the GP. The overall cost to society of falls requiring medical attention of some sort may well be much higher.

Similar calculations for the US found that the direct medical costs alone of falls amongst people aged over 65 were US$12.8 billion (based on units costs in 2000), but were more than US$19 billion when the costs of long-stand nursing care and complications were included[117]. Contemporaneous data showed that up to 85% of injury-related hospital admissions in Canada were following a fall[118].

The ageing of populations in many countries is likely to result in a significant increase in the overall economic cost. For example, a report prepared for the Australian government in 2003 highlighted that the overall cost of fall related injuries in older people will increase threefold in the first half of the century, assuming that age-specific rate remain stable.

1.5.8 *Summary*

The literature quantifying the impact on individuals and on wider society is smaller than that concerning the frequency of falls, but consistently shows that older people who fall have an increased risk of death in the years following the event as well as in the immediate aftermath, and that falls amongst older people are associated with a loss of confidence, function and independence.

In addition to the significant impact on individuals, there is an economic cost associated with falls which, even using unit costs from 2000, amount to

hundreds of millions annually. In the absence of intervention to reduce the rate of falls, the UK's changing demography means that these costs are likely to continue to increase.

1.6 What is known about the role of medications in falls in older people

Since the late 1970s, epidemiological studies have identified many risk factors for falls in older people including past history of falls, socio-demographics (advanced age, mobility, female sex, ethnicity/race, living alone) and lifestyle (inactivity, use of walking aid, alcohol consumption), physiology and clinical conditions (postural instability, sensory and neuromuscular function, impaired cognition, stroke, Parkinson's disease, depression, neurological signs, incontinence, acute illness, arthritis, orthostatic hypotension, vestibular disorders) together with environment (poor footwear, inappropriate spectacles), psychology (fear of falling) and medication use[119].

Evidence from a range of studies for the iatrogenic effect of medications on falls in older people dates back more than a quarter of a century[120]. Reduced levels of mental alertness, impaired transmission within the central nervous system, sedation, confusion, reduced neuromuscular coordination and balance, and drug-induced parkinsonism are all plausible mechanisms by which various medications may degrade the balance system[121]. However, commentators note that, in general, the pharmaceutical industry has not recorded falls or any intermediate measures of postural stability as an outcome measure during drug development[121]. Consequently, despite the high prevalence of prescribing amongst older people, the majority of the evidence for the possible role of medications arises from observational studies. Many of these are small and subject to confounding or to other issues impacting their reliability. Confounding by indication and small study size is a feature of the literature in most of the following sections.

1.6.1 Centrally acting medication

The association between prescribing of centrally acting medication and falls in older people has been examined in a large number of studies. Leipzig et al published a systematic review in 1999 which, based on the pooled odds ratios of the 40 studies which met their inclusion criteria, found a significant association with falls in older people for anti-psychotics (pooled OR 1.50, 1.25 - 1.79), anxiolytic/hypnotics (pooled OR 1.54, 1.40 - 1.70), any antidepressant (pooled OR 1.66, 1.4 - 1.95), tricyclic antidepressants (pooled OR 1.51, 1.14 - 2.00), and benzodiazepines (pooled OR 1.48, 1.23 - 1.77)[122]. They also found that these effects were independent of age of participants, their frequency of falling, and study setting. The authors noted that there was evidence of heterogeneity between studies of some medication classes and that the evidence was based entirely on data from observational studies whose design made little allowance for confounding, dosage or duration of therapy. In a placebo controlled trial, Campbell et al found that psychotropic medicine withdrawal led to a lower risk of falling in the intervention group[123]. Based partly on this, England's National Institute for Health and Clinical Excellence has recommended that "older people on psychotropic medications should have their medication reviewed, with specialist input if appropriate, and discontinued if possible to reduce their risk of falling"[124].

In 2007, a review by Hartikainen et al[125] included studies of pharmaceutical preparations coming on to the market since Leipzig et al's earlier review, e.g. selective serotonin reuptake inhibitors, atypical antipsychotics. The review did not provide a pooled result using formal statistical methods but found that SSRIs were associated with falls. No association with falls was found in the two studies investigating atypical antipsychotics. Kallin et al's study in residential care settings suggests that SNRIs may be safer than SSRIs in terms of risk of falls[126], but at the start of this project there was no data on the risk of falls associated with SNRIs in older people in a community setting. (Recently, Coupland et al's study of the adverse effects of antidepressants included some sub-analysis for Venlafaxine, for which the estimates of one year risk of falls was similar to that for SSRIs[127].)

Woolcott et al undertook a meta-analysis of studies of falls associated with these medication classes[128]. They used Bayesian techniques to incorporate the results of studies included in Leipzig et al's meta-analysis with data from more recent studies. The Bayesian pooled estimates they derived for the main classes of centrally acting medication were very close to the pooled odds ratios of Leipzig's earlier studies.

1.6.2 Analgesics

A smaller number of studies examine possible associations for analgesic agents. Findings from these have been mixed and subject to confounding by the musculoskeletal conditions they are used to treat. A second systematic review by Leipzig et al found no significant association for NSAIDs, aspirin, narcotic nor non-narcotic analgesics[129]. Woolcott et al's Bayesian meta-analysis produced a pooled estimate for NSAIDs, for which the point estimate was almost unchanged (Bayesian pooled estimate 1.21).

1.6.3 Cardiovascular medication

The literature on cardiovascular medication and falls in older people is also scant compared to that for centrally acting medication. Leipzig et al's 1999 review studied cardiac medications including any diuretic, thiazide diuretics, loop diuretics, beta-blockers, centrally acting antihypertensives, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, nitrates, type 1A antiarrhythmics, and digoxin[129]. There were no randomised control trials meeting their selection criteria. The meta-analysis of the observational studies found weak associations with one or more falls for digoxin (pooled OR 1.22, 1.05 - 1.42), type 1A antiarrhythmics (pooled OR 1.59, 1.02 - 2.48) and use of any diuretic (pooled OR 1.08, 1.02 - 1.16). In his review of the epidemiology of medication related falls in older people, Cumming[130] observed inconsistent and undiscriminating classification of cardiovascular medications in many studies.

There have been a few studies published since the meta-analysis. Of these, several were included in the review by Hartikainen et al[125], who reported that

nine[36 126 131-137] of the twelve studies[138-140] addressing cardiovascular medication use and risk of falling found no association. More significantly, Woolcott et al's recent meta-analysis derived a new frequentist odds ratio for beta blockers of 1.14 (0.91 – 1.33) and an updated Bayesian odds ratio (with 95% credible interval) of 1.01 (0.86 – 1.17). Woolcott et al found that the difference compared to Leipzig's original estimate was close to statistical significance.

Woolcott et al also included analysis of antihypertensives which were not addressed in Leipzig's earlier meta-analysis, for which they found a frequentist pooled estimate of 1.26 (1.08 – 1.46). However, as previously noted by Cumming in respect of other studies[130], the meta-analysis was not able to differentiate between sub-classes of antihypertensive.

In common with Leipzig et al[122] and others, Woolcott et al highlight the problem that estimates of effect in these studies may be confounded by a number of factors including by indication. They observed that many of the studies included in the meta-analysis reported adjusted odds ratios, and that the pooled adjusted odds ratios were similar to the pooled unadjusted odds ratios. On this basis, they concluded that the role of confounding "was quite small in this regard".

Setting out to test the hypothesis that associations between medications and falls are confounded by medical conditions, Lee et al[141] found no association with falls for most cardiovascular and non-cardiovascular drug groups (including psychotropics) after adjusting for medical conditions, except for nitrates. The study involved 4000 participants but it is not clear whether it was powered to identify a small effect size in the subgroups analysed. More recently still, Carbone et al found no association between loop diuretics and falls amongst 3411 female users and 130444 non-users of loop diuretics[142].

Van der Velde et al conducted a cohort study in 139 older people to assess whether withdrawal of medication is associated with a reduction in the incidence of falls. They found that the withdrawal of cardiovascular

medication in particular was associated with a reduction in falls[143]. Unfortunately the study was not designed to differentiate the effects of different classes of cardiovascular medicine, which included (amongst others) adrenoceptor blockers, diuretics, calcium channel blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, nitrates, class III antiarrhythmics, and a nicotinic acid derivative. Nevertheless, the study is important in terms of the supporting evidence it provides of causality in the relationship between at least some cardiovascular medications and falls in older people. The lack of differentiation in the class attribution points to the role of polypharmacy (which is considered in the following section) alongside or instead of the role of specific medications.

Overall the evidence is sparse and arises from small-scale studies, or studies that do not differentiate between different classes of cardiovascular medication[144]. In particular, there is recent evidence that antihypertensives are associated with falls in older people but it is not clear whether the generalisation applies to all sub-classes or the extent to which some of the observed associations are due to residual confounding.

1.6.4 Polypharmacy

Polypharmacy is common amongst older people and its prevalence continues to increase[145]. Various studies have demonstrated an increased risk of falling with multiple medication prescribing. For example, Cumming et al[146] reported that the relative risk of falling was 1.4 for a single medication, rising to 2.2 for two medications and 2.4 for three or more. However, the apparent impact of polypharmacy may be due to underlying frailty or co-morbidities.

More recently, a cross-sectional study of more than 4000 older women found that, after adjusting for underlying co-morbidities, falls were no longer significantly associated with the number of prescribed medications[137]. Similarly, Lee et al found no association with polypharmacy[141]. In their recently updated joint guidelines, the British and American Geriatric Societies

summarised the evidence for the effect on falls of reducing polypharmacy as "fair"[147]. The guidelines emphasise the review of medications with a view to reducing a range of associated problems (e.g. confusion, constipation, nausea, continence problems, tiredness, insomnia, depression) but, in view of wider considerations about the balance of possible benefits and harms, were not in a position to make a general recommendation for or against routinely reducing polypharmacy in older people who have fallen.

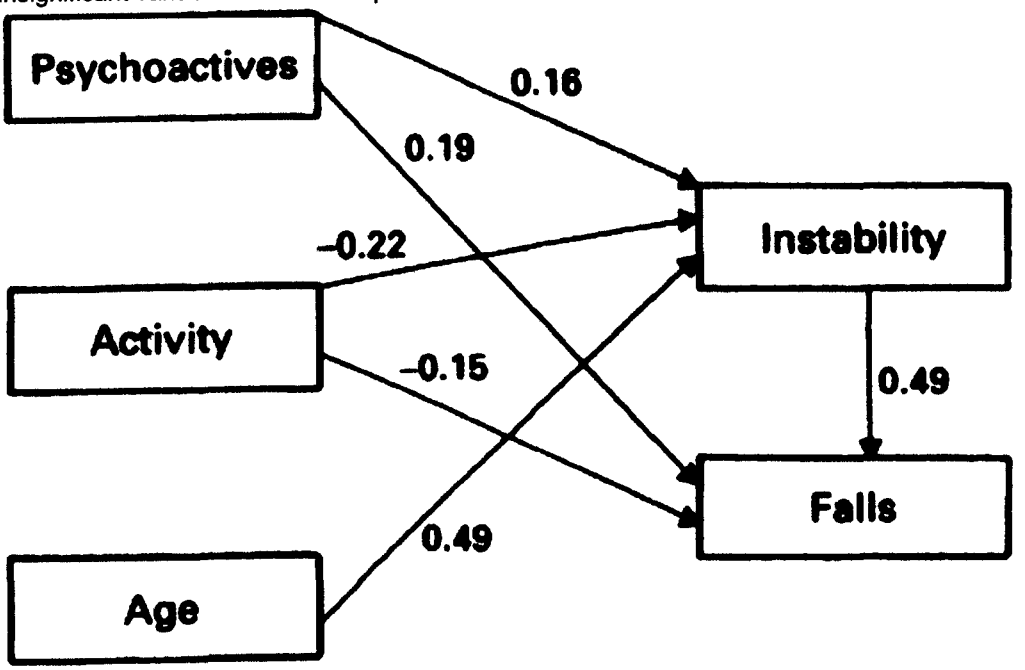
These studies provide further evidence that research to measure the possible impact of a particular medication must take account of the prescribing of other medications. Implications of this for study design include the need for accurate measurement of exposure to a range of medications, sufficient power to detect modest differences in their effects, and strategies for differentiating the effects of multiple risk factors.

1.6.5 Evidence of mechanisms by which medications cause falls

For some medications, an association with falls has long been recognised and the mechanisms are relatively well established. For some other medications the mechanism by which they have an effect are more speculative. This section sets out some of this evidence, starting with those medication groups for which evidence about the mechanism is strongest.

Lord et al outline the evidence for the mechanism by which central acting medications in general are causally linked with falls in the elderly[121]. Evidence about possible mechanisms by which central acting medications are causally linked with falls in the elderly is strongest for benzodiazepines, which are associated with reduced reaction times and increased postural sway[148-150]. The relationship is modelled in Figure 1-3 which indicates that approximately half of the association between psychoactive medication and falls is mediated via reduced stability[151].

Figure 1-3 Path analytic model for the relationship between psychoactive medication use and falls from Lord et al
The standardised relative strengths of the effects are indicate by the numbers above the path arrows. (Notes: Psychoactives: nil, one or two. Activity: hours per week. Age: age in years. Poor balance control: a composite measure incorporating measures of tactile sensitivity, vibration sense, quadriceps strength, reaction time, sway and clinical stability. Falls: two or more falls versus nil or one. Postural hypotension was found to be a statistically insignificant variable in the development of the final model.



In their 2009 review Darowski et al summarise the evidence for mechanisms by which antidepressant medication may contribute to falls in older people[152]. Causal links may be mediated through sedation and impaired premotor planning and reaction times, impaired balance, insomnia, alerting effects and deranged sleep architecture leading to daytime drowsiness and increased nocturia, orthostatic hypotension, cardiac conduction or rhythm disturbances, and a tendency to cause movement disorders (see Table 1-1). However, the authors noted that most of the evidence comes from studies based on participants with a younger age profile than typical fallers, and that evidence of no adverse effect in younger fallers is not the same as evidence of no association for older people. It might be speculated that similar mechanisms exist for SNRIs, but the study found no data for the effect of SNRIs on falls.

Table 1-1 Adverse effects of antidepressants which may contribute to falls, from Darowski et al

Antidepressant class	Individual antidepressant	Adverse effect					
		falls	orthostatic hypotension	sedation	arrhythmias	balance impairment	sleep disturbance
Tricyclic antidepressants	Amitriptyline	+++	+++	+++	+	++	+++
	Clomipramine	+++	+++	+++	+	No data	+++
	Dosulepin	+++	+++	+++	+	No data	+++
	Doxepin	+++	+++	+++	+	++	+++
	Imipramine	+++	+++	+++	+	No data	+++
	Lofepramine	+++	+++	+++	+	No data	No data
	Nortriptyline	+++	++	+++	+	No data	+++
	Trimipramine	+++	+++	+++	+	No data	–
Noradrenergic and specific serotonergic antidepressants	Trazodone	+++	+++	+++	+	No data	+
Tetracyclic antidepressants	Mianserin	+++	+++	+++	+	No data	++
	Mirtazapine	+++	+++	+++	+	No data	–
Monoamine oxidase inhibitors	Phenelzine	No data	+++	No data	–	No data	+++
	Isocarboxazid	No data	+++	No data	–	No data	+++
	Tranylcypromine	No data	+++	No data	–	No data	+++
Reversible inhibitors of monoamine oxidase A	Moclobemide	No data	–	–	–	No data	++
Selective serotonin reuptake inhibitors	Citalopram	+++	+	+	–	+++	+++
	Escitalopram	No data	No data	No data	No data	No data	+++
	Fluoxetine	+++	+	+	+		+++
	Fluvoxamine	+++	++	–	–		+++
	Paroxetine	+++	++	–	–		+++
	Sertraline	+++	+	–	–	+++ (early transient effect)	+++
Selective serotonin and norepinephrine reuptake inhibitors	Venlafaxine	No data	+++	+	+	No data	+
	Duloxetine	No data	++	+	No data	No data	No data
Selective norepinephrine reuptake inhibitors	Reboxetine	No data	++	+	No data	No data	+++
	Bupropion	No data	–	–	+	–	+
	Hypericum (St John's wort)	No data	–	–	–	No data	+

+ indicates weak correlation between the adverse effect and drug; ++ indicates intermediate correlation between the adverse effect and drug; +++ indicates strong correlation between the adverse effect and drug; – indicates no correlation between the adverse effect and drug.

In the case of antihypertensives, although an association with falls via orthostatic hypotension has long been suspected[153], the relationship with drug-related orthostatic hypotension remains unclear[154 155]. In part, this is due to the volatility of orthostatic hypotension and the difficulty of assessing its severity.

1.6.6 Generalising from evidence about impact of medications on fractures

There is evidence about the impact of some of these medications on risk of fracture. Hip fracture provides a reliable recorded marker of when a fall has occurred, but also reflects other factors such as osteoporosis. Nevertheless,

it represents a subset of falls for which the consequence is specific and relatively severe. It carries public health implications which are correspondingly large including costs to the public purse which, for the NHS are estimated to be in the range £1.4 billion annually and as much as double this if all costs to society are included[156].

Takkouche et al's meta-analysis of studies[157] measuring the effect of centrally acting medication and fractures found increased risk of fracture for benzodiazepines (pooled RR 1.34, 1.24 – 1.45), antipsychotics (pooled RR 1.59, 1.27 – 1.98) and antidepressants (pooled RR 1.60 (1.38 - 1.86) which were similar to the pooled and Bayesian odds ratios in Leipzig et al and Woolcott et al's meta-analyses of falls[128 129]. On the other hand, the pooled OR for hypnotics was not significant (pooled RR 1.15, 0.94 – 1.39). For non-barbiturate antiepileptics the pooled RR was 1.54 (1.24 – 1.93) and 2.17 (1.35 – 3.50) for barbiturate antiepileptics. In common with other meta-analyses[122 129], the authors noted a concern about the degree to which these effects were subject to residual confounding, and also about publication bias. Exploring associations with SSRIs in particular, Hubbard et al found that the increase in risk of fracture associated with antidepressant medication was greatest in the first 14 days following the initiation of prescribing (adjusted OR 6.30, 2.65- 14.97)[158]. In the same study, Hubbard et al undertook self-controlled case series analysis by which they estimated that amongst people prescribed SSRIs the relative incidence of fracture in the first 14 days following first prescription compared to unexposed period was 1.96 (1.35 – 2.83). They interpreted these results as evidence of an acute adverse effect, and of a bias in the case-control study resulting in an overstatement of the size of the true effect.

Vestergaard et al found dose-dependent odds ratios of between 1.4 and 2 for the most frequently prescribed SSRI (citalopram) and mostly non-significant effects in SSRIs for which prescribing was less prevalent[159]. In a large prospective cohort study (n=5008) Richards et al also found a positive effect for SSRIs and this effect persisted for the duration of the 5 years of follow-up[160].

Wiens et al's meta-analysis of observational studies of antihypertensives and fractures[161] found a pooled relative risk of 0.86 (0.81 – 0.92) for thiazides, and 1.14 (0.84–1.54) for non-thiazide diuretics. For beta blockers there was a statistically significant reduction (pooled RR 0.86, 0.70 - 0.98). They found no significant associations between fractures and exposure to alpha-blockers or calcium channel blockers, and there was only a single study which looked at ACE inhibitors for which the pooled relative risk was 0.86 (0.70 – 0.98). The apparent protective effect of thiazides and beta blockers suggests that patients prescribed these medications may experience a reduced risk of fracture. Nevertheless, leaving aside the possibility that the observed effect is attributable to some factor other than the medication itself, it is not clear whether a reduced risk of fracture is necessarily an indication that the same group experience a reduced risk of falling.

One method by which a possible causal link between medications and fractures may be mediated is that of reduced bone mineral density[162]. The degree to which reduced bone mineral density explains all of the observed association between a medication and fractures is uncertain, as is the mechanism by which reduced bone mineral density might be associated with falls. A link between exposure to a medication and an increased risk of fracture, causal or otherwise, does not provide good grounds for concluding that there is a corresponding increased risk of falls.

This together with the fact that effects observed for fractures and falls for some medications are in opposite directions (e.g. beta blockers), limits the degree to which an understanding of the effect of medications on fractures will properly inform an understanding of medication and falls.

1.6.7 Summary

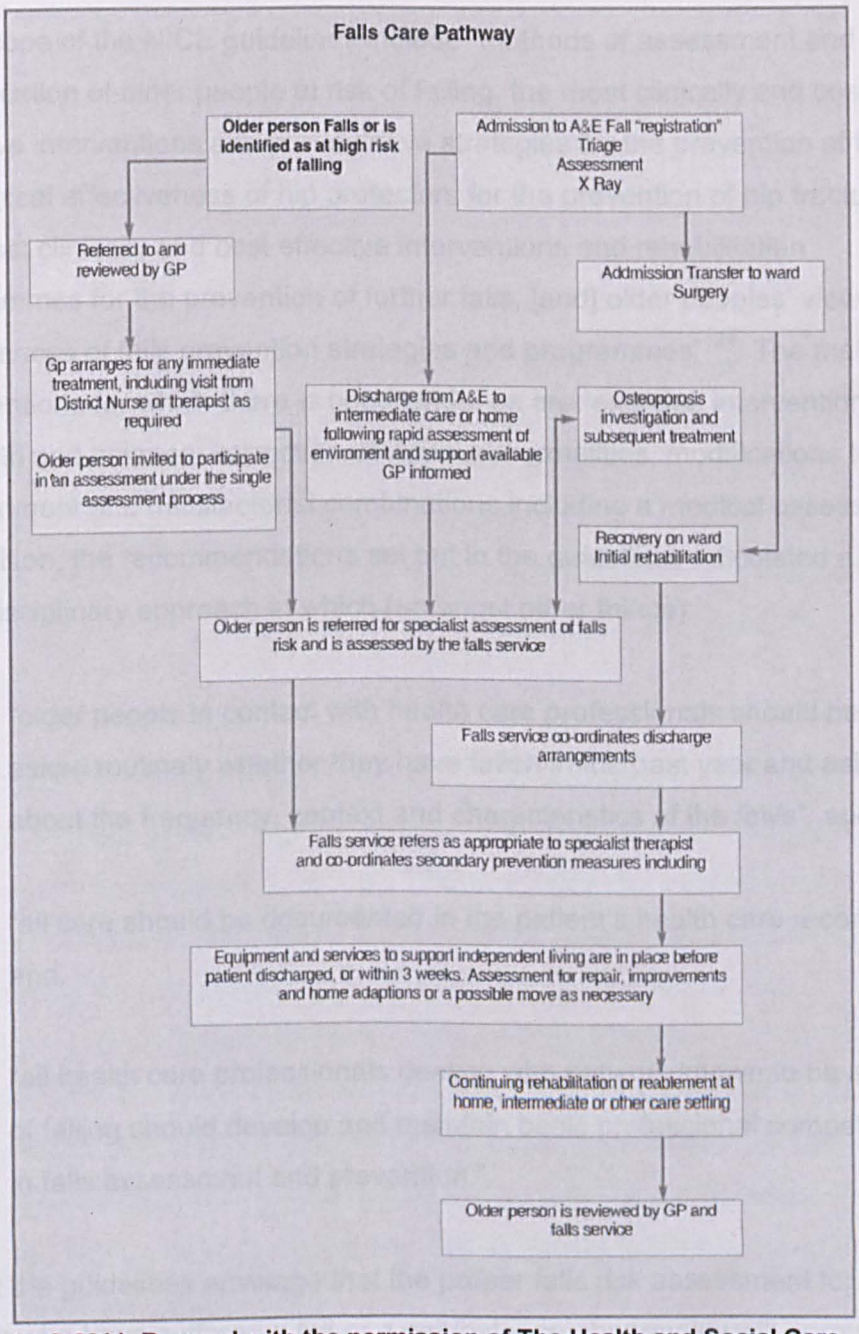
Much of the evidence for the effect of medications on falls is derived from observational studies, many of which are small and may be subject to confounding. The strongest evidence is for the effect of centrally acting medications. Reviews of the relatively scant evidence for the effect of cardiovascular medications indicate that the evidence base could be

strengthened by studies which differentiate more clearly between classes of cardiovascular medication and which adjust for the confounding effects of comorbidities and other prescribing. This gap in the evidence base is significant not only because of the prevalence of prescribing for cardiovascular disease medication, but also because of their possible role in polypharmacy which is increasing in prevalence, and is associated with falls. There is also a gap in the evidence base concerning the falls profile of SNRIs.

1.7 Arrangements for the management of falls in older people

Improving the prevention and management of falls in older people has been a government priority for more than a decade. In England, this was given expression in one of a series of National Service Frameworks, which were published in the early years of the New Labour government to set out the actions for several areas of public health need. The National Service Framework (NSF) for Older People was published in 2001 with an intent to "reduce the number of falls which result in serious injury and ensure effective treatment and rehabilitation for those who have fallen"[163]. The NSF envisaged GPs at the heart of the pathway (see Figure 1-4).

Figure 1-4 Falls pathway as envisaged by the National Service Framework for Older People[163]



Against this background the National Institute for Health and Clinical Excellence (NICE) commissioned a multidisciplinary group to develop a

comprehensive set of clinical guidelines for the assessment and prevention of falls in older people[124].

The scope of the NICE guidelines include "methods of assessment and identification of older people at risk of falling, the most clinically and cost effective interventions and preventative strategies for the prevention of falls, the clinical effectiveness of hip protectors for the prevention of hip fracture, the most clinically and cost effective interventions and rehabilitation programmes for the prevention of further falls, [and] older peoples' views and experiences of falls prevention strategies and programmes"[124]. The main interventions for which there is good evidence are: exercise interventions for strength and balance, correction of visual abnormalities, modifications to the environment and multifactorial combinations including a medical assessment. In addition, the recommendations set out in the guidelines articulated a multidisciplinary approach in which (amongst other things):

> "older people in contact with health care professionals should be asked routinely whether they have fallen in the past year and asked about the frequency, context and characteristics of the fall/s", and
>
> "all care should be documented in the patient's health care records" and,
>
> "all health care professionals dealing with patients known to be at risk of falling should develop and maintain basic professional competence in falls assessment and prevention."

Whilst the guidelines envisage that the proper falls risk assessment for people who have suffered a fall or a gait/balance abnormality will normally be conducted in the setting of a specialist falls service, the responsibility for making a referral is explicitly attributed to the professionals at the point of presentation which, for many people, is either their GP or a hospital accident and emergency department who, according to the NSF, are charged with informing the GP.

1.8 Justification and aims of thesis

Falls in older people are a major public health challenge. As many as a third of older people experience a fall, with results for the individual ranging from the inconsequential through to hospital admission, loss of confidence or loss of independence. Wider impacts include the cost of health and social care associated with the consequences of the fall, together with the cost of informal care. For countries with ageing populations, these costs are forecasted to increase.

Recent health service initiatives, including the National Service Framework for Older People[163] and national clinical guidelines for falls prevention and treatment[124], envisage an important role for general practitioners and primary care within the care pathway for the prevention and treatment of falls in England. Yet there is little published data on the recording and incidence of falls seen in primary care, with which to consider the implications of this approach.

These policy responses to the scale and impact of falls in older people recognise evidence for the role of particular medications and polypharmacy in the multifactorial aetiology of falls. Nevertheless, the evidence base for the effect on falls in older people of some of the most commonly prescribed medications, including cardiovascular medications, is meagre and inconsistent. In particular, evidence for the possible effect of antihypertensive medications is inconsistent and is compromised by a poor differentiation between sub-classes of medication and uncertainty about the extent to which observed effects are subject to residual confounding. There is also a gap in the evidence concerning SNRIs, which some have suggested may be safer than SSRIs.

Therefore a longitudinal database of general practice records is used to quantify the burden of falls in primary care in the UK, and to address gaps and shortcomings in the evidence base regarding medications commonly prescribed to older people.

Specifically, the aims are:

- To quantify the overall incidence of recorded falls among older people in primary care in the UK, and to determine whether it varies over recent years or by socio-demographic attributes
- To quantify risk of death associated with falls in older people in primary care
- To establish whether the falls risk profile of more recently introduced serotonin noradrenalin reuptake inhibitors is more favourable than that of selective serotonin reuptake inhibitors
- To establish whether being prescribed antihypertensive medication modifies the risk of falling in older people, differentiating between specific sub-classes of medication, and assessing the extent of any confounding
- To identify any other classes or sub-classes of medication prescribed in primary care whose apparent falls risk warrants investigation in future studies

1.9 Ethical approval

A request for ethical approval was submitted to Nottingham Research Ethics Committee under their reference 06/Q2403/15. Nottingham Research Ethics Committee granted their approval for this research project and confirmed it in writing on 12th October 2006.

1.10 Funding for the study

University of Nottingham research student fees have been generously funded by the East Midlands Strategic Health Authority.

1.11 Structure of the thesis

The chapters following this introduction will describe the primary care database used to address the study aims, together with the evidence for its

validity, and the methods used to prepare it for detailed analysis in the subsequent cohort and aetiological studies.

The main body of the thesis consists of several chapters describing the studies of incidence and of association with antidepressant and cardiovascular medications. The chapter containing a description of the cohort studies with their key results is preceded by a chapter setting out the methods used and their rationale.

Similarly, the chapters which describe the studies of associations with antidepressant and cardiovascular medication are preceded by a second methods chapter. This sets out the case-control and self-controlled case series methods in detail, including their potential shortcomings and underlying assumptions.

The penultimate chapter reports the findings of a further study intended to identify other classes of medication which may be associated with falls in older people.

The findings from all the studies are brought together in a conclusion which sets out their implications with recommendations for policy and practice.

2 Methods development: incidence and mortality

The previous chapter reviewed the relevant literature relating to the field of study, and the aims and objectives for the project. This chapter describes the methods used to execute the study. It opens with a description of the source and structure of the data used to address the research questions, and the evidence for its validity. It then sets out a detailed description of the methods developed for the cohort and aetiological studies, so that in subsequent chapters the discussion can be focussed on the results of the analyses and their interpretation.

2.1 The Health Improvement Network

Parts of this section draw from a review of evidence for the validity of THIN that is reported in a dissertation by the author submitted to the University of Nottingham for a Masters in Public Health[164].

2.1.1 Background

The Health Improvement Network (THIN) is a computerised longitudinal primary care database, containing patient records from general practices in the United Kingdom. It is the result of a collaboration between EPIC (www.epic-uk.com) which is a non-profit making organisation that facilitates access to electronic research data, and Cegedim (www.cegedim.com) who develop and supply the Vision general practice computer system to about 2000 GP practices in the UK[165]. The THIN data are derived from general practices using Vision. In return for providing data, practices receive help with software training and audit.

THIN was developed by Dr Alan Dean who played a leading role in the management and development of the General Practice Research Database (GPRD) from 1994. THIN is modelled on GPRD and uses the same data structures. Many practices that contribute data to THIN also contribute data to GPRD.

The primary reason for using THIN in these studies (rather than GPRD) was because of the availability of a license to use the data within the Department of Epidemiology and Public Health at the University of Nottingham.

2.1.2 Data anonymity

To prevent the identification of individuals, patient data in THIN has been anonymised by removal of names and addresses of patients, names of practices, and the day of the month of birth.

2.1.3 Coverage

The version of THIN, from which the data for the studies of incidence and mortality were selected, represented records from 336 general practices up to July 2007. Later studies in the project used a more recent version of the database, which was able to draw on data from additional practices.

2.2 The data

2.2.1 Content & structure

THIN contains diagnostic and prescribing data recorded by general practitioners as part of routine clinical care. It includes information from secondary hospital referrals and emergency admissions, and information about date and cause of death. These data are contained in several tables which are summarised in Table 2-1.

Table 2-1 Description of the main tables of data in THIN

Database Table	Description of data
Patient	Demographic data, including year of birth, sex, and period in database
Medical	Data on all illnesses diagnosed (Read coded), including emergency visits and hospital referrals
Therapy	Details of each prescription (including drugs prescribed acutely) with name, form, strength and dose (multilex coding system)
Additional health data	Data on height, weight, smoking habit and blood pressure.

THIN also holds information about the health authority region in which the patient was last resident and quintile of Townsend score, which is a marker of deprivation for the small geographical area comprising the patient's residence and approximately 150 households. It is derived from 2001 census data comprising prevalence of household access to a car, owner occupation, overcrowding, and unemployment[166].

2.3 Validity

The weight that is attributed to findings from these studies depends in part on the validity of the measures of outcomes and exposures recorded in THIN. The most compelling evidence for the validity of THIN includes peer-reviewed findings of validation studies of THIN. It is also supported by validation studies of GPRD, which derives its data from the same network of practices.

2.3.1 Validation studies

There are a growing number of published validation studies of THIN. For example, Lewis et al conducted a series of case-control studies in THIN to explore known disease associations[167]. For the vast majority of hypotheses they found associations consistent with those reported in the published literature. Lo Re et al undertook a formal validation of recorded diagnoses of Hepatitis C virus (HCV). They found that that among the 74 patients who had a specific HCV diagnosis, HCV was confirmed in 64 giving a positive predictive value of 86% (77% - 93%)[168]. Others have looked at events as diverse as smoking cessation prescriptions[169], diagnoses of psoriasis[170], non-melanoma skin cancer[171] and found that the information in THIN supports research objectives. In addition to peer reviewed studies, a number of validation studies are reported in conference proceedings[172]. The validity of THIN for the study of mortality is demonstrated by Hall who investigated the recording of deaths and suicides and found that a record of death in THIN has a positive predictive value of 99.6%[173]. In 95% of the deaths the recorded date of death was within 1 day of the actual date of death.

2.3.2 *Validation studies of GPRD*

Approximately half of the practices contributing to GPRD also contribute data to THIN[169]. Therefore evidence for the validity of GPRD is a relevant consideration. Lewis et al's study of known disease associations[167] found almost identical results irrespective of whether the practice concerned contributed to GPRD or only to THIN. In other words they found no evidence that the reliability of data in THIN is different to that in GPRD.

Amongst more than 500 peer-reviewed studies based on GPRD, there are several which relate to its validity[174]. For example, Jick et al[175 176] validated the recording of medical information in GPRD from primary and secondary care and found it to be near complete. The literature also contains reviews of studies evaluating the quality of other aspects of GPRD [177 178], much of which relates to pharmaco-epidemiological aspects of the data.

2.3.3 *Other considerations regarding the reliability of THIN*

Additional factors point towards the credibility of THIN as a reliable record of patient details and health events.

Firstly, THIN represents an investment from which the owners (EPIC) derive a stream of revenue from licensing fees paid by the pharmaceutical and other organisations wishing to undertake research using primary care data. Furthermore, EPIC's business model involves providing management reports to general practices who are contributing patient data to THIN. Together these show that it is critical to EPIC's commercial exploitation of THIN that the quality of the data is high.

Secondly, EPIC publishes details of known quality issues relating to data within THIN[165]. The possible impact of these issues is discussed below, but the fact that EPIC are explicit about these limitations adds to the credibility of the argument for the general validity of THIN.

2.3.4 *Management of data quality in THIN*

EPIC arrange periodic downloads of data from general practices and undertake basic checks on data integrity. Individual records with integrity errors are flagged so that they can be excluded from the analysis or be given other special treatment. Details of data quality issues identified include those where data is missing (e.g. the dates of certain events), inconsistent (e.g. an event appears to occur after the patient has been transferred out), or of uncertain reliability (e.g. differentiation of actual from attempted suicide) [177].

In some instances, recognised issues of data quality or integrity are flagged on individual records. Patients with records that have been flagged in this way were excluded by the initial data extract routines which were executed according to the normal procedures of the research department.

Theoretically, this may have resulted in the exclusion of people who would otherwise have been selected as cases. To quantify the possible impact, the reader is referred to the results of applying the same 'rules' to an earlier version of the dataset which resulted in the exclusion of about 10% of cases[179]. If the prevalence of data quality issues is the same amongst fallers in this more recent version of the data, one might expect the estimates of incidence to be impacted by up to 10%. However, EPIC report that in general it is records relating to the earliest years of data collection (i.e. years which precede the study period) that are incomplete. Records during the study period will be subject to a lower prevalence of integrity errors. Therefore the impact of data quality issues on estimates of incidence is likely to be less than 10%.

2.3.5 *Population coverage of THIN*

98% of the general population in the UK are registered with a general practitioner[180]. All sections of the population are represented in the versions of THIN used in this study, which covered approximately 3% of the UK population[165]. Szatkowski et al found that the demographic of THIN is "broadly nationally representative" when compared to data provided by the

Office of National Statistics[181]. Similarly, Rodriguez and Gutthann cite work which allows for a comparison of the age and sex distribution of the GPRD population with that available for the general population from census data and has shown these to be "closely similar" [178].

2.3.6 *Conclusion about dataset*

Evidence from a number of sources indicate the validity of THIN (and of GPRD on which THIN is based) and that it provides a representative sample of those registered with general practitioners in the UK. Where there are known quality issues in the data their likely impact is small.

2.4 Tools for initial data extraction and statistical analysis

2.4.1 *Initial data extract*

Data were extracted from THIN using Microsoft Access routines executed according to the Department of Epidemiology and Public Health's normal procedures by Mr Christopher Smith (Senior Research Fellow). These procedures include logic to filter data which are known to be incomplete or to have errors. They also ensure that the selection of any controls is properly randomised. All subsequent routines for managing the data, and for applying the statistical analysis, and its interpretation were developed and undertaken by the author.

The specification of the initial extract required that the start date was defined as the later of their date of registration at the practice or the date of practice computerisation, and a stop date was defined as the earlier of either the last THIN data collection or the date of death. The data extract was provided to the author as a Microsoft Access .mdb file.

2.4.2 *Statistical analysis*

The data extracts were converted to Stata formats using StatTransfer[182]. All statistical analysis was undertaken in Stata version 9[183].

2.5 Analysis of incidence

This section sets out the methods used to measure the incidence of falls and to model the effects of relevant demographic variables. Attention is given to some considerations which are particular to the THIN data, including approaches to dealing with the possibility of prevalent recording and of recurrent recording of the same event.

2.5.1 Identifying the outcome of interest

The key outcome of interest is a recorded fall. In this study, fall events were identified using Read codes. Read codes comprise the comprehensive set of symptoms and diagnoses available to primary care practitioners in the UK for recording the reason for a consultation or other event.

Table 2-2 summarises analysis which shows that out of the wide range of Read codes available, more than 80% of events relating to falls were recorded using the term "Fall – accidental". This term and a further seven account for 99% of fall events recorded in THIN.

Table 2-2 Frequency of the most commonly occurring Read codes related to falls (excluding codes related to Assessments or Referrals)

Falls-related Read Code		Number of occurrences	% of total occurrences
TC...11	Fall - accidental	314,409	82.61%
16D..00	Falls	18,566	4.88%
R200.12	[D] Geriatric fall	15,035	3.95%
TC...00	Accidental falls	15,028	3.95%
TCz..00	Accidental falls NOS	5,220	1.37%
TCy..00	Other falls	2,794	0.73%
16D1.00	Recurrent falls	2,334	0.61%
16D2.00	Number of falls in last year	1,232	0.32%
TC5..00	Fall on same level from slipping, tripping or stumbling	996	0.26%
U10..00	[X]Falls	690	0.18%
TC0..00	Fall on or from stairs or steps	575	0.15%
Further 159 codes, individually comprising <500 (0.1%) of total		3,706	0.97%
Total occurrences of falls-related read codes		380,585	100.00%

Some infrequently used codes for falls correspond to events during hazardous occupational activities (e.g. "fall from scaffolding"). In this study, these events were included in the definition of falls, noting that occurrences of these codes are rare. However, codes for falls risk assessments were excluded on the grounds that they signify a perception of risk on the part of the clinician which does not necessarily arise from an actual fall event.

The fall codes used for calculating incidence and mortality patterns are listed in Appendix B.

2.5.2 Differentiating between prevalent and incident recording

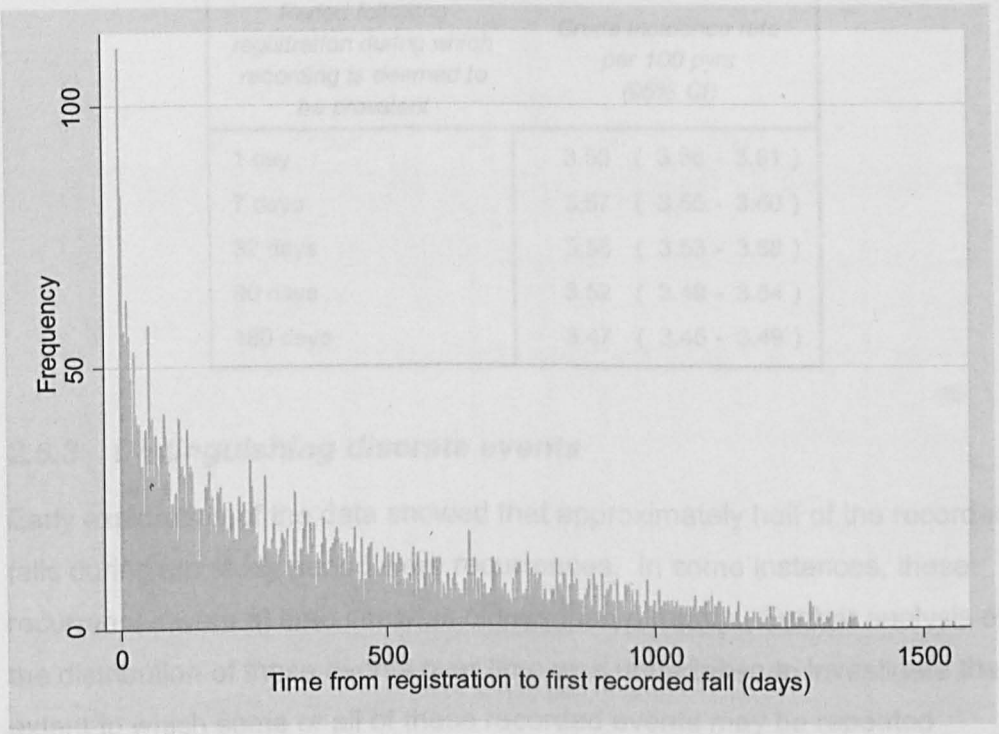
2.5.2.1 General evidence of prevalent recording in THIN

Lewis et al assessed the validity of using the first recorded diagnosis as the index date for calculating incidence[184]. They compared variations in rates of incidence from time of patient registration for a range of acute, chronic and neoplastic diseases. They found that reported incidence rates are highest in the months after patient registration and that it takes as much as 12 months for them to return to baseline. They considered the rationale behind various possible explanations for this finding, and concluded that incidence is over-reported in the first months after a patient registers with a practice as a result of prevalent cases being recorded as incident ones.

2.5.2.2 Analysis of prevalent recording of falls

The role of prevalent recording of falls was investigated in the THIN dataset by exploring the elapsed time between date of registration and date of first recorded fall. For periods close or very close to the date of registration, there was found to be a much higher frequency of falls than for other periods. This was most pronounced for the falls recorded on the same date as the date of registration. This is interpreted to be evidence of prevalent falling, i.e. recording that was contemporaneous with registration and for which the recorded date of the event is not reliable for the purposes of identifying incident events.

Figure 2-1 Chart showing the frequency distribution of time from registration to first recorded fall



In consideration of this, it was decided to adjust for prevalent recording of falls in the analysis on the basis that some of (but not necessarily all) the recorded falls in the first few days following registration represent prevalent recording. Therefore, for the cohort studies, the simplifying assumption was made that all falls recorded on the date of registration should be treated as prevalent falls (i.e. they should be excluded from subsequent analysis), and to treat all falls on dates following registration as incident cases.

A sensitivity analysis was undertaken by recalculating crude incidence rates under a series of different assumptions about the period of time during which recording is deemed to be prevalent. The results of this are provided in Table 2-2, which shows that the impact of this assumption on calculations of crude incidence rates is small.

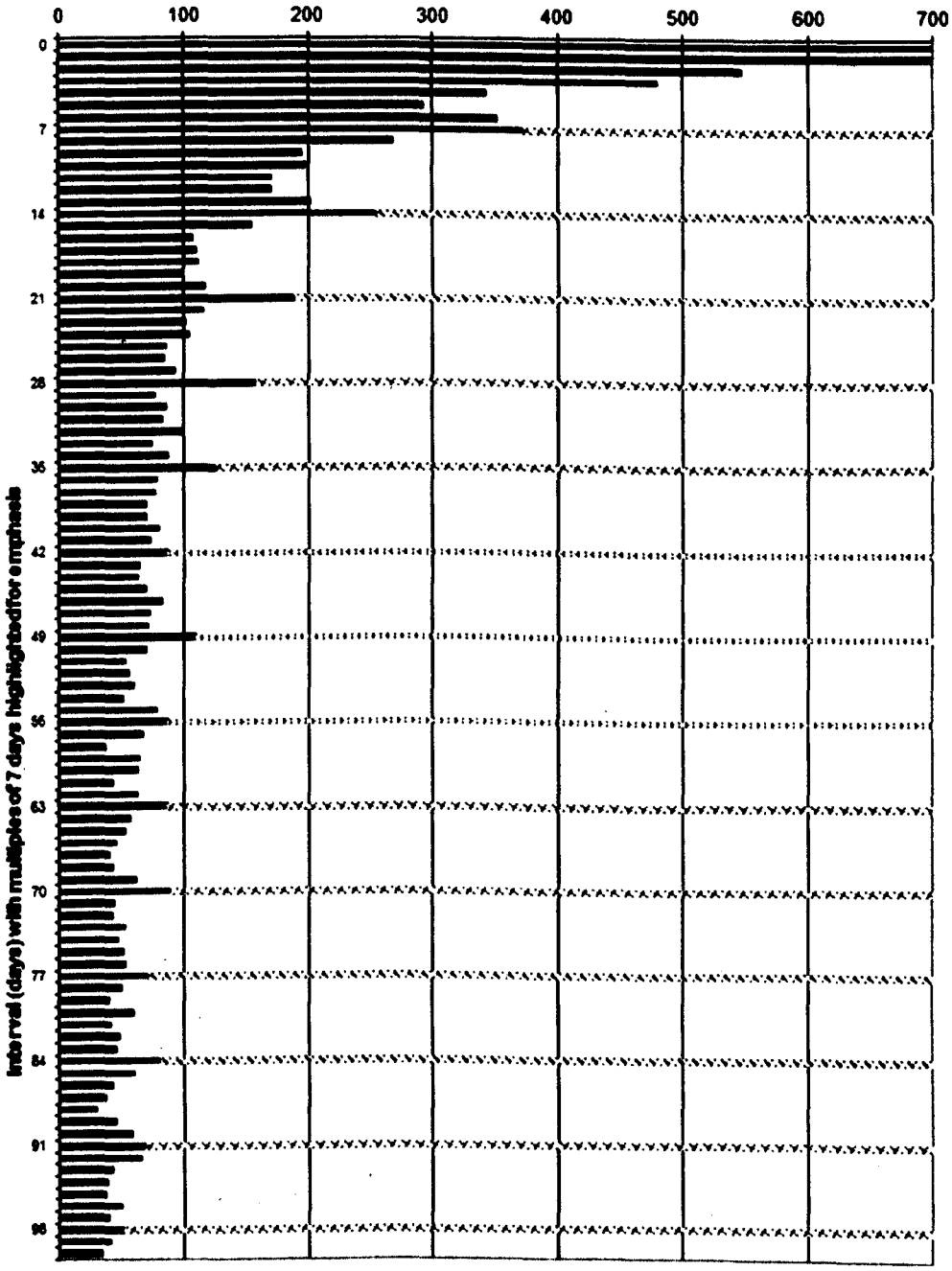
Table 2-3 Analysis of sensitivity to different assumptions about the time period during which recording is deemed to be prevalent

Period following registration during which recording is deemed to be prevalent	*Crude incidence rate per 100 pyrs (95% CI)*
1 day	3.58 (3.56 - 3.61)
7 days	3.57 (3.55 - 3.60)
32 days	3.55 (3.53 - 3.58)
90 days	3.52 (3.49 - 3.54)
180 days	3.47 (3.45 - 3.49)

2.5.3 Distinguishing discrete events

Early exploration of the data showed that approximately half of the recorded falls during the study period were recurrences. In some instances, these recurrences were at time intervals of less than a month. Further analysis of the distribution of these events over time was undertaken to investigate the extent to which some or all of these recorded events may be repeated recording of the same event. The distribution of the time intervals between apparently recurrent events was analysed and plotted on the histogram in Figure 2-2.

Figure 2-2 Frequency distribution of different time intervals between apparently recurrent fall events



The histogram shows a pattern of peaks at time intervals which are multiples of seven days. Recurrences at time intervals of greater than about ten days, were most likely to occur at an interval that is a multiple of seven days. It seems highly unlikely that such a pattern occurred by chance.

2.5.3.1 Possible explanations for the temporal pattern of recorded falls

One possible explanation is that the pattern reflects an underlying variation in actual events. Whilst it seems just plausible to attribute the timing of falls to an extrinsic event such as a weekly visit to the shops (say), it is not clear what kind of extrinsic or intrinsic factors could cause this pattern to persist over such long time intervals.

An alternative explanation is that the pattern results from factors that controlled the timing of *follow-up* consultations. For example, particular individuals may have been invited for a follow-up appointment at "same time next week" or "same day in a fortnight". Arrangements of this sort could go some way to explaining recurrences that peak at 7, 14, 21 and 28 days. But once again, it seems unlikely that follow-up appointments fully explain the persistence of 7-day peaks so many weeks after the initial recorded event.

It seems more likely that the persistence of the pattern beyond intervals of 28 days reflects other factors. These could include the fact that particular patients were more likely to receive medical attention on a particular day of the week (when a doctor visits a nursing home, say, or when a patient's 'favourite' doctor who may work part-time holds a surgery). Another contributory factor may have been the arrangements that determined the timing of the recording of the event within a general practice. For example, where there was a delay in recording patient consultations on a practice system (because the consultation took place at the patient's home, say, or when the system was not functioning) the healthcare professional or clerical staff responsible at a practice may have had a tendency to undertake the coding on a particular day of the week.

The conclusion drawn from this analysis of time intervals between apparent recurrences is that the temporal variation in incidence is likely to be a reflection of arrangements which affect the timing of consultations and recording. In other words, many of these recorded events do not represent recurrent falls but are simply repeated recording of a single fall event. An important implication of this was that a method was needed to reliably distinguish between successive records, which arose due to repeated recording of a single event and successive records which represent discrete events.

2.5.3.2 Distinguishing discrete falls based on a minimum time that should elapse between events

An alternative approach was adopted based on the sensitivity of incidence rates to some key assumptions made about the duration of time that must have elapsed after an initial fall event before a subsequent event can be counted as a discrete event. This involved recalculating the crude incidence for rate using a series of different assumptions about the duration of time that must elapse between discrete events. The shortest duration was 3 days, the longest plausible duration was assumed to be 90 days.

It is unlikely that any one of these assumptions is likely to be 'true' in the sense that the cut-off point will provide a 100% reliable means of distinguishing discrete events from repeat recorded events. But by testing the sensitivity of the resulting calculations of incidence, it is possible to quantify the impact of the likely inaccuracy of the assumption.

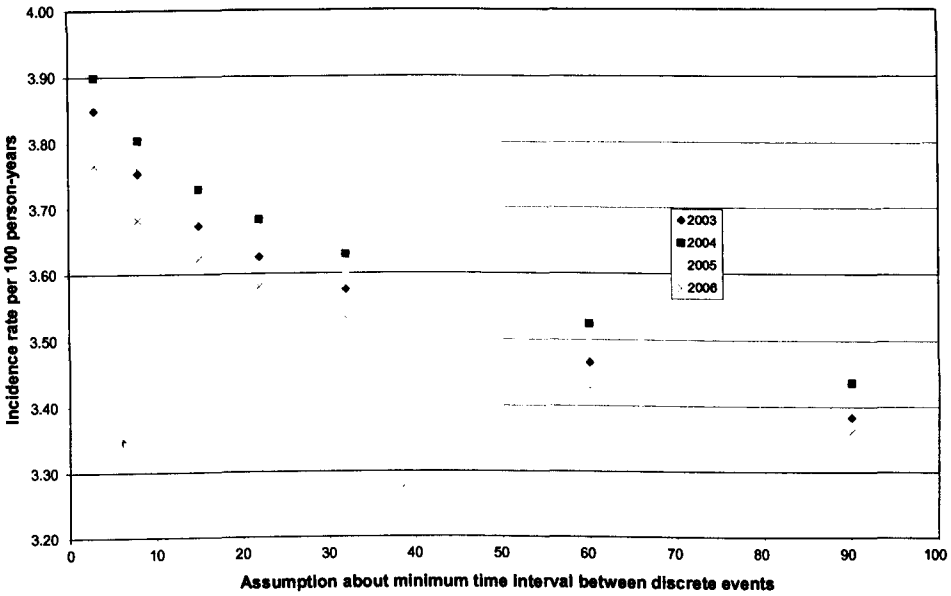
It is to be expected that where the minimum duration of time that must elapse between events is short, then most of the recorded events will be counted as discrete events and this will result in an estimated incidence rate that is relatively high. Also, it is to be expected that where the minimum duration is longer, then fewer recorded events will be counted as discrete, and this will result in lower incidence rates. To the extent that recorded falls are independent events it is also reasonable to expect that the relationship

between the lengths of time used to identify discrete events and the resulting incidence rates is a linear function.

Chart 2-2 shows the results of this sensitivity analysis. The incidence rates calculated using different minimum intervals vary by approximately 10% from about 3.4 to about 3.9 per 100 person-years. It also shows that the relationship between the minimum interval between discrete events and incidence rate is not linear for minimum intervals of less than 32 days. In other words, for minimum intervals of less than 32 days there is evidence of some clustering of recorded falls. This may be a reflection of the clustering of actual falls, or of repeat recording of the same fall, or of a combination of these.

Therefore, 32 days was identified as the minimum interval of time that must elapse between successive recorded falls for them to be counted as discrete events. It was chosen because there is a strong possibility that incidence rates derived using minimum intervals of less than 32 days may be inflated by repeat recording of the same event, but there is no evidence of repeat recording for minimum intervals of 32 days or longer.

Chart 2-2 Sensitivity of our estimate of crude incidence to assumptions about the minimum elapsed time interval between discrete fall events



2.5.4 Location of the consultation where the fall was recorded

A field called 'locate' on the medical record contains information about the location in which the consultation took place[165] (e.g. surgery consultation, casualty visit, attendance by out of hours GP service, phonecall, etc.). This was analysed to determine whether it might be used to assist in the differentiation of discrete fall events or in support of possible analysis of the sequelae of recorded falls.

Analysis of fall events in the study period showed that 50% of events were coded as "surgery consultations" and a further 12% as "acute visit by GP to home". 4% were "phonecall from patient". As many as a dozen other codes were used less frequently, including "casualty attendance" (3.3%) and "hospital admission" (0.08%). 6% of events were coded as "other".

It appears from this distribution that the majority of fall events relate to consultations taking place in the GP surgery or as a result of a visit to the patient's home by a GP. As few as 5% of the total number of fall events relate to notifications of consultations in a hospital setting.

Except for the very small number of falls recorded to identify a hospital admission, the values of 'locate' do not offer a simple basis for differentiating discrete events, nor for quantifying the severity or sequelae of a fall. Therefore, no further work was undertaken using the data in this field in subsequent anlyses.

2.5.5 Case definitions

Based on the analysis described above, incident cases of falls were defined as:

> An event recorded using one of the Read codes whose descriptor corresponds to a fall (see Appendix B), which occurs after the day of registration and more than 31 days after any previous fall.

Recurrent falls were defined as:

> Second or subsequent events recorded using one of the Read Codes which corresponds to a fall (see Appendix B) which occurs between 1 month and 1 year of the previous fall. This case definition was adopted to maintain alignment with other studies which commonly define recurrence as a second or subsequent fall within a 12 month period.

2.5.6 Demographic variables

THIN records demographic data relating to the actual individual (e.g. sex, year of birth), and to the geography of the last recorded residential address of the individual (e.g. regional health authority, and an indicator of the average socioeconomic status of residents of their neighbourhood). These data have been used as a basis for analysing falls by demography.

It should be noted that in THIN the measurement of an individual's age is imprecise because only the year of birth is recorded and (for the purposes of calculating ages and mid year populations) it is assumed that everyone is born on 1 July in their year of birth.

The socio economic status of a patient in THIN is imputed from the quintile into which the Townsend score of their immediate neighbourhood falls. Townsend score is derived from 2001 census information which describes prevalence of household access to a car, owner occupation, overcrowding, and unemployment[166].

Other datafields in THIN were also explored to assess their potential for supporting analysis related to the living arrangements of fallers. As detailed in the Introduction, the literature shows that incidence of recorded falls are generally higher in institutions than in the community[45]. This may reflect the relative co-morbidity and frailty of residents of institutions, as well as different recording behaviours[36]. Therefore, although anecdote suggests that GPs tend not to use read codes to identify patients from nursing or residential homes, work was undertaken to explore whether there is sufficient reliably recorded information in THIN by which to stratify the analysis of incidence in terms of living arrangements.

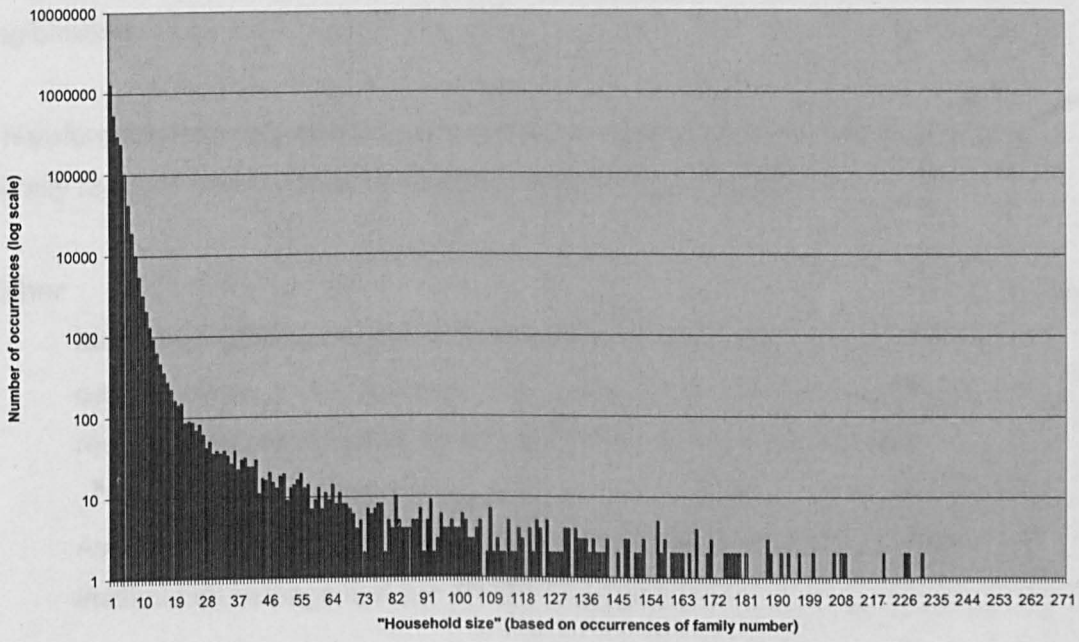
2.5.6.1 Completeness and reliability of data about living arrangements

There are two types of data which record information about living arrangements. Firstly, each individual was allocated a "family number" at the time of registration, to link together patients living at the same address. Secondly, the AHD and medical tables contain information about a patient's type of residence. The following section describes the steps taken to establish whether these data could be used to infer whether the patient was living in an institutional setting at the time of a recorded fall event.

2.5.6.2 Family number

Analysis of the all-age population in THIN established that about 60% of individuals are attributed a family number that is shared by more than four people, and that about 10% of individuals have a family number shared with more than seven people (see Figure 2-3).

Figure 2-3 Chart showing frequency distribution of occurrence of household in THIN



Discussions with EPIC identified that although the default purpose of the field 'family number' is to link patients living at the same address, it can also be used to link family members living at different addresses (for example, to link dependant parents to a patient living at a different address) [185]. Since THIN does not contain address details it is not possible to quantify the prevalence of this use of family linkage.

It is also unclear whether the family number assigned to a patient at registration is updated when a patient moves address. Unless the practice chooses to 'create a new family' or 'move to another family' a patient will retain the same number they were given at registration. Furthermore, another consideration is that people living at the same address may not have been registered with the same GP.

These issues notwithstanding, a method was developed and trialled to attribute "institutional living" on the basis that people with the same family number represent a single household, and that where the number of older

people in a single household is high this represents some kind of institutional living arrangement. This status relates to what is recorded at the time of registration.

Therefore the following criteria were applied to identify whether a particular 'family number' corresponds to an institutional living arrangement:

Either

More than 50 occurrences of this family number (assumption is that in each practice, an institutional living arrangement for older people will result in >50 registrations against the same family number), and

Average duration of registration is greater than 90 days (to exclude institutional settings that are acute hospitals), and

Mean year of birth is earlier than 1947 (to exclude institutional living arrangements for children or younger adults)

Or,

More than 3 occurrences of this family number (assumption is that in each practice, a small institution will result in >3 registrations against the same family number), and

More than 75% of those registered against the family number were aged 60 years or over during the study period (to exclude institutional living arrangements for children or younger adults)

2.5.6.3 Type of residence & housing arrangements

Information about institutional living was also sought from data on the AHD and Medical tables. Information about the type of residence is recorded on the AHD table using a code "1091000000" along with a parameter which takes one of six values corresponding to: nursing home, rest home, warden supported, sheltered accommodation, own home, other. Housing arrangements may also be recorded on the Medical table using one or more of the medcodes listed in Table 2-3. Unlike the family number data which

has no date recorded with it, the events on the medical and AHD tables are date-coded, which means their timing relative to a history of fall events can be determined.

Table 2-4 List of medcodes used to indicate institutional living arrangements

Medcode	Description
13F5.00	Part III accommodation
13F5.11	Part 3 accomodation
13F5100	Part III accomodation arranged
13F5111	Part 3 accomodation arranged
13F5200	Resident in part III accomodation
13F6.00	Nursing/other home
13F6100	Lives in a nursing home
13F7.00	Residential institution
13F7100	Lives in a welfare home
13F7200	Lives in an old peoples home
13F8.00	Hospital patient
13F8.11	Hospital inpatient
13F8100	Long stay hospital inpatient
13FK.00	Lives in a residential home
13FS.00	Long stay hospital inpatient
13FT.00	Lives in an old peoples home
13FX.00	Lives in care home

Occurrences of these medcodes on the medical table and events coded as "nursing home" or "rest home" from the AHD table were identified and treated as evidence of institutional living arrangements wherever they were recorded prior to the fall event.

Another assumption underlying this approach to identifying living arrangements is that once a person is recorded as having one of these institutional living arrangements, they do not revert to independent living.

2.5.6.4 Estimates of incidence by living arrangement

Using the methods described in this chapter, crude incidence rate of falls was calculated for people with and without the institutional living arrangements described above.

The estimated incidence for people ascribed with an institutional living arrangement was 1.30/100 person-years (1.22 – 1.39), compared to 3.86/100 person years (3.84 – 3.89) for those in a non-institutional setting.

This finding is counter-intuitive and different to what was expected, based on prior knowledge that falls and falls recording are more common amongst the relatively frail population of residential and nursing homes[45 96 103]. Based on this finding, and the fact that it was not possible to establish the validity of our criteria for identifying institutional living, it was decided that no further effort should be invested in this method of identifying living arrangements, and that it does not currently provide a reliable exposure on which to base other calculations.

2.5.7 Calculating incidence rates

2.5.7.1 Population at risk

For the purposes of studying the incidence rate for falls, the population at risk was defined as people aged over 60 years who were registered with practices which contributed data to THIN for the entire period 2003-2006 inclusive aged over 60 years. The start date of the period was set at 2003 to include data from before the publication of the NICE guidance for falls in older people[124] and to exclude older data which may be subject to different quality issues. The end date was set at 31st December 2006 because this represented the most recent full year of data. The July 2007 release of THIN was used which was the latest version available at the start of the study. (For later studies a subsequent version of the THIN database was used which was released in October 2008).

The lower age cut-off of 60 years was chosen to facilitate later comparison with other studies including this agegroup and, in the subsequent modelling of the effect of other factors, to provide a full picture of the effect of increasing age. For the purposes of maintaining anonymity, THIN does not record a patient's age. Therefore the age of each subject was estimated by assuming that their birth date was 1 July.

Crude incidence rates were derived using total person-years at risk which was calculated using mid year population levels.

2.5.8 *Modelling incidence*

Incidence rates were modelled in order to estimate the effect on falls of increasing age, female sex, geographical region, and socio-economic deprivation. The incidence of rare events is commonly modelled using Poisson regression. The proper use of the Poisson distribution assumes that the events of interest are occurring randomly in time and independently of one another[186].

However, it is frequently the case that recurrent events are not independent[187]. For example, in the case of falls amongst older people recurrences may be clustered around particular individuals[5]. A number of alternative approaches have been put forward for modelling incidence rates in these situations and for deriving a better estimate of relative incidence than is possible with poisson regression[188]. In many instances, negative binomial regression produces a better estimates[187].

In a Poisson distribution the mean and the variance are equal; data whose variance is greater than the mean are said to be over-dispersed. Robertson et al describe a formal test for this in which a likelihood ratio test is performed to assess whether the data are over-dispersed and are better fitted to a negative binomial model[188]. This is the formal test employed in the study of incidence.

2.6 Analysis of survival

2.6.1 *Case definitions and comparator*

To compare the mortality of fallers and non-fallers, a cohort of 10,000 fallers were randomly sampled from all those who had at least one fall event, (defined according to the case definition set out in Section 2.5.5) during 2003 to 2006. A general population comparator cohort of non-fallers was randomly sampled using an index date which was taken as the date for the first fall. For this comparator cohort we matched individually by randomly selecting people of the same age and sex, and who had no falls in the study period,

and who were registered with the same general practice and which was contributing data for them at the index date.

Up to six comparators were randomly matched for each case. This matching ratio was selected on the basis that it was the maximum that would ensure that in most practice-age-sex subgroups there were sufficient non-fallers from which to select the required number of comparators.

A cohort of fallers and of non-faller comparators were also prepared to estimate mortality amongst recurrent fallers. Once again the cohort of 10,000 fallers was randomly sampled, but using the definition of recurrent faller set out in Section 2.5.5. Another general population comparator cohort of non-fallers was developed using the same methods as described above, except that the index date was defined as the date of first recurrence.

In this way a total of four cohorts were created: a cohort of fallers with a cohort of non-faller comparators, and a cohort of recurrent fallers with their own comparator cohort of non-fallers.

2.6.2 Contemporaneous fracture

Recorded fractures of the hip, wrist and forearm were also identified using the relevant Read codes to analyse whether survival of fallers and recurrent fallers is significantly associated with a contemporaneous fracture.

2.6.3 Modelling survival

We calculated the crude mortality rates for the cohorts and used Cox regression to compare mortality patterns between the cohorts of fallers and their controls, and between recurrent fallers and their controls, stratifying on their matched groups. The start point for fallers was the date of first fall; for recurrent fallers it was the date of the recurrent fall. The end point was the earliest of the following events: date of de-registration from the practice, or last recorded data download to THIN, or date of death (certification for which is formally notified to general practices by the statutory health authorities). We compared mortality patterns for fracture in the same way.

3 Incidence of falls amongst older people in primary care, and risk of death

This chapter addresses the first two project aims:

- to quantify the overall incidence of recorded falls among older people in primary care in the UK, and to determine whether it varies over recent years or by socio-demographic attributes, and
- to quantify risk of death associated with falls in older people in primary care

3.1 Introduction

As previously noted, recent health service initiatives in England, including the National Service Framework for Older People[163] and national clinical guidelines for falls prevention and treatment[124], envisage an important role for general practitioners and primary care within the care pathway for the prevention and treatment of falls. Yet there is little published data on the recording and incidence of falls seen in primary care, with which to consider the implications of this approach.

Therefore a study was designed, whose methods are set out in the previous chapter, to quantify the extent of falls known to primary care in the UK in the period 2003-2006 in terms of overall incidence and distribution in different regions and socio-economic groups, and to estimate the relative risk of death for older people who fall or who are diagnosed with fractures to the hip, wrist and forearm.

3.2 Results

3.2.1 Incidence

There were 79,295 recorded fall events in 61,248 individuals aged over 60 years of age between 2003-2006 inclusive. These falls were recorded over a total time at risk of 2.2 million person-years, giving an overall crude incidence rate of 3.58 (3.56 - 3.61) recorded falls per 100 person-years (see Table 3-1).

Table 3-1 Crude incidence rate of falls and recurrent falls in people aged 60 years and over, in THIN 2003-2006

	Person-years	Falls		Recurrent falls	
		Events	Crude incidence rate per 100 pyrs (95% CI)	Events	Crude incidence rate per 100 pyrs (95% CI)
Total	2214763	79295	3.58 (3.56 - 3.61)	14870	0.67 (0.66 - 0.68)
Sex					
Women	1219628	56239	4.61 (4.57 - 4.65)	10843	0.89 (0.87 - 0.91)
Men	995135	23056	2.32 (2.29 - 2.35)	4029	0.41 (0.39 - 0.42)
Agegroup (years)					
60 - 64	620250	5844	0.94 (0.92 - 0.97)	474	0.08 (0.07 - 0.08)
65 - 69	431643	7005	1.62 (1.59 - 1.66)	677	0.16 (0.15 - 0.17)
70 - 74	374983	9948	2.65 (2.60 - 2.71)	1267	0.34 (0.32 - 0.36)
75 - 79	313944	14070	4.48 (4.41 - 4.56)	2437	0.78 (0.75 - 0.81)
80 - 84	285853	17694	6.19 (6.10 - 6.28)	3651	1.28 (1.24 - 1.32)
85 - 89	115936	13734	11.85 (11.65 - 12.05)	3323	2.87 (2.77 - 2.97)
90 - 94	55115	8393	15.23 (14.91 - 15.56)	2281	4.14 (3.97 - 4.31)
95 +	17039	2607	15.30 (14.72 - 15.90)	760	4.46 (4.15 - 4.79)
Region					
South Central	274076	10644	3.88 (3.81 - 3.96)	1882	0.69 (0.66 - 0.72)
East Midlands	99637	3246	3.26 (3.15 - 3.37)	565	0.57 (0.52 - 0.62)
East of England	190731	7111	3.73 (3.64 - 3.82)	1654	0.87 (0.83 - 0.91)
London	202536	8093	4.00 (3.91 - 4.08)	1571	0.78 (0.74 - 0.81)
North East	78314	3191	4.08 (3.94 - 4.22)	821	1.05 (0.98 - 1.12)
North West	234878	8805	3.75 (3.67 - 3.83)	1583	0.67 (0.64 - 0.71)
Northern Ireland	66634	1978	2.97 (2.84 - 3.11)	472	0.71 (0.65 - 0.78)
Scotland	142773	4802	3.36 (3.27 - 3.46)	869	0.61 (0.57 - 0.65)
South East Coast	217466	7401	3.40 (3.33 - 3.48)	1278	0.59 (0.56 - 0.62)
South West	262210	10577	4.03 (3.96 - 4.11)	2022	0.77 (0.74 - 0.81)
Wales	114199	3255	2.85 (2.76 - 2.95)	505	0.44 (0.41 - 0.48)
West Midlands	203081	6638	3.27 (3.19 - 3.35)	1104	0.54 (0.51 - 0.58)
Yorkshire & Humber	128228	3555	2.77 (2.68 - 2.87)	544	0.42 (0.39 - 0.46)
Townsend quintile					
1 (Least deprived)	546843	15959	2.92 (2.87 - 2.96)	2740	0.50 (0.48 - 0.52)
2	496642	16321	3.29 (3.24 - 3.34)	2938	0.59 (0.57 - 0.61)
3	433517	15726	3.63 (3.57 - 3.69)	2728	0.63 (0.61 - 0.65)
4	362623	15444	4.26 (4.19 - 4.33)	3000	0.83 (0.80 - 0.86)
5 (Most deprived)	240940	11000	4.57 (4.48 - 4.65)	2210	0.92 (0.88 - 0.96)
9 (Unavailable)	134198	4845	3.61 (3.51 - 3.71)	1254	0.93 (0.88 - 0.99)
Year					
2003	539016	19249	3.57 (3.52 - 3.62)	3478	0.65 (0.62 - 0.67)
2004	548966	19906	3.63 (3.58 - 3.68)	3605	0.66 (0.64 - 0.68)
2005	556281	20009	3.60 (3.55 - 3.65)	3862	0.69 (0.67 - 0.72)
2006	570500	20131	3.53 (3.48 - 3.58)	3925	0.69 (0.67 - 0.71)

The crude incidence rate of recorded falls was 4.61 and 2.32 per 100 person-years amongst women and men respectively. Crude incidence rose from 0.94 per 100 person-years in those aged 60-64 to 15.30 per 100 person-years in those aged 90 and over. For women and men the crude rate of recorded recurrent falls was 0.89 and 0.41 per 100 person-years respectively. The age-gradient was steeper in recurrent falls than in falls, rising from 0.08 per 100 person-years amongst the youngest, to 4.46 per 100 person-years in the oldest.

There was a strong socio-economic gradient in which the crude incidence of falls increased by over 50% from least to greatest quintile of deprivation.

This represents an absolute excess of 1.64 falls per 100 person-years in the most deprived quintile. For recurrent falls the crude rate increased by 80% in the same socio-economic groups.

There were statistically significant differences in the crude incidence of falls and recurrent falls between some regions. These patterns remained significant after adjustment for sex, age, socio-economic status and year in multivariate analysis (Table 3-2). In crude or adjusted analysis, there were no significant changes in recorded incidence of falls in any of the years of the study period, and no clear trend in the occurrence of recurrent falls.

Table 3-2 Adjusted incidence rate ratios for recorded falls and recurrent falls in people aged 60 years and over, in THIN 2003-2006

	Falls	*Recurrent falls*
	Mutually adjusted incidence rate ratios (95% CI)	*Mutually adjusted incidence rate ratios (95% CI)*
Sex		
Women	1.00	1.00
Men	0.67 (0.66 - 0.69) $p<0.0001$	0.68 (0.64 - 0.71) $p<0.0001$
Agegroup (years)		
60 - 64	1.00	1.00
65 - 69	1.68 (1.58 - 1.78)	1.90 (1.64 - 2.20)
70 - 74	2.67 (2.53 - 2.82)	4.06 (3.55 - 4.64)
75 - 79	4.34 (4.12 - 4.58)	8.35 (7.36 - 9.47)
80 - 84	5.71 (5.42 - 6.01)	13.48 (11.94 - 15.22)
85 - 89	10.24 (9.70 - 10.81)	28.96 (25.59 - 32.76)
90 - 94	12.27 (11.55 - 13.04)	40.22 (35.38 - 45.73)
95 +	12.44 (11.47 - 13.49) $p<0.0001$	43.19 (37.16 - 50.20) $p<0.0001$
Region		
South Central	1.00	1.00
East Midlands	0.94 (0.88 - 1.01)	0.95 (0.84 - 1.09)
East of England	0.99 (0.94 - 1.05)	1.13 (1.02 - 1.25)
London	1.01 (0.95 - 1.06)	1.06 (0.96 - 1.18)
North East	1.09 (1.01 - 1.17)	1.58 (1.40 - 1.77)
North West	1.00 (0.95 - 1.06)	1.04 (0.94 - 1.14)
Northern Ireland	0.88 (0.81 - 0.96)	1.10 (0.96 - 1.27)
Scotland	0.90 (0.85 - 0.96)	0.93 (0.82 - 1.04)
South East Coast	0.87 (0.82 - 0.92)	0.82 (0.74 - 0.91)
South West	1.01 (0.96 - 1.06)	1.05 (0.95 - 1.15)
Wales	0.81 (0.76 - 0.87)	0.71 (0.62 - 0.82)
West Midlands	0.91 (0.86 - 0.96)	0.88 (0.80 - 0.98)
Yorkshire & Humber	0.75 (0.70 - 0.80) $p<0.0001$	0.65 (0.57 - 0.74) $p<0.0001$
Socio-economic status (Townsend quintile)		
1 (Least deprived)	1.00	1.00
2	1.05 (1.01 - 1.09)	1.07 (0.99 - 1.15)
3	1.13 (1.08 - 1.17)	1.10 (1.02 - 1.19)
4	1.27 (1.22 - 1.32)	1.33 (1.24 - 1.44)
5 (Most deprived)	1.35 (1.30 - 1.42)	1.45 (1.34 - 1.58)
9 (Unavailable)	1.17 (1.10 - 1.24) $p<0.0001$	1.31 (1.18 - 1.46) $p<0.0001$
Year		
2003	1.00	1.00
2004	0.98 (0.94 - 1.02)	0.97 (0.90 - 1.03)
2005	1.01 (0.97 - 1.04)	1.05 (0.98 - 1.12)
2006	1.00 (0.97 - 1.04) $p=0.390$	1.04 (0.97 - 1.11) $p=0.051$

By varying the time interval that must elapse before a consecutive fall-coded event is counted as a discrete event (rather than as a consultation associated with a previous fall event), the resulting crude incidence rate varied between 3.84 and 3.40 per 100 person-years respectively. In other words, at worst case, our simplifying assumption that events recorded within a calendar month of each other should be counted as only a single fall impacted the size of the resulting incidence rate by less than 10%.

3.2.2 Mortality

There was an overall crude all-cause mortality rate of 1102 per 10,000 person-years (1052 - 1153). The corresponding mortality rate for controls was 579 per 10,000 person-years (564 - 594). Amongst recurrent fallers the mortality rate was 1677 per 10,000 person-years (1610 - 1746).

In Cox regression modelling (Table 3-3) the mortality rate ratio for older people who fall was 1.78 (1.68 - 1.88), and for recurrent fallers was 2.06 (1.96 - 2.18), compared to those who do not fall. The rate ratio was almost unchanged when the analysis was repeated without people who had a recorded fracture of the hip, wrist or forearm contemporaneous to their fall. It was also almost unchanged when repeating the analysis excluding people who had a recorded fracture contemporaneous with or subsequent to the fall (also Table 3-3). The proportional hazards assumption was met in all instances. Compared to non-fallers, the hazard rate ratio of a subsequent fracture of hip, forearm or wrist in fallers is 3.00 (2.64 - 3.39) for fallers and 3.52 (3.10 - 4.00) for recurrent fallers (data not shown), in whom it is as high as 8.43 (5.22 - 13.61) amongst people aged 60-74 years.

Table 3-3 Hazard ratios (for all cause death with/without fractures) for fallers and recurrent fallers compared to non-fallers

Event	*Fallers (single and recurrent) - compared to non-fallers* *Hazard rate ratios (95% CI)*	*Recurrent fallers - compared to non-fallers* *Hazard rate ratios (95% CI)*
Death	1.78 (1.68 - 1.88)	2.07 (1.96 - 2.18)
Men	2.38 (2.17 - 2.62) p_{int}<0.0001	3.05 (2.77 - 3.35) p_{int}<0.0001
Women	1.53 (1.43 - 1.65)	1.75 (1.65 - 1.87)
Aged 60-74	2.91 (2.33 - 3.63) p_{int}<0.0001	5.27 (3.95 - 7.03) p_{int}<0.0001
Aged 75-84	1.91 (1.77 - 2.06)	2.61 (2.42 - 2.82)
Aged 85+	1.52 (1.39 - 2.62)	1.57 (1.46 - 1.70)
Death for people with no contemporaneous fracture	1.78 (1.69 - 1.89)	2.06 (1.95 - 2.17)
Men	2.37 (2.16 - 2.62) p_{int}<0.0001	3.00 (2.73 - 3.31) p_{int}<0.0001
Women	1.54 (1.43 - 1.65)	1.74 (1.63 - 1.86)
Aged 60-74	2.88 (2.30 - 3.60) p_{int}<0.0001	5.37 (4.02 - 7.19) p_{int}<0.0001
Aged 75-84	1.92 (1.78 - 2.08)	2.60 (2.41 - 2.81)
Aged 85+	1.52 (1.39 - 1.66)	1.56 (1.44 - 1.68)
Death for people with no contemporaneous or subsequent fracture	1.81 (1.71 - 1.92)	2.11 (2.00 - 2.23)
Men	2.41 (2.19 - 2.66) p_{int}<0.0001	3.09 (2.80 - 3.40) p_{int}<0.0001
Women	1.55 (1.44 - 1.68)	1.78 (1.66 - 1.91)
Aged 60-74	2.82 (2.25 - 3.54) p_{int}<0.0001	5.61 (4.15 - 7.58) p_{int}<0.0001
Aged 75-84	1.94 (1.79 - 2.11)	2.67 (2.46 - 2.89)
Aged 85+	1.55 (1.42 - 1.70)	1.60 (1.48 - 1.73)

p_{int} is test for interaction between sex/agegroup and risk of death associated with falling

Figure 3-1. Kaplan Meier plot for fallers (compared to non-fallers)

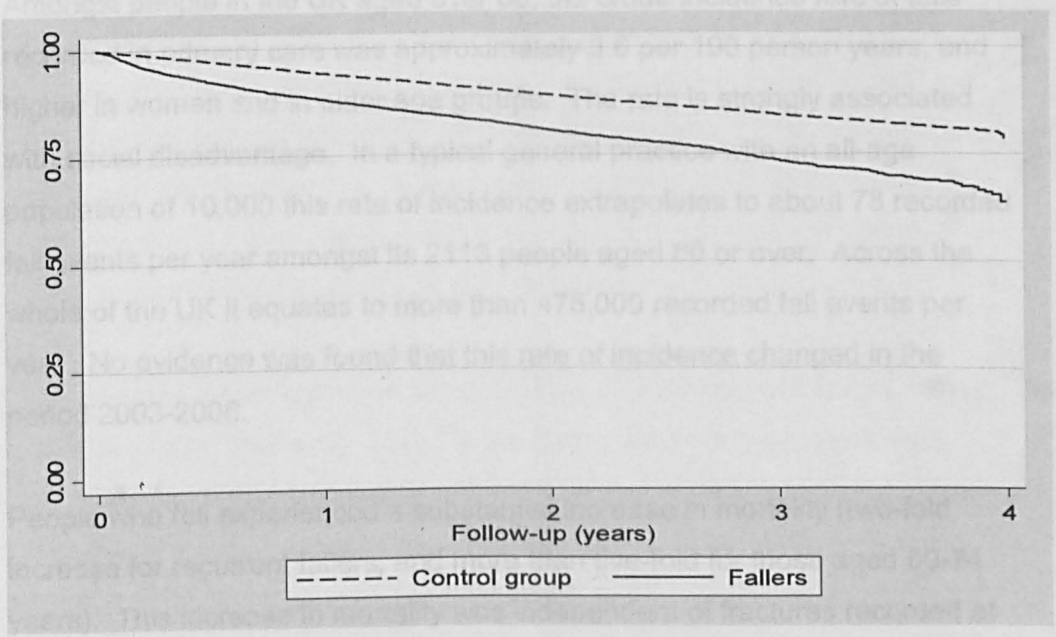
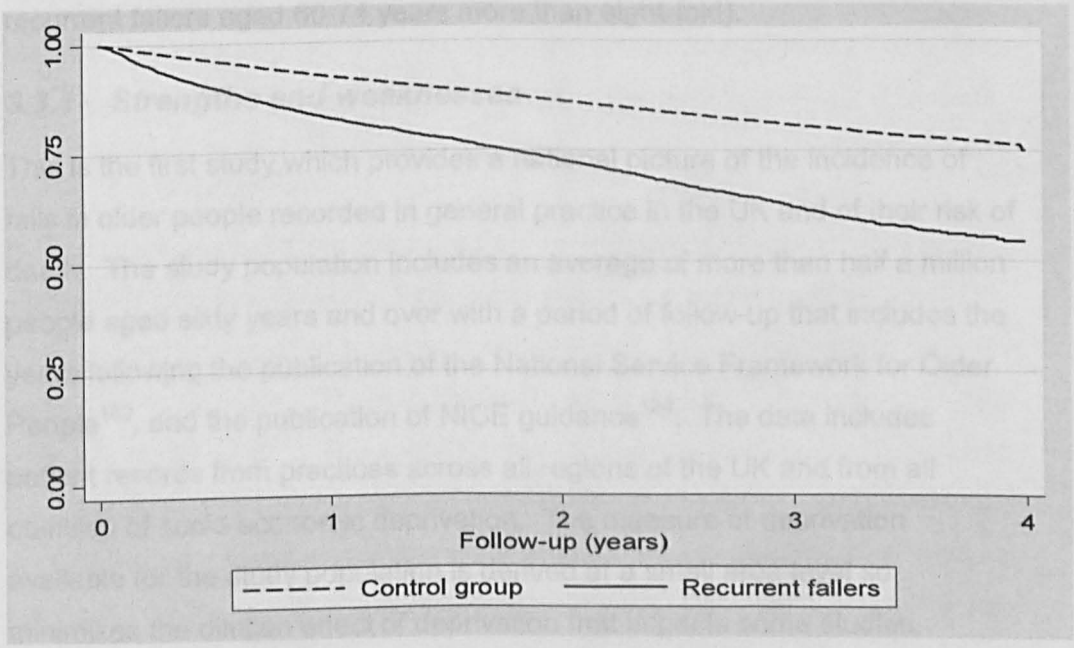


Figure 3-2 Kaplan Meier plot for recurrent fallers (compared to non-fallers)



3.3 Discussion

Amongst people in the UK aged over 60, the crude incidence rate of falls recorded in primary care was approximately 3.6 per 100 person years, and higher in women and in older age groups. The rate is strongly associated with social disadvantage. In a typical general practice with an all-age population of 10,000 this rate of incidence extrapolates to about 78 recorded fall events per year amongst its 2113 people aged 60 or over. Across the whole of the UK it equates to more than 475,000 recorded fall events per year. No evidence was found that this rate of incidence changed in the period 2003-2006.

People who fell experienced a substantial increase in mortality (two-fold increase for recurrent fallers, and more than five-fold for those aged 60-74 years). This increase in mortality was independent of fractures recorded at the time of the fall or subsequently. Furthermore people who fall have an increased rate of subsequent fracture (approximately three-fold and, for recurrent fallers aged 60-74 years more than eight-fold).

3.3.1 Strengths and weaknesses

This is the first study which provides a national picture of the incidence of falls in older people recorded in general practice in the UK and of their risk of death. The study population includes an average of more than half a million people aged sixty years and over with a period of follow-up that includes the years following the publication of the National Service Framework for Older People[163], and the publication of NICE guidance[124]. The data includes patient records from practices across all regions of the UK and from all quintiles of socio-economic deprivation. The measure of deprivation available for the study population is derived at a small area level so minimizes the dilution effect of deprivation that impacts some studies.

The main potential weakness relates to the reliability of recorded falls as a measure of falls seen in primary care. Although a comprehensive set of codes were used to identify recorded falls, it is likely that the estimates do not

include some of the fall cases attending primary care because, for example, the fall code has not been recorded in the notes, or was recorded as free text, or because the code for the medical consequence of the fall (hip fracture, say) has been recorded instead. As a result of these gaps in the data, the estimates of incidence will be underestimates of the true incidence of falls seen in primary care. Nevertheless, since being able to identify those who have had a fall or a recurrent fall is critical for managing this at-risk group, the rates derived in this study are important.

The impact of these "gaps" on the estimates of mortality risk is less certain. It can be argued that such "gaps" in the data represent events with non-significant sequelae, and that events may be reasonably presumed to have a lower risk of subsequent mortality than events which warranted medical attention and recording. On the other hand, to the extent that the code for a fall is not used for those with more serious medical consequences requiring hospitalisation (e.g. hip fracture) or death, these mortality rate ratios may represent underestimates of the subsequent risk of death. In the absence of additional evidence about the true scale and profile of such gaps in the data, it is not possible to quantify with any certainty the direction of any such bias.

3.3.2 Other studies

Previous studies have provided data on the incidence of falls in older people in different settings. The incidence of attendance relating to falls injury in people aged 60 years and over in a sample of 18 A&E departments was estimated to be 5 per 100 person-years in 1999, though the precision of this estimate is not clear[57]. The same study reported the incidence of fall related hospital admissions at 1.7 per 100 person-years. Medical records in primary care should incorporate a record of consultations in secondary care, so these data are consistent with the possibility that our results underestimate the total number of falls that should be present in patient records. It is not possible to use these data to calculate a comparable estimate of the incidence of admission because coding to show where a diagnosis was made is not complete in primary care records. In Finland, a study of falling injuries leading to medical treatment found an overall cumulative incidence rate of

5.5 per 100 person-years amongst people aged 65 years and over[98], which is similar to the overall cumulative incidence rate of falls of 4.6 per 100 person-years amongst people aged 65 and over found in this study (data not shown). All of these data from primary and secondary care report incidence rates that are much lower than that found in questionnaire surveys in community settings, which suggest that during a year 28-35% of people aged over 65 have at least one fall and that approximately one third of these falls require medical attention. The most likely explanation for a disparity of this scale is that health professionals do not routinely ask about, or systematically record, recent falls.

The associations with female sex and increasing age are consistent with studies based in the community setting. Regarding the effect of relative deprivation, the literature is inconsistent. West et al found that hospital admissions for fall-related injury and hip fractures in those aged 70 years and over in the Trent region of England were higher in relation to relative deprivation[58]. However, the Health Survey for England found no association between self-reported falls and deprivation, but used a much weaker marker of deprivation than that which is available in THIN[81]. In this study there was a clear socio-economic gradient for recorded falls and recurrent falls for men and for women. It is not clear the degree to which this association is explained by co-morbidity. The differences in the adjusted incidence rate ratios between some regions may be due to underlying variations in the incidence of falls, differential recording behaviour in primary care, or to residual confounding by factors related to socio-economic status.

The finding that recurrent fallers aged 60 and over have an overall risk of death about twice that of non-fallers is broadly consistent with the findings of community-based studies[14 111 112], and confirms that older people who fall represent a vulnerable group of patients. Furthermore these results suggest that this vulnerability is not simply a function of subsequent risk of fracture.

3.3.3 *Implications*

Identifying people who fall, and especially those who fall recurrently, provides an opportunity to intervene on a group who are vulnerable irrespective of whether they have a subsequent fracture.

The falls standard of the National Service Framework (NSF) for older people and the NICE guidelines on the prevention of falls both highlighted the effectiveness of secondary prevention of falls, and the critical role of primary care professionals in identifying those who have had a fall, and referring to specialised falls prevention services those people whose falls history indicates they are at risk. To identify this group, NICE guidelines recommend that older people in contact with health professionals are asked routinely whether they have fallen in the past year. The gap between the incidence of falls recorded in primary records and that measured in the community, which has not changed over recent years, suggests that this has yet to become part of routine practice. According to NICE recommendations, people at risk who require referral to a falls service include all those who have received medical attention for a fall or have fallen more than once in a year. Estimates derived in this study give an indication of the numbers of such events that are identifiable in medical records, and these figures are much greater than the actual number of patients seen at falls clinics in 2006, which averaged at less than 0.5 per 100 person-years[189]. The implication of these findings is that opportunities to identify patients at risk of falling, and to intervene in this vulnerable group, are currently being missed.

The overall incidence of recorded falls, and the high mortality associated with those who fall, indicates the scale of the burden and its unequal distribution amongst different social groups. The rate of recorded falls has remained unchanged in recent years. Greater emphasis on identifying and recording those who fall and delivering appropriate interventions are important for reducing the individual and societal costs of falling.

4 Methods development: aetiological studies

Several of the project aims relate to establishing the falls risk profile of medications. This chapter describes the methods used to:

- establish whether the falls risk profile of more recently introduced serotonin noradrenalin reuptake inhibitors (SNRIs) is more favourable than that of selective serotonin reuptake inhibitors (SSRIs),
- quantify the extent to which being prescribed antihypertensive medication modifies the risk of falling in older people, and
- identify any other classes or sub-classes of medication prescribed in primary care whose apparent falls risk warrants investigation in future studies.

The methods involve two distinct study designs: classic case control design, and self-controlled case series analysis.

Subsequent chapters describe how these two study designs were used to estimate the risk of falling associated with two different exposures: firstly, antidepressant prescribing and, secondly, the risk associated with anti-hypertensive prescribing. In addition, case-control analysis was used to estimate the risk of falling associated with prescribing of medication in each of the BNF subgroups.

For the avoidance of repetition, the core methods for all these studies are set out in this chapter, so that in the subsequent chapters discussion can be focussed on the results of the analyses and their interpretation.

4.1 Between-subject analysis to estimate risk of falls associated with prescribing exposures

The necessary design for this analysis may be conceived as a nested case control within the previously described cohort study. This section sets out the design in detail, along with the considerations leading to its use.

4.1.1 Outcome of interest

The introduction summarised evidence that there are some people who fall for whom it may be inaccurate (or at least premature) to consider the event as a symptom, because their distribution is characteristic of a random event. The same study also showed that amongst people who fall more than once, the proportion whose fall event is a random event is much lower[5]. Therefore, in seeking to design a study to test the hypothesis that falls are associated with exposures to specific medications, attention turned to how best to frame the outcome of interest.

Initially, consideration was given to whether the outcome should be 'recurrent fall'. An advantage of this would be that cases defined using this outcome measure would contain relatively few people for whom the event could be regarded as the result of a random process. However, two issues emerged.

Firstly, it is possible that in some or many patients receiving medication, prescribing may be changed as a result of the fall (i.e. there may be a causal link in one direction between prescribing and a first fall, and a link in the other direction between the first fall and subsequent prescribing). On this basis, it was recognised that using recurrent fall as the outcome would be problematic.

Secondly, prior knowledge from similar studies[158] suggested that (for SSRIs) any temporal association between medication and falls would be strongest in the first few weeks following the onset of prescribing. Work completed earlier in the project on distinguishing between multiple discrete fall events and repeated recording of the same event resulted in an approach which defines a recurrent fall as one which occurs at least a month after a previous recorded fall. In other words, the methods developed for this project do not enable recurrences to be reliably identified when they occur at intervals of less than one month.

Taking these two issues together, it was concluded that it would be problematic to use recurrent falls as an outcome against which to assess short term temporal associations with prescribing and that, in the interests of consistency and economy of effort, other options should be considered.

Therefore attention turned to how cases could be defined in terms of a first recorded fall. An advantage of using first fall is that it avoids the aforementioned problem associated with identifying recurrences, especially those occurring at short intervals. Furthermore it provides a simpler and more intuitive basis for defining the index date by which to identify potential controls. A disadvantage of using first fall is that, as noted above, many of these events may be the result of a random process with the result that the effect size for exposure to a putative risk factor will be weaker than if cases were defined in terms of recurrent falling.

4.1.2 Case definition

Cases were identified according to the following definition to ensure a proper consistency with the cohort study within which the case control is nested.

From a study population comprising the 386 primary care practices who contributed data for the entire period 2003-2006 and only those patients aged 60 years or over during this study period, cases were defined as those who experienced their first recorded fall during the study period (the index date) and who had at least 12 months of history in THIN prior to the fall.

Falls were defined using the same set of Read codes as in the earlier study. In this definition, practices were also required to have contributed data for the entire period. This requirement relates to the cohort study and was introduced to ensure that changes in incidence over time may not be attributed to bias arising from the characteristics of practices joining or leaving THIN during the study period.

Cases were required to have at least 12 months of history in THIN to ensure that each patient has a sufficient record of any prescribing in the period

leading up to the start of the study, and to limit the potential for a fall event to be misclassified as a first fall.

4.1.3 Controls, matching ratio & sample size

For each case, up to six general population controls were randomly sampled using an index date which was taken as the date for the first fall. These were matched on age, sex, and primary care practice, and had no recorded falls and were contributing data at the index date. As with the cases, controls were required to have at least 12 months of recorded history prior to the index date.

This matching ratio was selected on the basis that it was the maximum that would ensure that in most practice-age-sex subgroups there were sufficient non-fallers from which to select sufficient comparators to deliver the required minimum statistical power. The sample size needed for 95% power to detect a risk ratio of 1.2 using a 5% significance level was estimated using Egret SiZ[190]. Assuming that at least 5% of cases are exposed, and 6 controls per case, the number of case control sets needed is 9600.

4.1.4 Primary care prescribing as exposure

4.1.4.1 Identifying exposures

In all of the studies the main exposures of interest were prescriptions prior to the index date (and in some cases subsequent to it) of particular classes of medication. Prescriptions were identified by interrogating the Therapy table in THIN using the set of codes corresponding to the exposure of interest. For consistency and ease of interpretation medications were grouped according to their classification in the British National Formulary[191].

4.1.4.2 Temporality of exposure

Temporality of the exposures was classified in two different ways. Firstly, exposures were classified in terms of the elapsed time between the index event and *final* preceding prescription, as follows: current (last prescription within 60 days of index event), recent (last prescription was within 60-120 days of index event), previous (more than 120 days), never, or ever (any

prescription prior to index event) prescribed. Ever prescribed was added in order to test the extent to which an apparent association between first fall and a medication may be due to the characteristics of the group of patients to whom the medication is prescribed, rather than a contemporaneous causal effect of the medication itself.

Secondly, exposures were categorised in terms of the elapsed time from the time of the *first* prescription. In the study of SNRIs, these categories were defined as follows: 0 days (the same day as the prescription), 1-28 days, 29-56 days and greater than 56 days. These categories were selected with reference to Hubbard et al's study of the association between SSRI prescribing and hip fracture, from which it may be inferred that any effect of this group of medications on falls may be strongest in the first month after the start of prescribing. The relatively low prevalence of SNRI prescribing means that further subdivision of these time-bands would be likely to result in odds ratios with very wide confidence intervals. In the study of antihypertensives, for which the prevalence rate of prescribing is higher, narrower time-bands were defined: 0 days, 1-7 days, 8-14, 15-21, 22-28, and greater than 28 days.

For the analyses of both antidepressants and antihypertensives, the day of prescription (day 0) was separated from subsequent periods of elapsed time in order to quantify risk in the period following first prescription, without the ascertainment bias that would result from falls recorded on the day of the first prescription.

4.1.5 Choice of confounders

Adjustment for age, sex and practice-related factors (e.g. deprivation, or behaviour with regard to recording) was accommodated by sampling controls matched on these variables. Other potential confounders were identified by reference to the literature.

For estimating risk associated with antidepressants, potential confounders identified included: pre-existing diagnosis of coronary heart disease, diabetes

mellitus, cardiovascular disease, and prescribing of antipsychotics, hypnotics-anxiolytics, diuretics, digoxin or antiarrhythmics. For the study of antihypertensives, potential confounders included: pre-existing diagnosis of coronary heart disease, heart failure, atrial fibrillation, diabetes mellitus, and prescribing of other antihypertensives or antipsychotics.

Data for these was extracted from the Medical table in THIN using the relevant Read Codes to identify diagnoses of those diseases for each case and control. Similarly, potential confounding by prescribing of other medications was addressed by interrogating the Therapy table using the relevant medication codes to identify prescriptions of that medication for that patient. The impact of each variable identified as a potential confounder was assessed according to the rules set out in the next section.

In addition to the specific co-morbidities and prescribing which the literature highlighted as potential confounders, the need to take account of general frailty reflecting the cumulative effect of various co-morbidities was also identified. To achieve this, an adaption of Charlson index was used as a proxy for general frailty associated with proximity to death. Charlson index is a marker of one-year mortality based on previous diagnoses of 17 diseases, including myocardial infarction, congestive heart failure, peripheral vascular disease, diabetes, and cerebrovascular disease[192]. The algorithm for calculating the index was copied with permission from a postgraduate student in the department[193].

4.1.6 Estimation of odds ratio for exposure

Estimates of the odds ratio for exposure were derived using conditional logistic regression which accommodates the binary nature of the outcome (subjects have either fallen or not fallen) and the matched design (which requires an analysis which is conditional on the factors used for the matching).

In each study, a series of univariate models was used to test whether potential confounders were associated both with first fall and with the

exposure of interest, by comparing people who had ever/never been prescribed each of the medications. Amongst those people ever-prescribed, odds ratios were also calculated for current / recent and previously prescribed medication compared to those never prescribed.

For each class of medication, the influence of confounders was assessed via bivariate models, in which the odds ratio for exposure was monitored for a change of 10% or more with the addition to the model of the putative confounder. Confounders whose impact was 10% or more were included in a final multivariate model.

Technically, the estimation of an effect size which is controlled for confounders is based on an assumption that the exposure effect is the same across all values of the confounder. The extent to which there is evidence of a modified effect for different values of the confounder can be tested formally by including an interaction term and using the likelihood ratio test. In these studies it was identified a priori that age may modify the effect of a medication. Therefore the likelihood ratio test was used to assess the strength of evidence for a possible interaction between age and ever prescribed.. A p-value for the likelihood ration test of less than 0.05 was interpreted to be weak evidence of interaction.

4.1.7 Estimation of population attributable risk proportion

For exposures of specific interest, the population attributable risk proportion, which is an estimate of the proportion of an outcome (namely, first fall), was estimated using the formula described by Cole and McMahon[194]. The formula rests on assumptions that the controls are representative of the overall population, and the adjusted odds ratio is a good approximation of the relative risk, and the confounders are adequately controlled for.

4.1.8 Limitations of the method

One of the limitations of this method is that it remains unclear whether an observed effect is attributable to some extent to residual confounding, i.e. a level of confounding which remains after attempts to control for confounders.

Residual confounding may arise where the data do not contain adequate recording of variables which are likely to confound the association in question, and so cannot be adjusted for. For example, in this study, there may be residual confounding due to a greater degree of unmeasured frailty in cases compared to their controls, which contributes to an increased incidence of first falls irrespective of their exposure status. In the absence of a direct measurement or adequate proxy of the putative confounder (frailty), the effect of the confounder cannot be assessed or controlled for in the between-person analysis of the case-control design.

Therefore a further methodwas used to address the possibility of residual confounding. The design and its methodology is known as self-controlled case series, and involves a within-person analysis. Using this complementary approach the extent of possible residual confounding due to non-time varying factors in the between-person analysis of the case control method was quantified.

4.2 Within-subject analysis to estimate risk of falls associated with prescribing exposures

4.2.1 Self-controlled case series analysis

The self-controlled case series method was developed to investigate the association between the incidence of an event in periods of time with and without exposure [195]. The relevance of the method to this project is that it is not subject to the confounding which characterises classical case-control analysis and which arises from differences *between* cases and their controls which are fixed within individuals.

Before describing the method and its application to these studies, it is helpful to set out some of the features of the method highlighted by Whitaker et al[195]:

- Case series analysis is an application of the cohort approach, and provides estimates of *relative* incidence only.
- It requires only cases. As such, the estimates of incidence relate to different periods of exposure *within* subjects.

- The method can control for confounders which remain constant within the observation period, and for age.
- It works only when the overall risk of the event during the whole observation period is small
- A key limitation of the method is that it requires that the probability of an exposure is not dependent on the occurrence of the outcome.

4.2.2 Case definition

In the case series analyses undertaken, the method was applied using the same case definition as that set out in 4.1.2.

For the avoidance of any confusion, it should be noted that whereas the cases in the case control are considered to be exposed only when the exposure took place prior to the first recorded fall, in the self-controlled case series, cases are considered to be exposed if an exposure takes place at any point during the study period. For this reason, the number of cases in the case control and a corresponding case series analysis may be different: the difference is accounted for by the number of people whose first exposure occurs after their first fall.

4.2.3 Episodes of exposure

The prescribing record of individuals is punctuated by events on the Therapy table which record when a prescription was issued. In many instances the entries on the Therapy table recording prescribing for a particular patient are at fairly regular intervals of up to about two months duration. This is interpreted as the pattern of recording which arises where a patient requires a 'repeat prescription' at regular intervals because they have used up their previous supply of medication. In some cases, the record may include much longer intervals between prescriptions. This is assumed to represent a period of time during which the patient was not taking the medication and therefore was not currently exposed.

Based on analyses of the elapsed time between prescriptions which shows that most prescriptions are issued at intervals of less than 60 days (see

Figure 4-1 to Figure 4-4 inclusive), we calculated episodes of continuous exposure, where an episode is defined as a series of consecutive prescriptions at intervals of not more than 60 days, and which ends 60 days after the last prescription in the series.

Figure 4-1 Frequency distribution of the time interval between successive prescriptions of SNRIs for cases

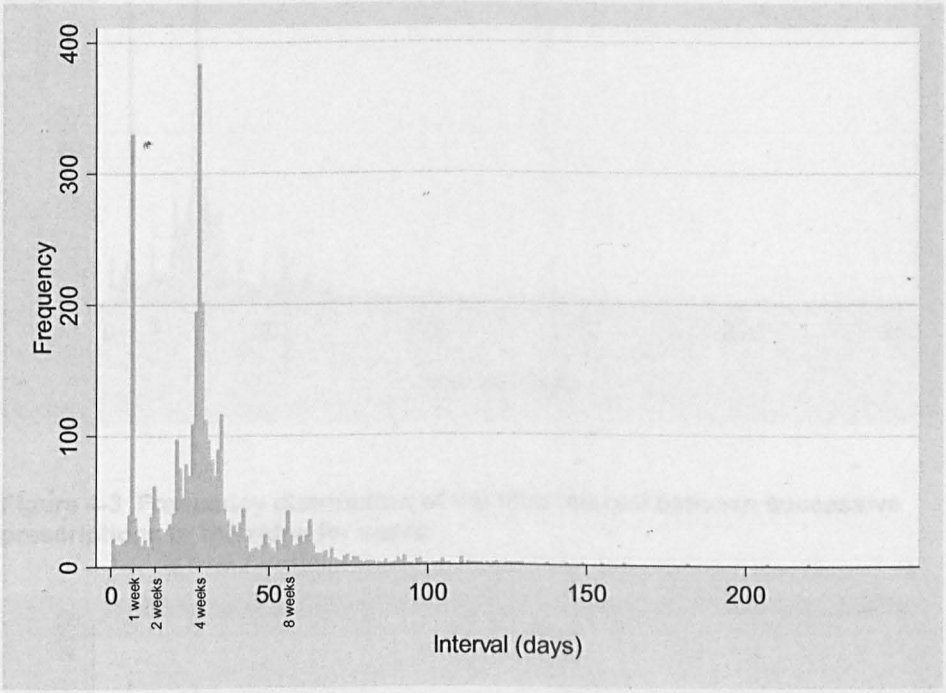


Figure 4-2 Frequency distribution of the time interval between successive prescriptions of SSRIs for cases

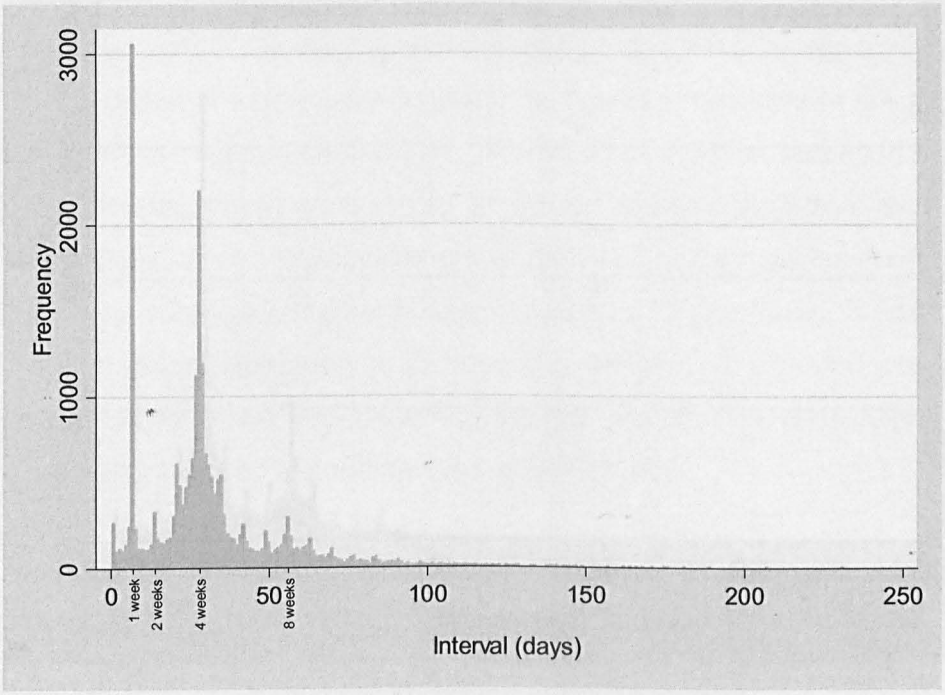


Figure 4-3 Frequency distribution of the time interval between successive prescriptions of thiazides for cases

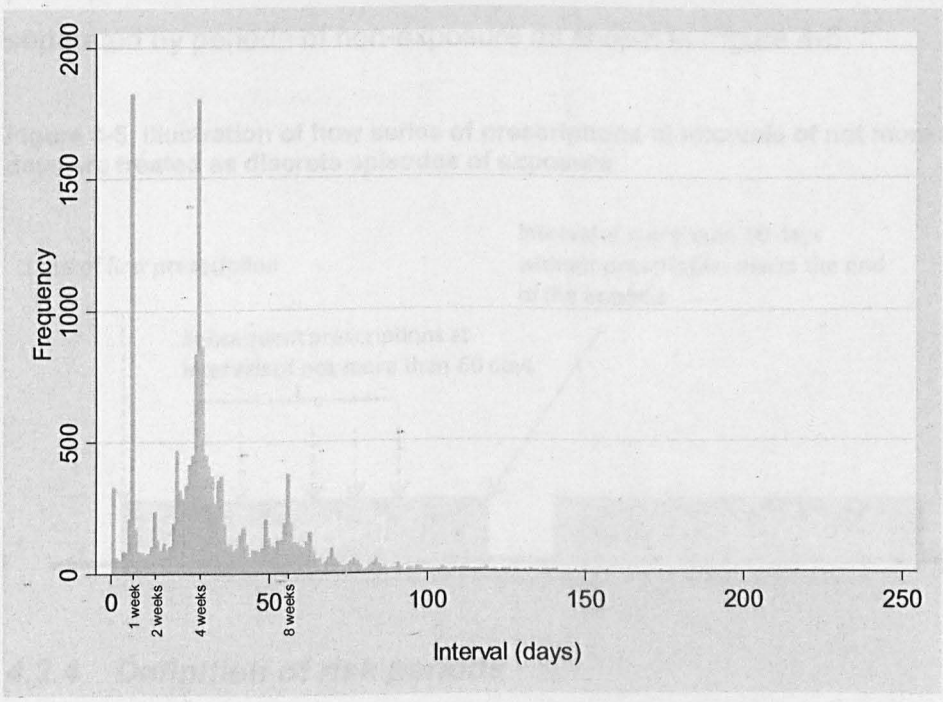
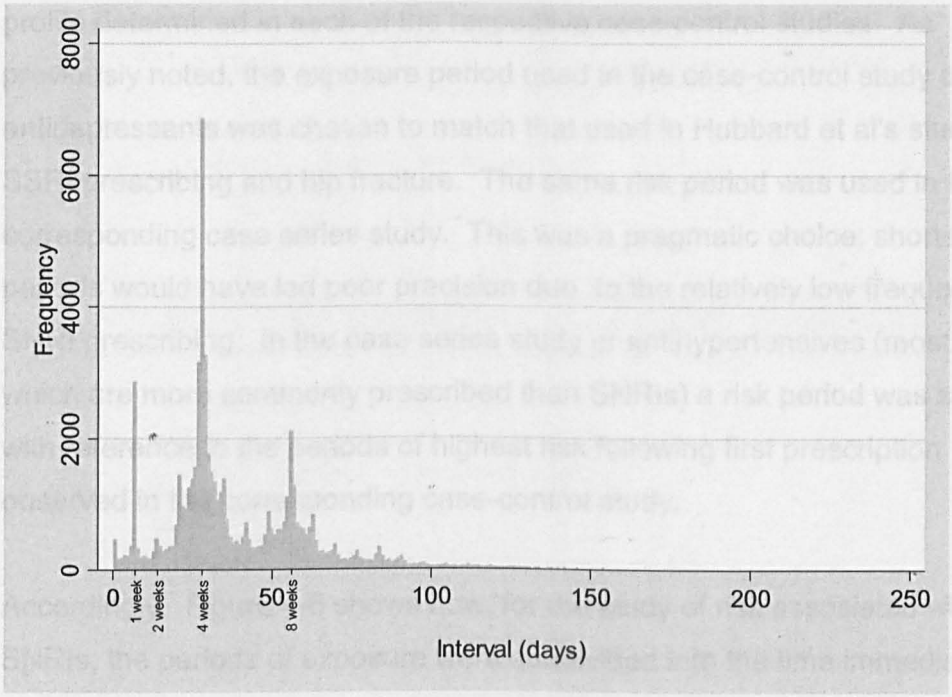
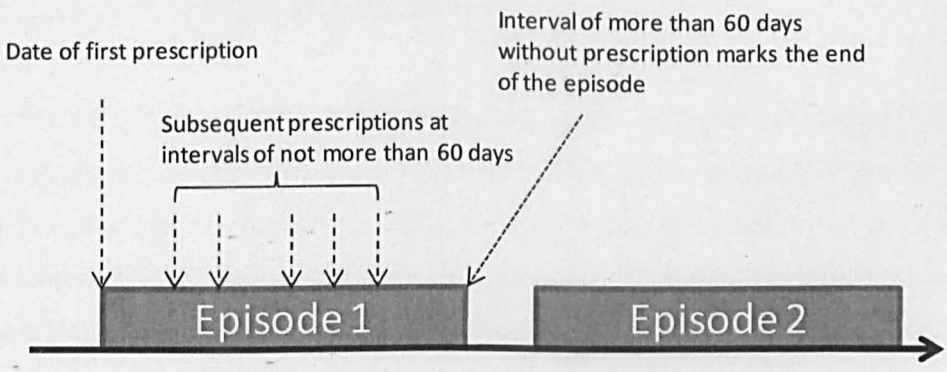


Figure 4-4 Frequency distribution of the time interval between successive prescriptions of beta blockers for cases



Using this definition of episodic exposure, the exposure history of a study participant can be conceived in terms of one or more episodes of exposure, separated by periods of non-exposure as shown in Figure 4-5.

Figure 4-5 Illustration of how series of prescriptions at intervals of not more than 60 days are treated as discrete episodes of exposure



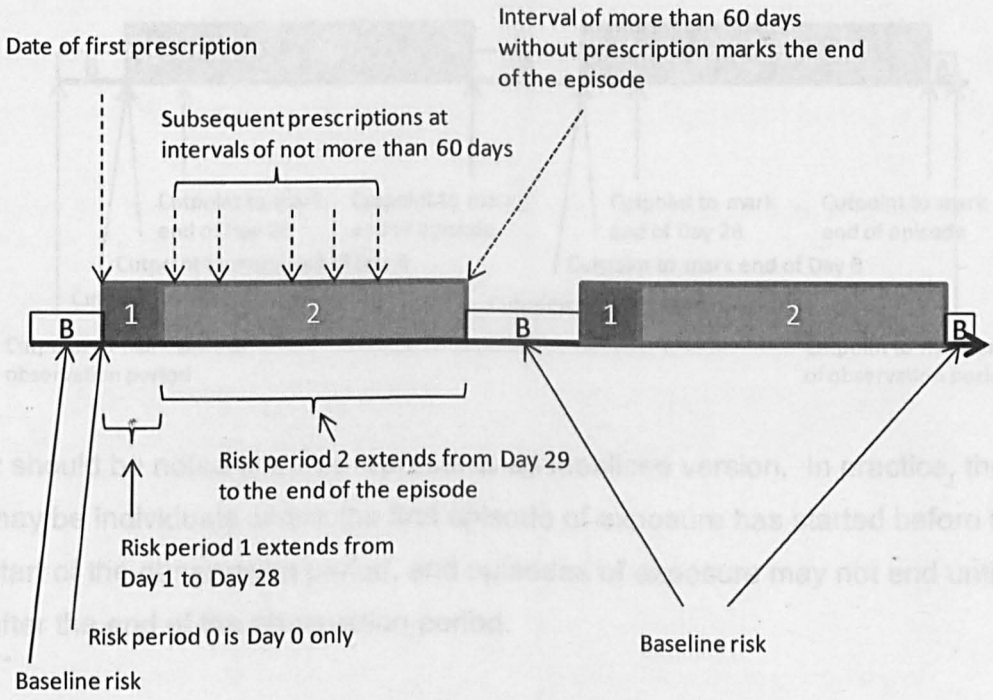
4.2.4 Definition of risk periods

The core of case series analysis is the estimation of relative incidence for different periods of exposure (risk periods). In the studies that follow, the

observation time for each person was divided into periods of non-exposure and exposure. Periods of exposure were sub-divided based on the risk profile determined in each of the respective case-control studies. As previously noted, the exposure period used in the case-control study of antidepressants was chosen to match that used in Hubbard et al's study of SSRI prescribing and hip fracture. The same risk period was used in the corresponding case series study. This was a pragmatic choice: shorter risk periods would have led poor precision due to the relatively low frequency of SNRI prescribing. In the case series study of antihypertensives (most of which are more commonly prescribed than SNRIs) a risk period was selected with reference to the periods of highest risk following first prescription observed in the corresponding case-control study.

Accordingly, Figure 4-6 shows how, for the study of risk associated with SNRIs, the periods of exposure were subdivided into the time immediately after the start of the episode of exposure (Days 1-28), and the time from Day 29 until the end of the episode. Day 0 (i.e. the same day as the start of the episode) was separated out to avoid ascertainment bias related to a greatly increased rate of falls recording at the time the first prescription is given (as described in Chapter 2). All remaining person-time was used as the baseline (unexposed) comparison period.

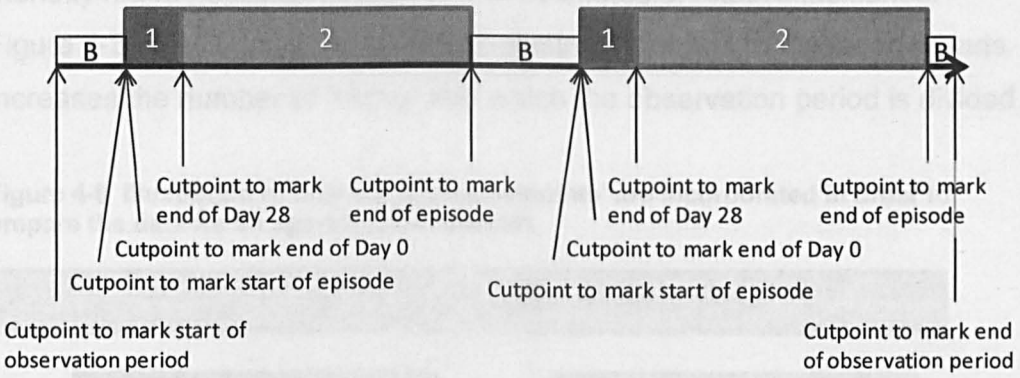
Figure 4-6 Illustration of how the entire observation time is divided into different risk periods



Computing the relative incidence of an event for each of the risk periods requires that the entire observation period for each individual is divided up and attributed to one of the risk periods. The method proposed by Whitaker et al for doing this involves setting "cutpoints" at the start and end of each risk period and at the start and end of the whole observation period, by which the whole period is divided into a series of "slices" of varying durations for which relative incidence can be calculated[195].

In the simplest case (no adjustment for age or confounders), these "slices" correspond exactly with the risk periods. This is the situation shown in Figure 4-7. As will be seen below, the incorporation of adjustment for age or other confounders will require the introduction of additional cutpoints which will subdivide risk periods into smaller "slices".

Figure 4-7 Illustration of the risk periods defined in the case series analysis of antidepressant prescribing and the corresponding "cutpoints" required to divide the observation period into relevant "slices".



It should be noted that this represents an idealised version. In practice, there may be individuals where the first episode of exposure has started before the start of the observation period, and episodes of exposure may not end until after the end of the observation period.

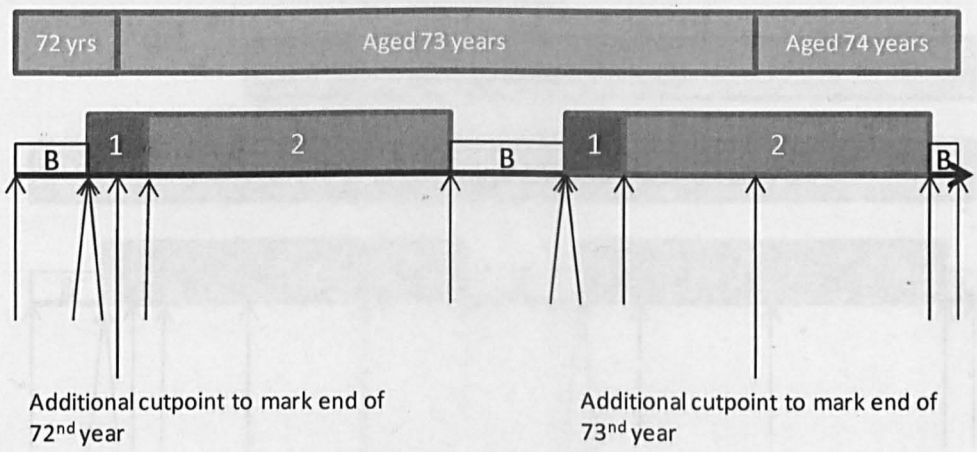
For simplicity, the initial analysis undertaken aggregated the respective risk periods from the various episodes (i.e. no distinction was made about whether the high risk period occurred in a first or subsequent episode of prescribing). As discussed below, this became the basis of what is described as the *standard analysis*. Subsequent analysis involved disaggregating first and subsequent episodes of prescribing, to assess whether any association that exists is primarily with the onset of prescribing in the very first episode only, or with the onset of prescribing in any episode.

4.2.5 Adjusting for age

Whitaker et al also describe how to include age effects in the model to correct for confounding by age[195]. Based on our finding from the same dataset that the incidence rate of recorded falls in older people is strongly related to age (rate ratio of approximately 12 for people aged 90 years compared to people aged 60-64 years)[196], we adjusted for likely age-related variation in the incidence of first fall using 1 year agebands. We did this by expanding the number of risk periods to allow for the full range of ages of study participants.

In sensitivity analysis we found that increasing the ageband intervals to 6-monthly made negligible impact on the estimates of relative incidence. Figure 4-8 shows how incorporating adjustment for age in 1 year agebands increases the number of "slices" into which the observation period is divided.

Figure 4-8 Illustration of how additional 'cutpoints' are incorporated in order to prepare the data for an age-adjusted analysis



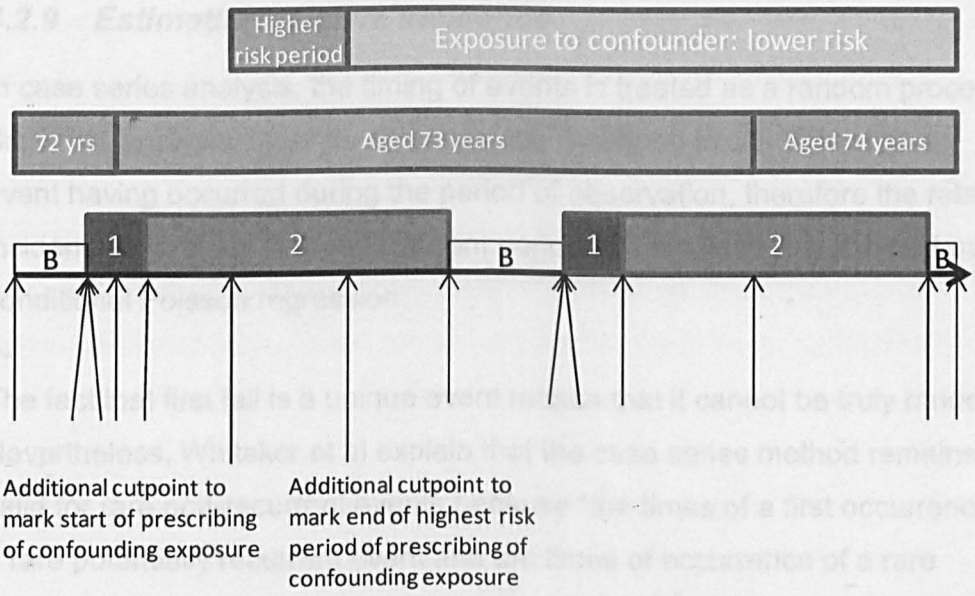
4.2.6 Other possible sources of confounding in case series analysis

The focus of analyses in the case series method is on the relative incidence of the event (first fall) for periods of risk which are defined relative to the exposure of interest. If there is a temporal association between the exposure of interest and exposure to some other factor which is known to be associated with falls in older people, then there is a possibility of confounding. (For example, if the onset of antidepressant prescribing is associated with the onset of antipsychotic prescribing, say, for which there is an established association with falls).

In such an instance, one way to address this is to adjust for the possible confounding. The method for doing this involves identifying episodes of exposure to the confounding medication and the associated risk periods for which there is evidence of an effect on falls. Additional cutpoints are introduced to reflect the periods of increased risk which might be attributable to the confounding medication. In this way the observation period is divided

into an increasing number of shorter "slices" (see Figure 4-9), each of which can be categorised in terms of its exposure to the confounder, and to age, as well as to the primary exposure of interest. The definition of these additional risk periods for the confounding prescribing is further complicated where the prescribing is recurrent.

Figure 4-9 Illustration of how the observation time is further divided in order to prepare for adjustment for a confounding exposure to episodic prescribing



4.2.7 Sample size

4.2.7.1 Case series analysis of antidepressants

Using the sampsi_sccs utility in Stata it was estimated that with an average follow-up of 6 years, 1900 cases exposed to SNRIs are required to provide 85% power to detect a risk ratio of 1.7 for an increased risk of fall in the first 28 days.

Therefore, in order to achieve sufficient precision in the estimates of relative incidence in the case series analysis of SNRIs the study population was extended to cover the entire period 2001-8 inclusive. This was because of the relatively small numbers of participants exposed to SNRIs in the period 2003-2006. In other respects, the case definition described above remained unchanged.

4.2.8 Case series analysis of antihypertensives

In contrast to this, the numbers of participants exposed to antidepressants or to antihypertensives in the period 2003-2006 were much higher and provided sufficient precision without any need for an extension of the study period. Based on an average follow-up of 3 years, 1100 exposed cases are required to provide 80% power to detect a risk ratio of 1.7 for an increased risk of fall in the first 21 days.

4.2.9 Estimating relative incidence

In case series analysis, the timing of events is treated as a random process. Since the analysis depends on cases, the likelihood is conditional on an event having occurred during the period of observation, therefore the relative incidence of first fall in these different periods of exposure is estimated using conditional Poisson regression.

The fact that first fall is a unique event means that it cannot be truly random. Nevertheless, Whitaker et al explain that the case series method remains valid for rare non-recurrent events because "the times of a first occurrence of a rare potentially recurrent event and the times of occurrence of a rare unique event cannot in practice be distinguished"[195]. There is no formal definition of what constitutes a "rare event" in this context, but the judgement of Professor Farrington who was instrumental in the early exploitation and subsequent development of the method[197], is that the incidence of recorded fall in THIN is sufficiently rare[196] to justify treating first fall as a random event[198].

4.2.10 Underlying assumptions and tests for breaches

In each case series study, sensitivity analysis was undertaken to assess the possibility of a breach of the assumption on which the method depends: that the occurrence of an event does not alter the probability of subsequent exposure. The first of these analyses was to test whether there might be a short-term dependency between a fall and subsequent exposures (as a result of, say, a medication review leading to a change in prescribing). As explained by Whitaker et al, in a situation such as this, a fall would be

unlikely to occur in the period immediately prior to an exposure (because the occurrence of the fall has led to a reduced probability of subsequent exposure) [195]. This would result in an incidence rate for the baseline period which is artificially low, with the result that the rate in the period following exposure would be exaggerated. To test for this potential dependency, the standard analysis (described above) was amended to include an additional observation period corresponding to the 30 days prior to the start of an episode. Incidence rate ratios for the standard analysis were compared with the respective risk periods in the sensitivity analysis, on the basis that a large difference in rate ratios would be evidence that events influence the probability of a subsequent exposure.

A second sensitivity analysis was performed to test for a breach of the assumption: that mortality subsequent to a fall alters the probability of subsequent exposure. Whitaker et al state that case series analysis of deaths (an example of the most extreme situation, for which there would be an inevitable dependency for subsequent prescribing!) may be undertaken "by taking the observation period as the time from exposure to the end of the planned observation period", provided that the death events are rare. However, given the advanced age of the participants and their associated mortality[196], it was decided that the second sensitivity analysis should comprise a test which removes from the standard analysis all people who died within 90 days of the recorded fall, to observe whether this resulted in a considerable change in the observed size of effect. Following consultation with Professor Farrington at the Open University, it was judged that the approach of excluding cases who died following a fall would be preferable to the alternative approach which itself rests on a further assumption (that mortality following a fall is rare) which it would be difficult to defend[198].

Whitaker at al set out a further test which, effectively, involved removing from the analysis all individuals whose fall was prior to exposure. (Their approach to achieving this is to redefine the observation period for each individual so that it starts at age at exposure. Since the analysis is conditioned on the number of events, an individual with no events will contribute nothing to the

estimation of the incidence rate). The purpose of this is to undertake an analysis in which there is no possibility of a prior fall event exerting an effect on the probability of a subsequent event. The analysis is now a comparison of incidence rates between different post-exposure periods. It no longer provides what the standard analysis does: a comparison of incidence rates before and after exposure. However the test requires that exposure for an individual is unique. This chapter has already described how recorded prescribing of the medications of interest in these studies are recurrent. This means that this test has limited utility in this study and therefore was set aside.

In their early explanation of the method, Whitaker et al noted that "a general approach to the analysis of event-dependent exposures is a topic of ongoing research". More recently, Farrington et al published an extension to the method for rare non-recurrent events which circumvents the problem of the underlying assumption regarding the independence of events and the probability of subsequent exposure[199]. Consideration is given to this in the final chapter

4.3 Application of the method

Initially, no distinction was made between risk periods occurring in different episodes of prescribing (i.e. the period corresponding to the onset of first ever prescribing was aggregated with the periods relating to the onset of prescribing in subsequent episodes). Age was adjusted for in 1 year agebands. In each study this was the basis of what was considered to be *standard analysis*.

Where the results of the earlier case control analysis indicated that the greatest effect would be found in the first episode of prescribing, the standard analysis was repeated, but separating out periods corresponding to first and subsequent episodes of exposure, and periods of non-exposure between episodes. This constituted an extension of the standard analysis.

Whitaker et al set out some of the Stata code to undertake these analyses[200]. In the following studies, their approaches have been combined and adapted to analyse relative incidence for exposures which may occur in a series of episodes of irregular duration and intervals, whilst adjusting for age and other possible confounders.

In adapting the code it has been written to facilitate the 'flexing' of key assumptions about the length of time that may elapse between prescriptions before an episode is deemed to have ended, and the definition of alternative risk periods (e.g. to assist with some of the sensitivity tests described below). It has also been written in such a way as to incorporate adjustment for other variables which may confound an observed association, as described in 4.2.6.

These methods were applied first of all to the study of SNRIs. The reason for this is that it seemed prudent to start by applying the method to a class of medication for which the association with falls is already relatively well established (whereas it is less clear in the case of antihypertensives). In addition it seemed that the gap in the literature could be addressed with greater certainty than might be the case with antihypertensives.

All of the following studies used the October 2008 version of THIN which became available since the earlier studies of incidence and mortality were completed (which used the October 2007 version).

5 Serotonin-norepinephrine reuptake inhibitors and falls

This chapter addresses the third project aim which is:

- to establish whether the falls risk profile of more recently introduced serotonin noradrenalin reuptake inhibitors is more favourable than that of selective serotonin reuptake inhibitors

5.1 Introduction

Antidepressant medications have been associated with an increased risk of falls and fracture in the elderly, and this increase in risk appears to be common to both the older tricyclic antidepressants (TCAs) and the more recent selective serotonin reuptake inhibitors (SSRIs)[129]. It has been suggested that newer dual action serotonin-norepinephrine (noradrenaline) reuptake inhibitors (SNRIs) may be safer in terms of fracture risk[159] and risk of falling in residential care and nursing homes[126] but there are no data on the risk of falls associated with the use of these drugs in older people in the community setting. Therefore the independent effect of SNRIs on the risk of falls in older people was investigated using classical case-control analyses and case series analysis. The methods for these are set out in detail in the previous chapter.

5.2 Results

As described in the previous chapter, 9682 people were identified who were aged >60 years and who experienced a first fall, and 52 100 matched controls (Table 5-1). The mean age of cases was 77.5 years, and 76.4 years for controls. Thirty two percent of cases and controls were male.

Table 5-1 Characteristics of cases and controls in THIN 2003-6

	Cases	*%*	*Controls*	*%*
n =	9682		52100	
Age				
Mean age (years)	77.5		76.4	
Gender				
Females	6602	68%	35573	68%
Males	3080	32%	16527	32%
CHD ever	6974	72%	34051	65%
Diabetes or CVD ever	5425	56%	23559	45%
Antipsychotic (current prescribing)	509	5%	1371	3%
Hypnotic/anxiolytic (current prescribing)	1208	12%	3744	7%
Diuretic prescription (current prescribing)	3657	38%	16459	32%
Digoxin (current prescribing)	594	6%	2022	4%
Type1a Anti-arrhythmics (current prescribing)	0	0%	0	0%

CHD = corononary heart disease. CVD = cardiovascular disease.

Results of the analyses of ever (previous/recent/current)/never prescribing are shown in Table 5-2. Prescribing of SNRIs was uncommon compared with prescribing of TCAs and SSRIs; of the controls, 806 (2%) had ever been prescribed an SNRI, and most of these (768) were prescribed venlafaxine, with small numbers having been prescribed reboxetine (41) or duloxetine (19). Cases who had experienced a first fall were more likely than controls to have ever been prescribed an SNRI (3%), and the unadjusted OR associated with having ever been prescribed an SNRI was 1.77 (1.53 - 2.05). The risk of first fall was highest in those currently prescribed an SNRI, with a 2.5-fold increase in risk compared with those who had never been prescribed an SNRI.

Table 5-2 Association between first recorded fall and prescribing of antidepressants in THIN 2003-6

Exposure	*Cases n=9682*	*Controls n=52100*	*Odds ratio (95% confidence intervals)*	*Odds ratio (95% confidence intervals) Adjusted for antipsychotics & hypnotics/anxiolytics*
SNRI				
Never prescribed	9426 (97%)	51294 (98%)	1.00	1.00
Ever prescribed	256 (3%)	806 (2%)	1.77 (1.53 - 2.05)	1.30 (1.12 - 1.51)
Previously prescribed	135 (1%)	516 (1%)	1.47 (1.21 - 1.78)	1.09 (0.90 - 1.33)
Recently prescribed	6 (0%)	34 (0%)	0.98 (0.41 - 2.35)	0.79 (0.33 - 1.90)
Currently prescribed	115 (1%)	256 (0%)	2.49 (1.99 - 3.12)	1.79 (1.42 - 2.25)
SSRI				
Never prescribed	7726 (80%)	45750 (88%)	1.00	1.00
Ever prescribed	1956 (20%)	6350 (12%)	1.88 (1.77 - 1.99)	1.55 (1.46 - 1.65)
Previously prescribed	1081 (11%)	4208 (8%)	1.57 (1.46 - 1.69)	1.31 (1.21 - 1.41)
Recently prescribed	111 (1%)	297 (1%)	2.24 (1.79 - 2.80)	1.85 (1.48 - 2.32)
Currently prescribed	764 (8%)	1845 (4%)	2.50 (2.29 - 2.74)	2.04 (1.86 - 2.24)
Tricyclic				
Never prescribed	7067 (73%)	42209 (81%)	1.00	1.00
Ever prescribed	2615 (27%)	9891 (19%)	1.64 (1.56 - 1.72)	1.38 (1.30 - 1.46)
Previously prescribed	1811 (19%)	7313 (14%)	1.54 (1.45 - 1.63)	1.30 (1.23 - 1.39)
Recently prescribed	106 (1%)	390 (1%)	1.70 (1.36 - 2.11)	1.44 (1.16 - 1.80)
Currently prescribed	698 (7%)	2188 (4%)	1.96 (1.79 - 2.14)	1.61 (1.46 - 1.76)

Of the potential confounders evaluated for inclusion in bivariate models, prescribing of antipsychotics and hypnotic-anxiolytic drugs altered the effect by 10%. In the final model, after adjustment for antipsychotic and hypnotic-anxiolytic prescribing, the effect of current use of SNRIs was reduced but still demonstrated an almost 80% increase in risk (adjusted OR 1.79; 1.42 - 2.25). The magnitude and significance of effects were very similar when prescriptions were limited specifically to venlafaxine.

Evidence of an interaction with age for ever prescribed TCAs ($p = 0.0003$) was found, for which the size of the effect (i.e. risk of first fall) increased with age. For ever prescribed SNRIs and SSRIs, no evidence of interaction with age was found ($p = 0.884$ and $p = 0.134$ respectively).

The risk of first fall was apparent within the first 28 days following first prescription of an SNRI (adjusted OR 3.42; 0.96 - 12.24) and was maintained in the subsequent 28 days (adjusted OR 4.40; 1.46 - 13.27) - see Table 5-3.

Table 5-3 Association between first recorded fall and first prescription of antidepressant in THIN 2003-6

First prescription (Days elapsed before first fall)	*Cases n=9682*	*Controls n=52100*	*Odds ratio (95% confidence intervals) Unadjusted*	*Odds ratio (95% confidence intervals) Adjusted for antipsychotics & hypnotics/anxiolytics*
SNRIs (Any)				
No prescriptions prior to index date	9426 (97.36%)	51294 (98.45%)	1.00	1.00
0 days	0 (0.00%)	1 (0.00%)		
1-28 days	5 (0.05%)	5 (0.01%)	5.10 (1.45 - 17.94)	3.42 (0.96 - 12.24)
29-56 days	7 (0.07%)	6 (0.01%)	6.91 (2.32 - 20.58)	4.40 (1.46 - 13.27)
>56 days	244 (2.52%)	794 (1.52%)	1.71 (1.48 - 1.98)	1.26 (1.09 - 1.47)
SSRIs				
No prescriptions prior to index date	7726 (79.80%)	45750 (87.81%)	1.00	1.00
0 days	6 (0.06%)	0 (0.00%)		
1-28 days	31 (0.32%)	67 (0.13%)	2.74 (1.79 - 4.22)	2.34 (1.52 - 3.62)
28-56 days	36 (0.37%)	54 (0.10%)	3.62 (2.35 - 5.58)	3.09 (2.00 - 4.78)
>56 days	1883 (19.45%)	6229 (11.96%)	1.85 (1.74 - 1.96)	1.52 (1.43 - 1.62)
Tricyclics				
No prescriptions prior to index date	7067 (72.99%)	42209 (81.02%)	1.00	1.00
0 days	8 (0.08%)	7 (0.01%)	7.38 (2.66 - 20.45)	7.12 (2.56 - 19.82)
1-28 days	29 (0.30%)	52 (0.10%)	3.51 (2.22 - 5.57)	3.18 (2.00 - 5.07)
28-56 days	21 (0.22%)	65 (0.12%)	1.91 (1.16 - 3.15)	1.65 (0.99 - 2.73)
>56 days	2557 (26.41%)	9767 (18.75%)	1.62 (1.54 - 1.71)	1.36 (1.29 - 1.44)

When the analysis was validated by searching for the anticipated effects of other antidepressants, an increased risk of first fall with ever having been prescribed either a TCA (unadjusted OR 1.64) or an SSRI (unadjusted OR 1.88) was found (see Table 5-2); these values were very similar in size to the effects on hip fracture previously described for a similar cohort[158]. The adjusted OR for first fall with current exposure to SSRIs was 2.04 (1.86 - 2.24), which was slightly greater than that for TCAs 1.61 (1.46 - 1.76) and similar to other findings for antidepressants[128]. Both TCAs and SSRIs were associated with an acute increase in risk in the first few weeks after the first prescription, which was more marked for TCAs than for SSRIs. The effect of SNRIs on the first fall in the analyses was very similar to that seen for SSRIs and for TCAs.

When the data were extended to cover the period 2001–8 (as described in the previous chapter in 1.1.3) there were 1916 fall cases exposed to SNRIs. On conducting the self-controlled case-series analysis (Table 5-4) to compare the risk of falls in periods of exposure with baseline (unexposed) periods, the risk was found to be significantly increased in the period 1–28 days after commencement of an episode of SNRI treatment (although

smaller than that seen in the case-control analyses) and in the period from day 57 to the end of treatment. Adjustment for the confounders used in the case-control model did not alter the effect by 10%. The results were also very similar when exposure was restricted to venlafaxine treatment alone.

Table 5-4 Association between SNRI antidepressant exposure (any treatment episode) and first fall: case-series analysis in THIN 2001-8

Period of exposure	*First falls (n)*	*Follow-up time (person years)*	*Incidence rate ratio (95% confidence intervals)*
Any SNRI			
Unexposed (pre/post/between episodes)	1308	8960.7	1.00
Day 0 of episode	17	11.7	10.03 (6.15 - 16.36)
Day 1 - 28 of episode	71	329.9	1.49 (1.15 - 1.93)
Day 29 - 56 of episode	56	330.5	1.18 (0.88 - 1.57)
Day 57 - end of episode	464	2669.4	1.29 (1.08 - 1.53)

When this standard analysis was repeated on the same data but separating out periods of first and subsequent exposure, the risks of fall in the periods following first exposure were higher than in those following a subsequent exposure (see Table 5-5).

Table 5-5 Association between first or subsequent episodes of SNRI prescribing and first fall: case series analysis in THIN 2001-8

Period of exposure	*First falls (n)*	*Time at risk (Pyrs)*	*Incidence rate ratio (95% confidence intervals)*
Any SNRI			
Unexposed (time before first episode)	1223	8352.9	1.00
Day 0 of first episode	9	3.9	13.41 (6.93 - 25.97)
Day 1 - 28 of first episode	36	109.1	1.90 (1.35 - 2.68)
Day 29 - 56 of first episode	28	110.4	1.48 (1.01 - 2.17)
Day 57 - end of first episode	266	1320.6	1.43 (1.16 - 1.76)
Unexposed (time between episodes)	85	611.7	1.00 (0.72 - 1.38)
Day 0 of subsequent episode	8	7.9	6.86 (3.33 - 14.15)
Day 1 - 28 of subsequent episode	35	220.8	1.07 (0.72 - 1.58)
Day 29 - 56 of subsequent episode	28	220.2	0.86 (0.56 - 1.31)
Day 57 - end of subsequent episode	198	1344.9	1.02 (0.78 - 1.33)

Both of the analyses to test for a possible breach in the underlying assumption concerning the independence of falls and the probability of subsequent exposure resulted in only small changes in the estimated size of the effect (see Table 5-6 below). This was interpreted as there being only weak evidence for a breach of the assumption regarding independence of falls and probability of subsequent exposure, and that the effect of any bias related to mortality following a fall is small.

Table 5-6 Sensitivity analysis to test dependence between fall event and risk of subsequent exposure to SNRI antidepressant in THIN 2003-8

Period of exposure	*First falls (n)*	*Time at risk (Pyrs)*	*Including a pre-exposure period IRR (95% CI)*	*First falls (n)*	*Time at risk (Pyrs)*	*Excluding cases who died within 90 days of fall IRR (95% CI)*
Any SNRI						
Unexposed periods	1268	8722.9	1.00	1029	7317.5	1.00
30 day period prior to any episode	40	237.7	1.11 (0.80 - 1.55)			-
Day 1 - 28 of episode	71	329.9	1.51 (1.16 - 1.96)	52	266.2	1.41 (1.04 - 1.91)
Day 29 - 56 of episode	56	330.5	1.19 (0.89 - 1.59)	44	267.1	1.19 (0.86 - 1.65)
Day 57 - end of episode	464	2669.4	1.30 (1.09 - 1.55)	331	2060.5	1.23 (1.00 - 1.50)

5.3 Discussion

The risk of first fall was increased almost 2-fold in people currently prescribed an SNRI, and this increase in risk was apparent in the first month after the first prescription. The sizes of effect were similar to those seen for SSRIs and TCAs. Based on the prevalence in this population during the study period, the relative risk corresponds to a population attributable risk proportion in the region of 0.5%. In the within-person analysis, the effect of SNRIs was slightly smaller than seen in the between-person analysis. This remained the case even when the analysis differentiated between risk periods associated with first ever and subsequent exposures. This suggests that the findings of the case-control analysis may have been overestimates.

5.3.1 Study Strengths and Weaknesses

The main strengths of the study include the large number of cases and the fact that the data were collected prospectively, which means that recall of medication exposures and of falls is not a source of bias. In the UK, antidepressant medications are available only on prescription, and previous

studies have shown these to be well documented where there is a computerized system[201]. Therefore, in settings in which practices contribute to THIN, the data provide a reliable measure of prescribing.

Medications were differentiated according to standard classifications in the British National Formulary[191]. The data and analysis were validated using other classes of antidepressants and these exhibited the expected pattern of risk, based on evidence from other studies.

The main potential weaknesses of the study are the validity of the recording of fall events, and the incomplete control of confounding. As previously discussed, falls recorded in primary care are a subset of the falls self-reported in surveys. Data are not available to describe which self-reported falls are more likely to be recorded in primary care, but the earlier study in this project found that patients with recorded falls are an important group who experience increased mortality compared with non-fallers (2-fold increase for recurrent fallers, and a more than 5-fold increase for recurrent fallers aged 60–74 years), which suggests that recorded falls are more likely to be those for which medical attention was required[196]. Nevertheless, incomplete recording of falls raises the possibility of differential ascertainment of falls for patients receiving antidepressant medication. Such a bias would have led to overestimated ORs. However, the day of the prescription was excluded from the exposure time, which avoided ascertainment bias of falls recorded at the time of initial prescribing. Moreover, the sizes of effect found for TCAs and SSRIs are very similar to those previously reported in this dataset for hip fracture, which is relatively unlikely to be under-recorded[158].

The possibility that these results are affected by confounding by co-morbidity was explored in several ways. In the case-control analysis, a number of potential confounders were controlled for and the final model was adjusted for prescription of antipsychotics and hypnotic-anxiolytics, which were the only potential confounders to reduce the OR for the effect of SNRIs. The extent to which the effect was attributable to characteristics of the patients rather than to prescribing was explored by comparing the risk for people

currently and previously prescribed SNRIs; this analysis revealed much stronger effects for current prescribing.

Finally, further analysis was undertaken using the case series method, which controls for factors that vary between individuals, such as frailty and severity of depression. These factors may remain constant for long periods but the fact that they can and do vary over time within individuals means that there is some uncertainty about the extent to which the case series method fully adjusts for their effect. This applies particularly to depression, the symptoms of which may wax and wane, whereas underlying frailty tends to increase over the long term

Two analyses were applied to test sensitivity to the assumption underlying the method: that the occurrence of a fall does not affect the risk of a subsequent exposure. These were judged to be reasonable assumptions because there was only weak evidence of 'depletion' in the incidence of falls in the period prior to exposure, or of significant bias due to mortality following a fall.

The smaller size of effect in the case-series analysis (compared to the case control) suggests that the case-control analysis may have overestimated the true effect, because of bias. Nevertheless, the finding of increased fall risk in the first 28 days after the start of treatment with SNRIs in the case-series analysis suggests an independent adverse effect of this drug on fall risk.

The extent, if any, of non-compliance to medication, could not be assessed and both methods rely on the dates of prescriptions to approximate periods of exposure and non-exposure. However, it should be noted that misclassifications in exposure would result in underestimation of a true effect.

5.3.2 Other Studies

Several recent meta-analyses have demonstrated that antidepressant prescribing is associated with an increased incidence of falling, based on studies conducted in a variety of settings[128 129 202]. However, these studies

did not evaluate falls risk for SNRIs or the evaluation was not made for community dwelling older people. Coupland et al's recent cohort study was published after this study was completed[127]. It includes more than 60,000 patients in a similar dataset to THIN spanning an 11 year period, and provides estimates of the hazard of next fall for SSRIs (irrespective of whether the event is a first or subsequent recorded event). The adjusted hazard ratio for SSRIs is 1.66 (1.58 - 1.73). Their study also estimates a one year risk of falls for people prescribed Venlafaxine which is similar to their equivalent estimate for SSRIs. In a large, case-control study in Denmark (n = 498617), Vestergaard et al investigated the effect of the full spectrum of antidepressant groups on fracture risk and found significant associations with fracture at specific sites for SNRIs but no consistent increase in risk[159]. A study of residential care and nursing care homes in Sweden (n = 3604) found no significant increase in risk of falls with SNRIs, although the investigators did observe an effect with SSRIs[126]. Both of these studies suggested that SNRIs may be a safer alternative for older people than TCAs or SSRIs, which appear to be associated with both falls and fracture[126 128 129 158 160 203]. This study focuses specifically on the effect of SNRIs on risk of falls in the community and suggests there is an increase in risk similar to that for SSRIs, and an increased risk shortly after initiation of therapy.

A recent review observed that the mechanisms by which antidepressants increase risk of falls and related fractures are complex and may include orthostatic hypotension, arrhythmias, sedation, insomnia, movement disorders and confusion[152]. The specific mechanism by which SNRIs cause falls is not clear, but venlafaxine, which is the most commonly prescribed SNRI, has adverse effects in common with SSRIs and TCAs (e.g. drowsiness, confusion, insomnia, movement disorders, visual disturbance and hypotension), each of which are implicated as contributing to falls in older people[152].

The evidence for the relative efficacy of SNRIs compared with other antidepressants remains limited and inconsistent[204-206]. Nevertheless, SNRIs have been suggested by some to be the antidepressant of choice for the

elderly because of their low potential for drug interactions and possible favourable effect on pain associated with depression[205-207], although concerns about cardiotoxicity and toxicity in overdose have led the National Institute for Health and Clinical Excellence (NICE) to recommend that these drugs be used as second-line treatments. These results suggest that clinicians initiating prescribing of SNRIs should also be alert to the increased risk of falls.

5.3.3 Implications

This study provides evidence that SNRIs are associated with an increased risk of first falls in older people that is similar to that associated with other classes of antidepressants. Clinicians should be alert to these risks when prescribing SNRIs in older people.

In terms of methodology, the study shows how the application of the case series method described by Whitaker et al can be used to analyse the association between first fall and recurrent transient exposures in order to quantify the role of confounding in estimates derived from classical case control analysis. More specifically, it demonstrates the feasibility and value of applying classical case control and self -controlled case series analysis to address specific gaps in the evidence base for a specific subgroup of medications (SNRIs), so that their falls risk profile can be compared to what is already known about the risk profile of SSRIs and of antidepressants in general.

Having applied these methods to address a specific gap (evidence about the risk profile of SNRIs) in what is otherwise relatively well-evidenced literature (evidence about the falls risk profile of antidepressants in general), the focus of the next chapter turns to a study which seeks to apply the approach to a whole group of medications (antihypertensive medication and its subgroups) for which the evidence base concerning falls risk is less compelling.

6 Antihypertensives and falls

This chapter addresses the fourth project aim which is:

- to establish whether being prescribed antihypertensive medication modifies the risk of falling in older people, differentiating between specific sub-classes of medication, and assessing the extent of any confounding

6.1 Introduction

Antihypertensive medications have long been implicated as a potential cause of falls in older people, via orthostatic hypotension[153]. A meta-analysis of small studies found no overall association with falls for the main classes of cardiac and analgesic medications, including some of the main classes of antihypertensives. The review highlighted uncertainty about the extent to which the presence of a real effect may be obscured by the variable role of confounding by indication between pooled studies[129]. Woolcott et al's review included analysis of antihypertensives, for which they found a frequentist pooled estimate of 1.26 (1.08 – 1.46)[128]. However, as was noted by Cumming concerning many earlier studies[130], this more recent meta-analysis was not designed to differentiate between sub-classes of antihypertensive. Despite their widespread prescribing, there remains little recent data for class-specific effects on falls. Therefore the role of antihypertensive medications in older people with a recorded fall in primary care was investigated.

The previous chapter set out how classical case control and case series methods were applied to a group of medications for which the falls risk profile is relatively well evidenced (as described in the previous chapter). This chapter describes how the same two methods were applied to quantify the association between subgroups of antihypertensive medication and first fall.

The rationale and methods for the complementary use of these two study designs are set out in detail in the Methods chapter.

6.2 Results

6.2.1 Case control analysis

9682 people aged over 60 years who experienced a first fall were identified, and 52 100 controls (matched according to the criteria described in the methodology chapter). More than 88% of cases were matched to four or more controls; amongst the oldest cases fewer matched controls were secured for each case. Nevertheless each of the cases was successfully matched to at least one control of the exact same age, sex, and general practice. The mean age of cases was 77.5 years, and 76.4 years for controls. 32% of cases and controls were male (as shown in Table 5-1 in the previous chapter).

Results of our analyses of ever/never and previous/current prescribing were recorded in Table 6-1. In unadjusted analysis there were significant odds ratios for all classes of medication, ranging from 1.10 (1.05 – 1.16) for beta blockers to 1.48 (1.37 – 1.61) for thiazides. After adjustment for prior diagnoses of CHD, co-morbidities and other antihypertensives there were significant associations for thiazides 1.25 (1.15 – 1.36), ACE inhibitors 1.15 (1.05 – 1.25) and for beta blockers 0.90 (0.85 – 0.96).

Table 6-1 Association between first recorded fall and prescribing of antihypertensives, THIN 2003-6

Exposure	*Cases n=9682*	*Controls n=52100*	*Odds ratio (95% confidence intervals) Unadjusted*	*Odds ratio (95% confidence intervals) Adjusted for CHD, Charlson, and other antihypertensives*
Thiazide				
Never prescribed	8817 (91%)	49066 (94%)	1.00	1.00
Ever prescribed	865 (9%)	3034 (6%)	1.48 (1.37 - 1.61)	1.25 (1.15 - 1.36)
Previously prescribed	228 (2%)	851 (2%)	1.41 (1.22 - 1.65)	1.19 (1.02 - 1.39)
Recently prescribed	43 (0%)	161 (0%)	1.42 (1.01 - 1.99)	1.16 (0.82 - 1.64)
Currently prescribed	594 (6%)	2022 (4%)	1.52 (1.38 - 1.68)	1.28 (1.16 - 1.42)
Beta blocker				
Never prescribed	6246 (65%)	34562 (66%)	1.00	1.00
Ever prescribed	3436 (35%)	17538 (34%)	1.10 (1.05 - 1.16)	0.95 (0.90 - 1.00)
Previously prescribed	1463 (15%)	7003 (13%)	1.18 (1.10 - 1.25)	1.00 (0.94 - 1.07)
Recently prescribed	193 (2%)	944 (2%)	1.15 (0.98 - 1.35)	1.01 (0.86 - 1.19)
Currently prescribed	1780 (18%)	9591 (18%)	1.05 (0.99 - 1.11)	0.90 (0.85 - 0.96)
ACE inhibitor				
Never prescribed	6437 (66%)	37468 (72%)	1.00	1.00
Ever prescribed	3245 (34%)	14632 (28%)	1.30 (1.24 - 1.36)	1.09 (1.04 - 1.16)
Previously prescribed	1096 (11%)	4841 (9%)	1.32 (1.23 - 1.42)	1.15 (1.05 - 1.25)
Recently prescribed	169 (2%)	740 (1%)	1.32 (1.11 - 1.56)	1.09 (0.92 - 1.30)
Currently prescribed	1980 (20%)	9051 (17%)	1.28 (1.21 - 1.36)	1.07 (1.01 - 1.14)
Angiotensin-II receptor antagonist				
Never prescribed	8770 (91%)	47624 (91%)	1.00	1.00
Ever prescribed	912 (9%)	4476 (9%)	1.12 (1.04 - 1.21)	0.95 (0.87 - 1.03)
Previously prescribed	184 (2%)	915 (2%)	1.09 (0.92 - 1.28)	0.89 (0.75 - 1.05)
Recently prescribed	62 (1%)	275 (1%)	1.26 (0.95 - 1.67)	1.11 (0.83 - 1.47)
Currently prescribed	666 (7%)	3286 (6%)	1.12 (1.02 - 1.22)	0.95 (0.87 - 1.04)
Calcium channel blocker				
Never prescribed	6517 (67%)	36992 (71%)	1.00	1.00
Ever prescribed	3165 (33%)	15108 (29%)	1.19 (1.14 - 1.25)	1.01 (0.96 - 1.07)
Previously prescribed	1234 (13%)	5456 (10%)	1.28 (1.19 - 1.37)	1.07 (0.99 - 1.15)
Recently prescribed	173 (2%)	834 (2%)	1.18 (1.00 1.40)	0.99 (0.84 - 1.18)
Currently prescribed	1758 (18%)	8818 (17%)	1.14 (1.07 - 1.21)	0.98 (0.92 - 1.04)

For thiazides, the increased risk was significant for currently prescribed 1.28 (1.16 – 1.42), and in those previously prescribed. In beta blockers, the protective effect was significant for currently prescribed 0.90 (0.85 – 0.96) but not previously prescribed. But for ACE inhibitors (the other class in which there was a significant association with first falls), the effect of current prescribing was weaker than for previously prescribed 1.07 (1.01 – 1.14).

In the adjusted analyses no evidence of interaction with age was found, except for calcium channel blockers, in which there was a stronger positive

association with first fall amongst those aged 60 to 75 years than in those aged over 75.

Unadjusted and adjusted models of the risk of first fall after first prescription showed strong positive associations at 0 days for all classes of medication (except angiotensin-II receptor antagonists for which there were no cases in this subcategory) – see Table 6-2. But amongst antihypertensives for elapsed times of 1-7 days, 8-14 and 15-21 days, only thiazides showed significant odds ratios. In days 1-7 following a first prescription, the adjusted odds ratio of first fall for thiazides was 5.41 (1.62 – 18.14), at 8-14 days was 5.02 (1.63 – 15.51), and at 15-21 days remained 4.28 (1.19 – 15.42).

Table 6-2 Association between first recorded fall and first prescription for antihypertensive (or antidepressant), THIN 2003-6

First prescription (Days elapsed before first fall)	*Cases n=9682*	*Controls n=52100*	*Odds ratio (95% confidence intervals) Unadjusted*	*Odds ratio (95% confidence intervals) Adjusted for CHD, Charlson, and other antihypertensives*
Thiazide				
No prescriptions prior to index date	8817 (91.07%)	49066 (94.18%)	1.00	1.00
0 days	4 (0.04%)	2 (0.00%)	11.13 (2.02 - 61.24)	9.96 (1.86 - 54.45)
1-7 days	6 (0.06%)	5 (0.01%)	6.14 (1.84 - 20.47)	5.41 (1.62 - 18.14)
8-14 days	7 (0.07%)	6 (0.01%)	6.05 (1.98 - 18.44)	5.02 (1.63 - 15.51)
15-21 days	5 (0.05%)	5 (0.01%)	4.86 (1.38 - 17.08)	4.28 (1.19 - 15.42)
22-28 days	5 (0.05%)	11 (0.02%)	2.49 (0.84 - 7.36)	2.27 (0.74 - 6.92)
>28 days	838 (8.66%)	3008 (5.77%)	1.45 (1.34 - 1.58)	1.22 (1.12 - 1.33)
Beta blocker				
No prescriptions prior to index date	6246 (64.51%)	34562 (66.34%)	1.00	1.00
0 days	8 (0.08%)	3 (0.01%)	15.59 (4.12 - 58.99)	15.45 (4.07 - 58.58)
1-7 days	5 (0.05%)	21 (0.04%)	1.28 (0.47 - 3.46)	1.34 (0.50 - 3.59)
8-14 days	6 (0.06%)	19 (0.04%)	1.80 (0.71 - 4.54)	1.56 (0.61 - 3.99)
15-21 days	10 (0.10%)	29 (0.06%)	1.80 (0.86 - 3.77)	1.59 (0.75 - 3.34)
22-28 days	1 (0.01%)	22 (0.04%)	0.28 (0.04 - 2.09)	0.25 (0.03 - 1.86)
>28 days	3406 (35.18%)	17444 (33.48%)	1.10 (1.05 - 1.15)	0.94 (0.90 - 1.00)
ACE inhibitor				
No prescriptions prior to index date	6437 (66.48%)	37468 (71.92%)	1.00	1.00
0 days	13 (0.13%)	7 (0.01%)	11.20 (4.44 - 28.22)	10.47 4.14 - 26.48)
1-7 days	8 (0.08%)	36 (0.07%)	1.38 (0.64 - 2.99)	1.17 0.54 - 2.54)
8-14 days	10 (0.10%)	47 (0.09%)	1.29 (0.65 - 2.56)	1.18 (0.60 - 2.35)
15-21 days	11 (0.11%)	31 (0.06%)	2.14 (1.07 - 4.30)	1.98 (0.98 - 4.00)
22-28 days	14 (0.14%)	41 (0.08%)	2.08 (1.13 - 3.85)	1.86 (1.00 - 3.46)
>28 days	3189 (32.94%)	14470 (27.77%)	1.29 (1.23 - 1.35)	1.08 (1.03 - 1.15)
Angiotensin-II receptor antagonist				
No prescriptions prior to index date	8770 (90.58%)	47624 (91.41%)	1.00	1.00
0 days	0 (0.00%)	2 (0.00%)	0.00 (0.00 - infinity)	0.00 (0.00 - infinity)
1-7 days	4 (0.04%)	13 (0.02%)	1.85 (0.60 - 5.68)	1.45 (0.47 - 4.47)
8-14 days	2 (0.02%)	18 (0.03%)	0.64 (0.15 - 2.75)	0.57 (0.13 - 2.48)
15-21 days	3 (0.03%)	21 (0.04%)	0.78 (0.23 - 2.64)	0.71 (0.21 - 2.43)
22-28 days	4 (0.04%)	18 (0.03%)	1.19 (0.40 - 3.54)	1.20 (0.40 - 3.56)
>28 days	899 (9.29%)	4404 (8.45%)	1.12 (1.04 - 1.21)	0.95 (0.87 - 1.03)
Calcium channel blocker				
No prescriptions prior to index date	6517 (67.31%)	36992 (71.00%)	1.00	1.00
0 days	16 (0.17%)	3 (0.01%)	33.89 (9.87 - 116.34)	36.54 (10.61 - 125.85)
1-7 days	5 (0.05%)	36 (0.07%)	0.84 (0.33 - 2.13)	0.82 (0.32 - 2.10)
8-14 days	2 (0.02%)	31 (0.06%)	0.35 (0.08 - 1.49)	0.32 (0.07 - 1.35)
15-21 days	2 (0.02%)	41 (0.08%)	0.29 (0.07 - 1.20)	0.23 (0.06 - 0.96)
22-28 days	1 (0.01%)	35 (0.07%)	0.14 (0.02 - 1.04)	0.14 (0.02 - 1.02)
>28 days	3139 (32.42%)	14962 (28.72%)	1.19 (1.14 - 1.25)	1.01 (0.96 - 1.07)

6.2.2 Case series analysis

In applying the case series method to the dataset, the analysis consisted of exposed patients only. Therefore the number of exposed cases and the amount of follow-up time varied between classes of antihypertensive, ranging from 1128 cases with 3785 person-years of follow-up time for participants with an exposure to thiazides, to 4293 cases with 15 700 person-years for those exposed to an ACE inhibitor (Table 6-3).

Table 6-3 Association between episodes of antihypertensive and first fall: case series analysis in THIN 2003-6

Period of exposure	*First falls recorded*	*Follow-up (Pyrs)*	*Standard Analysis* *Incidence rate ratio (95% confidence intervals)*
Thiazide			
Unexposed periods	534	1931.7	1.00
Day 1 - 21 of episode	62	144.6	1.63 (1.20 - 2.20)
Day 22 - end of episode	522	1708.9	1.11 (0.91 - 1.37)
Beta blocker			
Unexposed periods	2134	8132.7	1.00
Day 1 - 21 of episode	156	589.0	1.13 (0.94 - 1.36)
Day 22 - end of episode	1565	5676.7	1.16 (1.04 - 1.30)
ACE inhibitor			
Unexposed periods	2313	8904.1	1.00
Day 1 - 21 of episode	156	578.2	1.11 (0.92 - 1.32)
Day 22 - end of episode	1768	6217.5	1.15 (1.04 - 1.28)
Angiotensin-II receptor antagonist			
Unexposed periods	727	2844.9	1.00
Day 1 - 21 of episode	51	217.3	0.92 (0.68 - 1.26)
Day 22 - end of episode	604	2185.6	1.09 (0.91 - 1.29)
Calcium channel blocker			
Unexposed periods	2179	8215.3	1.00
Day 1 - 21 of episode	104	551.2	0.75 (0.60 - 0.92)
Day 22 - end of episode	1588	5654.5	1.11 (0.99 - 1.23)

The incidence of first fall was increased in the first 3 weeks of thiazide prescribing (IRR 1.63, 1.20 – 2.20), but was not significantly increased in subsequent exposed periods. After disaggregating first and subsequent episodes of prescribing, it was apparent that the increased risk of falls in Day 1-21 was higher for the first episode of prescribing (IRR 2.80, 1.72 – 4.57), and for all subsequent periods of exposure the rate ratio is positive, but lower and non-significant (Table 6-4).

Table 6-4 Association between first and subsequent episodes of antihypertensive prescribing and first fall: case series analysis in THIN 2003-6

Period of exposure	*First falls recorded*	*Follow-up (Pyrs)*	*Incidence rate ratio (95% confidence intervals)*
Thiazide			
Pre-exposure period	462	1690.1	1.00
Day 1 - 21 of first episode	18	21.5	2.80 (1.72 - 4.57)
Day 22 - end of first episode	203	599.3	1.30 (0.99 - 1.71)
Between episodes	72	242.4	1.17 (0.79 - 1.73)
Day 1 - 21 of subsequent episode	44	123.1	1.33 (0.88 - 2.02)
Day 22 - end of subsequent episode	319	1108.7	1.01 (0.74 - 1.40)
Beta blocker			
Pre-exposure period	1778	6705.1	1.00
Day 1 - 21 of first episode	21	51.0	1.64 (1.06 - 2.56)
Day 22 - end of first episode	375	1307.8	1.23 (1.02 - 1.48)
Between episodes	356	1428.4	1.13 (0.93 - 1.37)
Day 1 - 21 of subsequent episode	135	538.0	1.13 (0.90 - 1.41)
Day 22 - end of subsequent episode	1190	4368.9	1.21 (1.02 - 1.42)
ACE inhibitor			
Pre-exposure period	1998	7636.7	1.00
Day 1 - 21 of first episode	29	85.3	1.27 (0.88 - 1.84)
Day 22 - end of first episode	561	1943.0	1.15 (0.99 - 1.33)
Between episodes	315	1267.5	1.02 (0.84 - 1.23)
Day 1 - 21 of subsequent episode	127	492.9	1.07 (0.86 - 1.34)
Day 22 - end of subsequent episode	1207	4274.5	1.16 (1.00 - 1.35)
Angiotensin-II receptor antagonist			
Pre-exposure period	663	2534.9	1.00
Day 1 - 21 of first episode	9	36.7	0.89 (0.46 - 1.73)
Day 22 - end of first episode	237	860.4	1.00 (0.80 - 1.26)
Between episodes	64	311.6	0.67 (0.48 - 0.96)
Day 1 - 21 of subsequent episode	42	180.6	0.80 (0.55 - 1.17)
Day 22 - end of subsequent episode	367	1323.5	0.96 (0.75 - 1.23)
Calcium channel blocker			
Pre-exposure period	1776	6543.0	1.00
Day 1 - 21 of first episode	9	62.1	0.53 (0.27 - 1.02)
Day 22 - end of first episode	372	1339.9	0.98 (0.83 - 1.17)
Between episodes	403	1675.2	0.89 (0.75 - 1.08)
Day 1 - 21 of subsequent episode	95	489.0	0.74 (0.58 - 0.95)
Day 22 - end of subsequent episode	1216	4311.7	1.08 (0.93 - 1.27)

For exposure to beta blockers, the incidence of first falls for the first 3 weeks of exposure was not significantly different to unexposed periods (IRR 1.13, 0.94 -1.36). For Day 22 onwards, the incidence rate was higher than in unexposed periods (IRR 1.16, 1.04 – 1.30). Having disaggregated first and

subsequent episodes, the rate ratio during the first 3 weeks of the very first episode of exposure was higher than in the baseline pre-exposed period (IRR 1.64,1.06 – 2.56). The incidence of falls remained increased, though with a smaller size of effect, for Day 22 until the end of first episode (IRR 1.23, 1.02 – 1.48) and in subsequent episodes from Day 22 to the end of the end of episode (IRR 1.21, 1.02 - 1.42).

Amongst the other classes of antihypertensive, the rate ratio for calcium channel blockers for the first 3 weeks of exposure was lower than the baseline period (IRR 0.75, 0.60 – 0.92), but this effect disappeared in the subsequent periods. For ACE Inhibitors there was an increased incidence rate for the period 22 days onward (IRR 1.15, 1.04 – 1.28) but not in the first 3 weeks of exposure. For Angiotensin Inhibitors none of the periods had an incidence rate that was significantly different to the baseline period.

Two further analyses were undertaken to test for a breach of the assumption underpinning the method: that fall events are independent of exposure to prescribing of antihypertensive medication. As described in the Methods chapter, the first analysis tests for the possibility that the incidence rate ratio for a fall in periods following exposure is overstated, as a result of a relative "depletion" of fall events in the period leading up to exposure. It achieved this by including a pre-exposure period to identify whether this would significantly impact the estimate of the incidence rate ratio in the period following exposure. In none of the subgroups of antihypertensive medications did the inclusion of the pre-exposure period impact the rate ratio by more than 4% (see Table 6-5).

The second analysis to test for possible dependence between a fall event and subsequent mortality (and therefore with subsequent exposure) involved repeating the standard analysis for all cases apart from those who died following a fall. This resulted in only small changes in the estimated size of the effect (see Table 6-5 below). This was interpreted as there being only weak evidence for a breach of the assumption regarding independence of a

prior fall and the probability of subsequent exposure, and that the effect of any bias related to mortality following a fall is small.

Table 6-5 Sensitivity analyses to test dependence between fall and probability of subsequent exposure to antihypertensive in THIN 2003-6

	Including a 30 day pre-exposure period			*Excluding cases who died within 90 days of a fall*		
Period of exposure	*First falls recorded*	*Follow-up (Pyrs)*	*Incidence rate ratio (95% confidence intervals)*	*First falls recorded*	*Follow-up (Pyrs)*	*Incidence rate ratio (95% confidence intervals)*
Thiazide						
Unexposed periods	498	1810.6	1.00	373	1394.8	1.00
30 day period* prior to any episode	36	121.1	1.13 (0.78 - 1.64)			-
Day 1 - 21 of episode	62	144.6	1.68 (1.22 - 2.29)	41	100.3	1.57 (1.08 - 2.27)
Day 22 - end of episode	522	1708.9	1.14 (0.92 - 1.43)	336	1120.0	1.12 (0.88 - 1.44)
Beta blocker						
Unexposed periods	2016	7662.1	1.00	1742	6797.5	1.00
30 day period* prior to any episode	118	470.6	1.08 (0.88 - 1.33)			-
Day 1 - 21 of episode	156	589.0	1.15 (0.95 - 1.39)	128	5081.1	1.09 (0.89 - 1.34)
Day 22 - end of episode	1565	5676.7	1.18 (1.05 - 1.34)	1301	4818.2	1.16 (1.02 - 1.31)
ACE inhibitor						
Unexposed periods	2192	8428.8	1.00	1921	7530.7	1.00
30 day period* prior to any episode	121	475.4	1.03 (0.85 - 1.26)			-
Day 1 - 21 of episode	156	578.2	1.11 (0.93 - 1.34)	129	486.3	1.09 (0.89 - 1.32)
Day 22 - end of episode	1768	6217.5	1.16 (1.04 - 1.30)	1389	5053.0	1.11 (0.99 - 1.25)
Angiotensin-II receptor antagonist						
Unexposed periods	688	2667.1	1.00	650	2543.4	1.00
30 day period* prior to any episode	39	177.8	0.83 (0.58 - 1.17)			-
Day 1 - 21 of episode	51	217.3	0.89 (0.64 - 1.22)	45	192.9	0.88 (0.63 - 1.22)
Day 22 - end of episode	604	2185.6	1.05 (0.87 - 1.26)	515	1916.6	1.00 (0.83 - 1.21)
Calcium channel blocker						
Unexposed periods	2057	7766.4	1.00	1830	7066.6	1.00
30 day period* prior to any episode	122	448.9	1.09 (0.89 - 1.33)			-
Day 1 - 21 of episode	104	551.2	0.76 (0.61 - 0.94)	89	22.1	0.76 (0.61 - 0.96)
Day 22 - end of episode	1588	5654.5	1.12 (1.00 - 1.26)	1269	4667.9	1.07 (0.95 - 1.21)

* may be less than 30 days for episodes separated by short intervals

Based on the case control analysis which found that the association with first falls is confounded by prescribing of other antihypertensives, further case series analyses were performed to assess possible confounding by any one of the antihypertensives. The approach to this involved adding in turn each of the antihypertensives for which a statistically significant association had been found in the earlier analysis. In none of the analyses did the incorporation of a confounder result in anything more than tiny changes to the estimates of relative incidence.

6.3 Discussion

6.3.1 Findings & interpretation

In this large case-control study of older people using prospectively collected exposure data, the risk of first fall for people ever-prescribed thiazides was about 25% higher than for those never prescribed. This effect related to current prescribing, and was stronger in the 3 weeks after the first prescription in which period the odds ratio of a first fall was about 5. Based on the prevalence of current thiazide prescribing in this population during the study period, the relative risk corresponds to a population attributable risk proportion in the region of 1%. Case series analysis also showed that the incidence risk ratio for this period is 2.80, and this suggests that the effect observed in the case-control study is real but may have been amplified by other differences between cases and controls.

For beta blockers we found a small protective effect which related to current but not previous prescriptions. However, in case series analysis there was a weakly positive effect for beta blockers, which is evidence that the weak protective effect of the case control study arose due to confounding (or chance) rather than the real effect of beta blockers.

The case control analysis found an increased risk of first fall for people ever prescribed ACE inhibitors, but this increase related equally to those who had discontinued prescriptions as those currently prescribed. There was weak evidence that the risk is higher around the third and fourth week after onset of prescribing. On their own, these findings do not suggest that ACE inhibitors cause falls, but that the group given ACE inhibitors were at higher underlying risk of falls. The case series analysis provides weak, equivocal evidence on this point: there was no increase in incidence rate for the onset of prescribing, but a slightly increased rate beyond 22 days.

In case series analysis, there was a lower incidence of first falls in the first 3 weeks of exposure to calcium channel blockers, which closely reflects the non-significant decrease in risk of first fall within the first 3 weeks of first

prescription observed in the case control study. It is not possible to say whether this is a real effect of calcium channel blockers or by what mechanism such an effect might be produced.

6.3.2 Strengths & weaknesses

The main strength of the studies is the large number of cases, the completeness of the exposure data for prescribing, the fact that the data were collected prospectively which means that recall is not a source of bias, and the assessment of residual confounding by applying complementary methods to a single dataset. Medications were differentiated according to standard classifications. Previous studies have demonstrated the validity of the data in THIN for pharmacoepidemiological research[167 168 173].

In the case control study, co-morbidity was controlled for in two ways. Firstly, possible confounding by a number of conditions and medications associated with falls was checked for and, as a result, adjustment was incorporated for diagnoses of CHD and for Charlson index which reduced the odds ratios in a way consistent with expectations. It should be noted that Charlson is designed as an index of one year mortality based on patients in a hospital setting, and may not correlate fully with comorbidity in a general population setting. Secondly, to explore the extent to which the effect was attributable to characteristics of the patients rather than the prescribing, the risk for people currently and previously prescribed was compared.

The possibility of residual confounding which could account for some or all of the positive effect observed for thiazides is acknowledged. Nevertheless by applying the self-controlled case series analysis to the same group of cases, a way is provided of assessing the extent to which the findings of the case control study may have been subject to residual confounding by factors which remain constant within individuals. Application of the case series method, which is not subject to residual confounding by factors which remain constant within individuals, showed that in the first weeks of thiazide prescribing there is a positive association with falls.

The main potential weaknesses of the case control study is the validity of the recording of fall events, and the possibility of non-compliance to medications. Regarding the recording of fall events, the earlier study of incidence and mortality suggested that falls recorded in primary care are a subset of the falls self-reported in surveys[196]. This raises the possibility of differential ascertainment for patients receiving antihypertensive medication. Such a bias, if it existed, would tend to increase the odds ratios. However, the fact that case control analysis found a mixture of positive, negative and non-significant effects between medication classes suggests that the effect of any ascertainment bias is probably small overall.

The extent of any non-compliance to medication cannot be assessed reliably. But it is noted that non-compliance would result in underestimation of a true effect in the case control study.

A limitation of the case series method relates to the requirement that events should not influence the probability of subsequent exposures. Whilst thiazide prescribing itself may be regarded as relatively safe (and therefore unlikely to be influenced by a fall), it could be an element in polypharmacy, which may be a risk factor for falls. As such, subsequent prescribing of thiazides may be influenced by a fall. Therefore this was tested for in a sensitivity analysis which included a 30 day observation period immediately prior to the exposure. This had little impact on the rate ratios, suggesting that any potential exaggeration of the incidence rate ratio in the period after exposure (due to there being fewer fall events in the period leading up to exposure) was minimal. In other words there was only weak evidence that exposure status is influenced by a prior recorded fall.

The degree to which risk of exposure is influenced by falls-related mortality was also assessed, by excluding participants who died within 90 days of the fall. This resulted in little change to the risk ratios, indicating that the effect on any bias resulting from mortality subsequent to a fall is small. The study data also satisfy other assumptions underlying the method including: the

requirement that the risk of first fall in the observation period be small, and that the timing of first fall with respect to age is variable.

The potential weaknesses of the case series analysis relate to uncertainty about what can be reliably inferred from prescribing records about actual exposure status. There are two possible aspects to this uncertainty. Each of them amounts to a misclassification of exposure period. Since either of these two misclassifications is non-differential, the most likely result would be a dilution of the true effect.

The first possible cause of misclassification relates to the assumption, based on the analysis of intervals between prescriptions, that prescriptions separated by not more than 60 days constitute a single continuous period of prescribing ending 60 days after the final prescription. The issue here is whether the prescribing history represents a complete record of what was actually prescribed. The rationale for this assumption is described in the Methods chapter, which also shows that relatively few prescriptions are recorded at intervals of more than 60 days. Therefore, it is likely that any error arising (from misclassifying intervals of more than 60 days as gaps in prescribing) would have a small diluting effect on the estimated size of the effect.

Secondly it is also assumed that there is a high level of patient compliance with recorded prescriptions. The issue here is whether the prescribing history represents a complete record of the medication received by the patient. It is noted that this second assumption is more likely to have been breached[208]. Once again any resulting misclassification is likely to be non-differential and therefore likely to result in a dilution of the true effect.

Finally, applying these complementary analyses to assess a large number of possible associations necessarily involves making many estimates of effect. One implication of this is that it increases the likelihood that one of the observed effects does not reflect a real difference.

6.3.3 *Other studies*

An association between antihypertensives and falls via orthostatic hypotension has been long-suspected[153] but the relationship with drug-related orthostatic hypotension is not clear[154 155]. Leipzig et al's[129] review of medications and falls included observational studies of antihypertensives and other cardiovascular medications. The meta-analysis found weak associations with one or more falls for digoxin (OR 1.22), type 1A anti-arrhythmics (OR 1.59) and use of any diuretic (OR 1.08). Since 1999, studies have been inconsistent in their findings with regard to antihypertensives and risk of falls[139 140], with many providing only an aggregated classification of antihypertensives[128 137]. Setting out to test the hypothesis that associations between medications and falls are confounded by medical conditions, Lee et al[141] found no association with falls for most cardiovascular and non-cardiovascular medication groups (including psychotropics), except for nitrates.

The association observed in this study between first recorded fall and prescribing of thiazides is consistent with the hypothesis that this class of antihypertensive medication is an independent risk factor for falls and that the risk is greatest in the first three weeks after the start of prescribing. The mechanism by which this occurs is not clear. However the literature indicates an initial hypotensive response to thiazide diuretics in the first few weeks of treatment, mediated by a reduction in plasma volume and cardiac output, and that these return to near baseline levels over several weeks with the longer term reduction in blood pressure driven by different underlying mechanisms[209 210]. This may explain the change in risk with time since initiation of treatment. Other possible explanations for the decrease in risk in consecutive weeks include the development of biological tolerance or coping mechanisms, or a degree of survival bias in which patients reporting problems are taken off the medication in the first three weeks, leaving a group of cases who are less susceptible to further falls.

The size of the observed association with thiazides is small over the long term but represents an almost three-fold risk during the first three weeks of first exposure. The prevalence of thiazide prescribing in older people (9% amongst first fallers[211]), means that the public health impact could be significant. The HYVET (Hypertension in the Very Elderly) trial demonstrated the benefit of hypertensive treatment, based on a diuretic with or without an additional ACE inhibitor, in reducing the risk of death from stroke, death from any cause and heart failure in the very elderly. This study is a further reminder to clinicians initiating prescribing of thiazides in older people to be alert to the possibility of an increased risk of falls in the first three weeks of prescribing.

It is possible that the weakly protective effect of beta blockers observed in the case control analysis could be causal. It has been suggested that if this reflects a true effect, it may be explained by a possible protective effect for vasovagal syncope, in which the beta blocker attenuates the raised levels of catecholamine preceding syncope[212] but it is not clear what this mechanism could be. However, the fact that this effect was not observed in the complementary case series analysis suggests that the protective effect of beta blockers observed in the case control study was most likely to have been due to chance.

With regard to the lower incidence of first falls in the first 3 weeks of exposure to calcium channel blockers, it is not possible to say whether this is a real effect of calcium channel blockers or by what mechanism such an effect might be produced but it is noted that calcium channel blockers used in the treatment of hypertension is commonly associated with headache, dizziness and oedema[191]. Furthermore, following their introduction, the fear amongst doctors that they would increase the risk of falls was greater than for other classes of antihypertensive and could have led to stronger warnings about their possible effect than were given for other classes of antihypertensive. It is possible that the onset or anticipation of these side effects results in greater caution or less mobility on the part of the patient, leading to a lower incidence of recorded falls in the first few weeks of medication.

More generally, whilst these findings provide evidence to support the warnings of an earlier meta-analysis[129] and a subsequent systematic review[125] that the results of individual studies are subject to confounding, they also demonstrate how the complementary application of the case series method can be used to assess the extent of possible confounding in classic case control analyses.

6.4 Implications

These complementary studies provide evidence that thiazides are associated with an increased risk of first falls and that this persists for at least the first three weeks of exposure, which suggests that this class of medication may not be as safe as previously thought. There is weaker evidence for a protective effect of calcium channel blockers in the first three weeks of exposure. Considering the complementary analyses together, there was no increase in falls risk for other classes of antihypertensive medication.

These studies also demonstrate that the case series method provides an effective way to assess the extent of residual confounding in case-control studies whose data include longitudinal information about exposure status and outcome.

7 Other medications and falls

This chapter addresses the final project aim which is:

- to identify any other classes or sub-classes of medication prescribed in primary care whose apparent falls risk warrants investigation in future studies

7.1 Introduction

A range of medications are associated with an increased risk of falls in older people[122 128 129]. For some of these classes (e.g. NSAID) the mechanism by which they may predispose older people to fall "is far from clear"[121]. Therefore in view of the lack of systematic studies of the falls profile of medications, a further hypothesis-generating study was performed to identify other classes of medication prescribed to older people whose fall profile may warrant further investigation in subsequent studies.

The methods for this are set out in detail in the chapter relating to the methods for the aetiological studies. This study uses the same nested case-control approach on the same dataset, using the same definitions of cases and controls, matching ratio, and classification of exposure according to the elapsed time between the index event and final preceding prescription. However, since the purpose of the study described in this chapter is simply to highlight subgroups of medication whose risk profile may warrant further study (not to draw conclusions about independent effects), it makes no attempt to adjust for confounders other than age and sex (used for matching), nor to estimate the extent of any residual confounding or other bias through use of case series analysis.

Classes of medication in the British National Formulary (BNF) which are not prescribed for older people by general practitioners were excluded from the analysis, along with medications for which the number of cases with an exposure ever was fewer than 10. Classes of medication included in the meta-analyses reviewed in earlier chapters[122 128 129] were also excluded.

7.2 Results

As described in previous chapters, 9682 people were identified who were aged >60 years and who experienced a first fall, and 52 100 matched controls. The mean age of cases was 77.5 years, and 76.4 years for controls. Thirty two percent of cases and controls were male. Their profile is described in Table 5-1.

Estimates of the odds ratios for first fall for ever (previous /recent /current) /never prescribing are summarised and presented in tables, by BNF chapter. Medication classes corresponding to treatment of the cardiovascular and central nervous systems, and analgesics were excluded for the reasons described in the Methods, along with obstetric-related medications for which there were fewer than 10 cases recorded with exposures. In all instances, the odds ratios are adjusted for age and sex, but not for other confounders.

Table 7-1 Association between first recorded fall and prescribing of medications for the gastro-intestinal system, THIN 2003-6

Exposure	*Cases n=9682*	*Controls n=52100*	*Odds ratio (95% confidence intervals) Unadjusted*
Dyspepsia & gastro-oesophageal disease			
Never prescribed	6721 (69%)	39681 (76%)	1.00
Ever prescribed	2961 (31%)	12419 (24%)	1.42 (1.36 - 1.50)
Previously prescribed	2187 (23%)	9325 (18%)	1.40 (1.33 - 1.48)
Recently prescribed	195 (2%)	822 (2%)	1.42 (1.21 - 1.67)
Currently prescribed	579 (6%)	2272 (4%)	1.51 (1.37 - 1.69)
Antispasmodics & gut motility			
Never prescribed	7319 (76%)	42206 (81%)	1.00
Ever prescribed	2363 (24%)	9894 (19%)	1.43 (1.35 - 1.50)
Previously prescribed	1904 (20%)	8314 (16%)	1.37 (1.29 - 1.45)
Recently prescribed	109 (1%)	433 (1%)	1.51 (1.22 - 1.86)
Currently prescribed	350 (4%)	1147 (2%)	1.79 (1.58 - 2.03)
Ulcer healing			
Never prescribed	5380 (56%)	33480 (64%)	1.00
Ever prescribed	4302 (44%)	18620 (36%)	1.46 (1.39 - 1.52)
Previously prescribed	1941 (20%)	9562 (18%)	1.29 (1.22 - 1.36)
Recently prescribed	251 (3%)	1151 (2%)	1.38 (1.20 - 1.59)
Currently prescribed	2110 (22%)	7907 (15%)	1.67 (1.58 - 1.77)
Acute diarrhoea			
Never prescribed	7560 (78%)	44453 (85%)	1.00
Ever prescribed	2122 (22%)	7647 (15%)	1.67 (1.58 - 1.77)
Previously prescribed	1641 (17%)	6401 (12%)	1.54 (1.45 - 1.64)
Recently prescribed	116 (1%)	356 (1%)	1.98 (1.59 - 2.45)
Currently prescribed	365 (4%)	890 (2%)	2.50 (2.21 - 2.84)
Chronic bowel disorders			
Never prescribed	9472 (98%)	51233 (98%)	1.00
Ever prescribed	210 (2%)	867 (2%)	1.35 (1.16 - 1.58)
Previously prescribed	130 (1%)	504 (1%)	1.44 (1.18 - 1.75)
Recently prescribed	11 (0%)	49 (0%)	1.33 (0.69 - 2.56)
Currently prescribed	69 (1%)	314 (1%)	1.22 (0.94 - 1.59)

Table 7-1 (continued)

Laxatives			
Never prescribed	5632 (58%)	37178 (71%)	1.00
Ever prescribed	4050 (42%)	14922 (29%)	1.76 (1.68 - 1.84)
Previously prescribed	2255 (23%)	9226 (18%)	1.60 (1.52 - 1.70)
Recently prescribed	364 (4%)	1204 (2%)	1.97 (1.74 - 2.23)
Currently prescribed	1431 (15%)	4492 (9%)	2.02 (1.89 - 2.16)
Anal & rectal preparations			
Never prescribed	8482 (88%)	46770 (90%)	1.00
Ever prescribed	1200 (12%)	5330 (10%)	1.27 (1.19 - 1.36)
Previously prescribed	1047 (11%)	4697 (9%)	1.26 (1.17 - 1.35)
Recently prescribed	59 (1%)	233 (0%)	1.44 (1.08 - 1.92)
Currently prescribed	94 (1%)	400 (1%)	1.32 (1.05 - 1.65)
Intestinal secretions			
Never prescribed	9610 (99%)	51807 (99%)	1.00
Ever prescribed	72 (1%)	293 (1%)	1.38 (1.06 - 1.79)
Previously prescribed	40 (0%)	185 (0%)	1.26 (0.89 - 1.78)
Recently prescribed	2 (0%)	18 (0%)	0.66 (0.15 - 2.85)
Currently prescribed	30 (0%)	90 (0%)	1.73 (1.14 - 2.64)

With the exception of medications for chronic bowel disorders and intestinal secretions, between one tenth and one third of people aged over 60 years have been prescribed subclasses of gastro-intestinal medication in primary care. In each subclass, there is a significant positive association between first fall and ever-prescribed with odds ratios ranging from 1.27 (1.19 - 1.36) for anal and rectal preparations to 1.76 (1.68 - 1.84) for laxatives. The point estimates of odds ratios for currently prescribed are higher than for recently and previously prescribed for all subclasses, with the exception of medications for chronic bowel disorders.

The highest unadjusted odds ratios for current prescribing were found in medications for acute diarrhoea OR 2.50 (2.21 - 2.84), laxatives OR 2.02 (1.89 - 2.16), antispasmodics OR 1.79 (1.58 - 2.03) and intestinal secretions OR 1.73 (1.14 - 2.64).

Table 7-2 Association between recorded first fall and prescribing of medications in primary care for the respiratory system

Exposure	*Cases n=9682*	*Controls n=52100*	*Odds ratio (95% confidence intervals) Unadjusted*
Bronchodilators			
Never prescribed	7060 (73%)	40945 (79%)	1.00
Ever prescribed	2622 (27%)	11155 (21%)	1.39 (1.32 - 1.46)
Previously prescribed	1319 (14%)	5795 (11%)	1.35 (1.26 - 1.44)
Recently prescribed	221 (2%)	883 (2%)	1.51 (1.30 - 1.75)
Currently prescribed	1082 (11%)	4477 (9%)	1.42 (1.32 - 1.52)
Corticosteroids			
Never prescribed	8068 (83%)	45323 (87%)	1.00
Ever prescribed	1614 (17%)	6777 (13%)	1.37 (1.29 - 1.45)
Previously prescribed	681 (7%)	2707 (5%)	1.45 (1.33 - 1.59)
Recently prescribed	168 (2%)	796 (2%)	1.23 (1.04 - 1.46)
Currently prescribed	765 (8%)	3274 (6%)	1.33 (1.23 - 1.45)
Cromoglicate, related, & leukotriene receptor antagonists			
Never prescribed	9570 (99%)	51645 (99%)	1.00
Ever prescribed	112 (1%)	455 (1%)	1.40 (1.14 - 1.73)
Previously prescribed	86 (1%)	310 (1%)	1.59 (1.25 - 2.02)
Recently prescribed	2 (0%)	21 (0%)	0.54 (0.13 - 2.32)
Currently prescribed	24 (0%)	124 (0%)	1.08 (0.69 - 1.68)
Antihistmaines, hyposensitations, & allergic emergencies			
Never prescribed	6780 (70%)	39267 (75%)	1.00
Ever prescribed	2902 (30%)	12833 (25%)	1.35 (1.28 - 1.41)
Previously prescribed	2187 (23%)	9325 (18%)	1.40 (1.33 - 1.48)
Recently prescribed	195 (2%)	822 (2%)	1.42 (1.21 - 1.67)
Currently prescribed	579 (6%)	2272 (4%)	1.51 (1.37 - 1.69)
Oxygen			
Never prescribed	9551 (99%)	51741 (99%)	1.00
Ever prescribed	131 (1%)	359 (1%)	1.94 (1.58 - 2.38)
Previously prescribed	53 (1%)	187 (0%)	1.45 (1.06 - 1.98)
Recently prescribed	13 (0%)	42 (0%)	1.84 (0.99 - 3.42)
Currently prescribed	65 (1%)	130 (0%)	2.71 (2.00 - 3.68)

Table 7-2 (continued)

Mucolytics						
Never prescribed	9625	(99%)	51926	(100%)	1.00	
Ever prescribed	57	(1%)	174	(0%)	1.86	(1.37 - 2.52)
Previously prescribed	28	(0%)	90	(0%)	1.81	(1.18 - 2.77)
Recently prescribed	6	(0%)	18	(0%)	1.81	(0.71 - 4.65)
Currently prescribed	23	(0%)	66	(0%)	1.94	(1.20 - 3.15)
Aromatic inhalations						
Never prescribed	9596	(99%)	51769	(99%)	1.00	
Ever prescribed	86	(1%)	331	(1%)	1.45	(1.13 - 1.86)
Previously prescribed	84	(1%)	319	(1%)	1.47	(1.14 - 1.89)
Recently prescribed	2	(0%)	5	(0%)	2.40	(0.47 - 12.37)
Currently prescribed	0	(0%)	7	(0%)		(-)
Cough preparations						
Never prescribed	7769	(80%)	44369	(85%)	1.00	
Ever prescribed	1913	(20%)	7731	(15%)	1.46	(1.37 - 1.55)
Previously prescribed	1792	(19%)	7245	(14%)	1.46	(1.37 - 1.55)
Recently prescribed	39	(0%)	187	(0%)	1.16	(0.82 2.80)
Currently prescribed	82	(1%)	299	(1%)	1.59	(1.24 - 2.04)
Systemic nasal decongestants						
Never prescribed	8784	(91%)	48061	(92%)	1.00	
Ever prescribed	898	(9%)	4039	(8%)	1.28	(1.18 - 1.39)
Previously prescribed	867	(9%)	3915	(8%)	1.28	(1.18 - 1.39)
Recently prescribed	15	(0%)	55	(0%)	1.67	(0.93 - 2.97)
Currently prescribed	16	(0%)	69	(0%)	1.38	(0.80 - 2.39)

For some subclasses of respiratory medication, more than a quarter of people aged over 60 years have been prescribed them in primary care, e.g. bronchodilators, antihistamines and hyposensitisation. In all subclasses, there is a positive association between first fall and ever-prescribed with odds ratios ranging from 1.28 (1.18 - 1.39) for systemic nasal decongestants to 1.94 (1.58 - 2.38) for oxygen.

With the exception of oxygen, the point estimates of odds ratios for currently prescribed are similar to those for ever prescribed. The highest odds ratios for current prescribing were found in medications for oxygen 2.71 (2.00 - 3.68), mucolytics 1.94 (1.20 - 3.15) and cough preparations 1.59 (1.24 - 2.04). For the relatively large number of older people prescribed bronchodilators, corticosteroids, antihistamines and hyposensitisations, the

odds of first fall is between one third and one half greater compared to the odds for their matched controls.

Table 7-3 Association between recorded first fall and prescribing of medications in primary care for infections, THIN 2003-6

Exposure	*Cases n=9682*	*Controls n=52100*	*Odds ratio (95% confidence intervals) Unadjusted*
Antibacterials			
Never prescribed	1415 (15%)	11710 (22%)	1.00
Ever prescribed	8267 (85%)	40390 (78%)	1.79 (1.68 - 1.91)
Previously prescribed	5727 (59%)	31444 (60%)	1.60 (1.50 - 1.70)
Recently prescribed	789 (8%)	3449 (7%)	1.96 (1.78 - 2.16)
Currently prescribed	1751 (18%)	5497 (11%)	2.75 (2.54 - 2.98)
Antifungals			
Never prescribed	8579 (89%)	47526 (91%)	1.00
Ever prescribed	1103 (11%)	4574 (9%)	1.38 (1.29 - 1.48)
Previously prescribed	993 (10%)	4208 (8%)	1.35 (1.25 - 1.46)
Recently prescribed	36 (0%)	136 (0%)	1.49 (1.03 - 2.16)
Currently prescribed	74 (1%)	230 (0%)	1.86 (1.43 - 2.43)
Antivirals			
Never prescribed	9106 (94%)	49551 (95%)	1.00
Ever prescribed	576 (6%)	2549 (5%)	1.23 (1.12 - 1.35)
Previously prescribed	515 (5%)	2401 (5%)	1.16 (1.05 - 1.28)
Recently prescribed	20 (0%)	70 (0%)	1.58 (0.96 - 2.61)
Currently prescribed	41 (0%)	78 (0%)	3.03 (2.07 - 4.42)
Antiprotozoals			
Never prescribed	7403 (76%)	42743 (82%)	1.00
Ever prescribed	2279 (24%)	9357 (18%)	1.43 (1.35 - 1.51)
Previously prescribed	1743 (18%)	7570 (15%)	1.36 (1.28 - 1.44)
Recently prescribed	105 (1%)	412 (1%)	1.45 (1.17 - 1.80)
Currently prescribed	431 (4%)	1375 (3%)	1.80 (1.61 - 2.02)
Anthelmintics			
Never prescribed	9636 (100%)	51908 (100%)	1.00
Ever prescribed	46 (0%)	192 (0%)	1.37 (0.99 - 1.90)
Previously prescribed	41 (0%)	188 (0%)	1.24 (0.88 - 1.75)
Recently prescribed	4 (0%)	1 (0%)	24.00 (2.68 - 214.72)
Currently prescribed	1 (0%)	3 (0%)	2.00 (0.21 - 19.23)

Amongst the subclasses of medication for infections (see Table 7-3), the prevalence of ever prescribing is highest in antibacterials (76%), then antiprotozoals (19%).

The odds ratios of first fall for ever prescribed ranges from not significantly different to 1 for antithelmintics through to antibacterials for which the odds ratio is 1.79 (1.68 - 1.91).

The odds ratio of current prescribing for antibacterials is 2.75 (2.54 - 2.98), and significantly higher than the odds ratio for recent or previous prescribing. For antivirals, this gradient is even more pronounced: the odds ratio of current prescribing is 3.03 (2.07 - 4.42) compared to 1.16 (1.05 -1.28) for previous prescribing. For antifungals and antiprotozoals, the estimates for current prescribing are 1.86 (1.43 - 2.43) and 1.80 (1.61 - 2.02) respectively.

Table 7-4 Association between recorded first fall and prescribing of medications in primary care for the endocrine system, THIN 2003-6

Exposure	*Cases n=9682*	*Controls n=52100*	*Odds ratio (95% confidence intervals) Unadjusted*
Diabetes			
Never prescribed	8496 (88%)	47477 (91%)	1.00
Ever prescribed	1186 (12%)	4623 (9%)	1.47 (1.37 - 1.58)
Previously prescribed	149 (2%)	693 (1%)	1.20 (1.00 - 1.44)
Recently prescribed	56 (1%)	291 (1%)	1.09 (0.82 - 1.46)
Currently prescribed	981 (10%)	3639 (7%)	1.55 (1.44 - 1.67)
Thyroid & antithyroid			
Never prescribed	8577 (89%)	47152 (91%)	1.00
Ever prescribed	1105 (11%)	4948 (9%)	1.23 (1.15 - 1.32)
Previously prescribed	84 (1%)	430 (1%)	1.06 (0.84 - 1.35)
Recently prescribed	94 (1%)	459 (1%)	1.16 (0.92 - 1.45)
Currently prescribed	927 (10%)	4059 (8%)	1.26 (1.16 - 1.36)
Corticosteroids			
Never prescribed	7192 (74%)	41993 (81%)	1.00
Ever prescribed	2490 (26%)	10167 (20%)	1.46 (1.39 - 1.54)
Previously prescribed	1784 (18%)	7967 (15%)	1.33 (1.26 - 1.41)
Recently prescribed	147 (2%)	561 (1%)	1.56 (1.30 - 1.88)
Currently prescribed	559 (6%)	1639 (3%)	2.03 (1.84 - 2.25)
Sex hormones			
Never prescribed	8357 (86%)	45547 (87%)	1.00
Ever prescribed	1325 (14%)	6553 (13%)	1.24 (1.15 - 1.33)
Previously prescribed	997 (10%)	4998 (10%)	1.24 (1.14 - 1.35)
Recently prescribed	68 (1%)	423 (1%)	0.98 (0.75 - 1.28)
Currently prescribed	260 (3%)	1132 (2%)	1.31 (1.14 - 1.51)
Hypothalmic & pituitary hormones, & anti-oestrogens			
Never prescribed	9416 (97%)	50839 (98%)	1.00
Ever prescribed	266 (3%)	1261 (2%)	1.13 (0.98 - 1.29)
Previously prescribed	166 (2%)	804 (2%)	1.11 (0.93 - 1.32)
Recently prescribed	11 (0%)	52 (0%)	1.16 (0.60 - 2.22)
Currently prescribed	89 (1%)	405 (1%)	1.15 (0.91 - 1.46)

Table 7-4 (continued)

Bone metabolism					
Never prescribed	8681	(90%)	48389	(93%)	1.00
Ever prescribed	1001	(10%)	3711	(7%)	1.52 (1.41 - 1.64)
Previously prescribed	316	(3%)	1294	(2%)	1.35 (1.19 - 1.54)
Recently prescribed	82	(1%)	347	(1%)	1.38 (1.08 - 1.75)
Currently prescribed	603	(6%)	2070	(4%)	1.65 (1.50 - 1.82)
Other endocrine					
Never prescribed	9457	(98%)	51379	(99%)	1.00
Ever prescribed	225	(2%)	721	(1%)	1.79 (1.53 - 2.09)
Previously prescribed	168	(2%)	587	(1%)	1.66 (1.40 - 1.99)
Recently prescribed	10	(0%)	35	(0%)	1.59 (0.78 - 3.24)
Currently prescribed	47	(0%)	99	(0%)	2.58 (1.81 - 3.68)

Approximately 10% of study participants have been prescribed medications for diabetes, thyroid conditions, and bone metabolism (see Table 7-3). Approximately 13% have ever been prescribed sex hormones, and more than 20% have been prescribed corticosteroids. The prevalence of ever prescribing of other endocrine, and of hypothalamic and pituitary hormones is approximately 1-2%.

The odds ratios of first fall for ever prescribed ranges from not significantly different to 1 for hypothalamic and pituitary hormones through to 1.79 (1.53 - 2.09) for other endocrine medications.

The odds ratio of current prescribing is highest for other endocrine medications OR 2.58 (1.81 - 3.68), and then for corticosteroids OR 2.03 (1.84 - 2.25). With the exception of medications for hypothalamic and pituitary hormones, odds ratios among other subclasses are significant, ranging from OR 1.31 (1.14 - 1.51) for sex hormones to 1.65 (1.50 - 1.82) for medications related to bone metabolism.

Table 7-5 Association between recorded first fall and prescribing of medications in primary care for gynaecology and urinary tract infection, THIN 2003-6

Exposure	*Cases n=9682*	*Controls n=52100*	*Odds ratio (95% confidence intervals) Unadjusted*
Vaginal & vulval conditions			
Never prescribed	8187 (85%)	45427 (87%)	1.00
Ever prescribed	1495 (15%)	6673 (13%)	1.31 (1.23 - 1.40)
Previously prescribed	1334 (14%)	5964 (11%)	1.31 (1.23 - 1.41)
Recently prescribed	73 (1%)	277 (1%)	1.52 (1.17 - 1.98)
Currently prescribed	88 (1%)	432 (1%)	1.19 (0.94 - 1.51)
Genito-urinary			
Never prescribed	7542 (78%)	42885 (82%)	1.00
Ever prescribed	2140 (22%)	9215 (18%)	1.34 (1.27 - 1.41)
Previously prescribed	1162 (12%)	4850 (9%)	1.38 (1.29 - 1.48)
Recently prescribed	115 (1%)	501 (1%)	1.33 (1.08 - 1.63)
Currently prescribed	863 (9%)	3864 (7%)	1.29 (1.19 - 1.39)

Almost one fifth of older people have ever been prescribed medications related to the genito-urinary system, and more than one tenth of older women have ever been prescribed medication for vaginal and vulval conditions (see Table 7-5).

For people currently prescribed medication for the genitourinary system, the odds ratio for first fall is 1.29 (1.19 - 1.39), but this is not significantly different to the odds ratio for people recently or previously prescribed. The odds ratio for first fall among older women currently prescribed for vaginal or vulval conditions is not statistically significant.

Table 7-6 Association between recorded first fall and prescribing of medications in primary care for malignant disease and immunosuppression, THIN 2003-6

Exposure	*Cases n=9682*	*Controls n=52100*	*Odds ratio (95% confidence intervals)*
Cytotoxics			
Never prescribed	9451 (98%)	51112 (98%)	1.00
Ever prescribed	231 (2%)	988 (2%)	1.28 (1.10 - 1.48)
Previously prescribed	149 (2%)	612 (1%)	1.31 (1.09 - 1.57)
Recently prescribed	17 (0%)	78 (0%)	1.23 (0.73 - 2.09)
Currently prescribed	65 (1%)	298 (1%)	1.23 (0.94 - 1.61)
Immune response			
Never prescribed	9615 (99%)	51868 (100%)	1.00
Ever prescribed	67 (1%)	232 (0%)	1.63 (1.24 - 2.15)
Previously prescribed	42 (0%)	140 (0%)	1.71 (1.21 - 2.43)
Recently prescribed	3 (0%)	8 (0%)	2.25 (0.60 - 8.48)
Currently prescribed	22 (0%)	84 (0%)	1.44 (0.89 - 2.31)
Sex hormones & hormone antagonists in malignant disease			
Never prescribed	9192 (95%)	49929 (96%)	1.00
Ever prescribed	490 (5%)	2171 (4%)	1.23 (1.11 - 1.37)
Previously prescribed	226 (2%)	1186 (2%)	1.08 (0.94 - 1.26)
Recently prescribed	35 (0%)	126 (0%)	1.48 (1.01 - 2.16)
Currently prescribed	229 (2%)	859 (2%)	1.39 (1.20 - 1.61)

Compared to other classes of medication, the prevalence of ever prescribing of medications in primary care for malignant disease and immunosuppression is low (see Table 7-6). The prevalence of ever prescribed is highest for sex hormones and hormone antagonists (4%).

The odds ratio of first fall for ever prescribing is highest for medications for immune response OR 1.63 (1.24 - 2.15). However, the odds ratio for current prescribing is not significant. Only in medications related to sex hormones and hormone antagonists is the odds ratio of first fall significant OR 1.39 (1.20 - 1.61).

Table 7-7 Association between first fall and prescribing of medications in primary care for nutrition and blood, THIN 2003-6

Exposure	*Cases n=9682*	*Controls n=52100*	*Odds ratio (95% confidence intervals) Unadjusted*
Aneamias & other blood disorders			
Never prescribed	7567 (78%)	44495 (85%)	1.00
Ever prescribed	2115 (22%)	7605 (15%)	1.59 (1.50 - 1.68)
Previously prescribed	1266 (13%)	4804 (9%)	1.52 (1.42 - 1.62)
Recently prescribed	171 (2%)	551 (1%)	1.79 (1.50 - 2.13)
Currently prescribed	678 (7%)	2250 (4%)	1.70 (1.55 - 1.86)
Fluids & electrolytes			
Never prescribed	9077 (94%)	49856 (96%)	1.00
Ever prescribed	605 (6%)	2244 (4%)	1.45 (1.31 - 1.59)
Previously prescribed	503 (5%)	1908 (4%)	1.41 (1.27 - 1.56)
Recently prescribed	33 (0%)	81 (0%)	2.34 (1.56 - 3.53)
Currently prescribed	69 (1%)	255 (0%)	1.45 (1.11 - 1.90)
Oral nutrition			
Never prescribed	9110 (94%)	50345 (97%)	1.00
Ever prescribed	572 (6%)	1755 (3%)	1.68 (1.52 - 1.86)
Previously prescribed	314 (3%)	1033 (2%)	1.57 (1.38 - 1.80)
Recently prescribed	42 (0%)	146 (0%)	1.48 (1.05 - 2.11)
Currently prescribed	216 (2%)	576 (1%)	1.93 (1.64 - 2.27)
Minerals			
Never prescribed	8086 (84%)	46298 (89%)	1.00
Ever prescribed	1596 (16%)	5802 (11%)	1.58 (1.49 - 1.69)
Previously prescribed	660 (7%)	2625 (5%)	1.46 (1.33 - 1.60)
Recently prescribed	155 (2%)	620 (1%)	1.47 (1.22 - 1.76)
Currently prescribed	781 (8%)	2557 (5%)	1.74 (1.60 - 1.90)
Vitamins			
Never prescribed	7920 (82%)	45916 (88%)	1.00
Ever prescribed	1762 (18%)	6184 (12%)	1.67 (1.57 - 1.77)
Previously prescribed	784 (8%)	3089 (6%)	1.49 (1.37 - 1.63)
Recently prescribed	147 (2%)	530 (1%)	1.66 (1.38 - 2.01)
Currently prescribed	831 (9%)	2565 (5%)	1.87 (1.72 - 2.04)

Table 7-7 (continued)

Bitters & tonics						
Never prescribed	9602	(99%)	51813	(99%)	1.00	
Ever prescribed	80	(1%)	287	(1%)	1.45	(1.12 - 1.89)
Previously prescribed	74	(1%)	274	(1%)	1.40	(1.06 - 1.83)
Recently prescribed	2	(0%)	3	(0%)	3.75	(0.63 - ###)
Currently prescribed	4	(0%)	10	(0%)	2.31	(0.72 - 7.36)
Metabolic disorders						
Never prescribed	9660	(100%)	52020	(100%)	1.00	
Ever prescribed	22	(0%)	80	(0%)	1.57	(0.98 - 2.53)
Previously prescribed	15	(0%)	56	(0%)	1.54	(0.87 - 2.72)
Recently prescribed	1	(0%)	6	(0%)	0.97	(0.12 - 8.09)
Currently prescribed	6	(0%)	18	(0%)	1.89	(0.75 - 4.80)

Amongst the range of medications prescribed in primary care for nutrition and blood (see Table 7-7), approximately 5% of older people are currently prescribed medications for anaemia, minerals and vitamins, and for these subclasses as many as 15% of people have been ever-prescribed. In the other subclasses, the prevalence of prescribing is much lower.

With the exception of medication for metabolic disorders OR 1.57 (0.98 - 2.53), in all other subclasses the odds ratios for ever prescribed reaches statistical significance, ranging from 1.45 (1.31 - 1.59) for fluids and electrolytes through to 1.67 (1.57 - 1.77) for vitamins and 1.68 (1.52 - 1.86) for oral nutrition.

The odds ratio of current prescribing is highest for oral nutrition OR 1.93 (1.64 - 2.27) and vitamins OR 1.87 (1.72 - 2.04) and, in the case of vitamins, this is higher than the odds ratio for people previously prescribed. For minerals, the odds ratio among people currently prescribed is also higher than amongst those previously prescribed: OR 1.74 (1.60 - 1.90) compared to 1.46 (1.33 - 1.60). The point estimate for the odds ratio of first fall among people currently prescribed fluids and electrolytes is lower, OR 1.45 (1.11 - 1.90), than that for people recently prescribed, OR 2.34 (1.56 - 3.53).

Table 7-8 Association between first fall and prescribing in primary care of medication for muskuloskeletal and joint diseases, THIN 2003-6

Exposure	*Cases n=9682*	*Controls n=52100*	*Odds ratio (95% confidence intervals) Unadjusted*
Rheumatic diseases & gout			
Never prescribed	1951 (20%)	15412 (30%)	1.00
Ever prescribed	7731 (80%)	36688 (70%)	1.71 (1.62 - 1.81)
Previously prescribed	3505 (36%)	19667 (38%)	1.45 (1.37 - 1.55)
Recently prescribed	599 (6%)	2631 (5%)	1.85 (1.67 - 2.05)
Currently prescribed	3627 (37%)	14390 (28%)	2.04 (1.92 - 2.17)
Neuromuscular disorders			
Never prescribed	7179 (74%)	42495 (82%)	1.00
Ever prescribed	2503 (26%)	9605 (18%)	1.58 (1.50 - 1.66)
Previously prescribed	1685 (17%)	7005 (13%)	1.46 (1.38 - 1.55)
Recently prescribed	125 (1%)	534 (1%)	1.42 (1.16 - 1.73)
Currently prescribed	693 (7%)	2066 (4%)	1.99 (1.82 - 2.18)
Soft tissue inflammation			
Never prescribed	5657 (58%)	36384 (70%)	1.00
Ever prescribed	4025 (42%)	15716 (30%)	1.70 (1.62 - 1.78)
Previously prescribed	3011 (31%)	12809 (25%)	1.55 (1.48 - 1.64)
Recently prescribed	231 (2%)	893 (2%)	1.76 (1.51 - 2.04)
Currently prescribed	783 (8%)	2014 (4%)	2.59 (2.37 - 2.83)

The prevalence of prescribing of medication in primary care for musculo-skeletal and joint diseases is high (Table 7-8). More than 70% of older people have been ever-prescribed medication for rheumatic diseases and gout, and more than a quarter of older people are currently prescribed for this. More than 30% have ever been prescribed medication for soft tissue inflammation, and almost 20% have been ever been prescribed for neuromuscular disorders.

For all three subclasses of medication, the odds ratio of first fall associated with ever-prescribed is positive and significant. Furthermore, the odds ratio for current prescribing is higher than for previously prescribed. It is highest for medication for soft tissue inflammation, OR 2.59 (2.37 - 2.83) then for

rheumatic diseases OR 2.04 (1.97 - 2.17), followed by neuromuscular disorders OR 1.99 (1.82 - 2.18).

Table 7-9 Association between first fall and prescribing in primary care of medications for the eye, THIN 2003-6

Exposure	*Cases n=9682*	*Controls n=52100*	*Odds ratio (95% confidence intervals) Unadjusted*
Anti-infective eye preparations			
Never prescribed	7129 (74%)	40777 (78%)	1.00
Ever prescribed	2553 (26%)	11323 (22%)	1.30 (1.24 - 1.37)
Previously prescribed	2324 (24%)	10399 (20%)	1.29 (1.23 - 1.36)
Recently prescribed	86 (1%)	391 (1%)	1.22 (0.96 - 1.55)
Currently prescribed	143 (1%)	533 (1%)	1.53 (1.27 - 1.85)
Corticosteroids & other anti-inflammatory			
Never prescribed	7823 (81%)	43816 (84%)	1.00
Ever prescribed	1859 (19%)	8284 (16%)	1.24 (1.17 - 1.31)
Previously prescribed	1679 (17%)	7419 (14%)	1.25 (1.17 - 1.32)
Recently prescribed	68 (1%)	295 (1%)	1.29 (0.99 - 1.68)
Currently prescribed	112 (1%)	570 (1%)	1.11 (0.91 - 1.37)
Mydriatics & cycloplegics			
Never prescribed	9549 (99%)	51619 (99%)	1.00
Ever prescribed	133 (1%)	481 (1%)	1.44 (1.19 - 1.76)
Previously prescribed	117 (1%)	425 (1%)	1.44 (1.16 - 1.77)
Recently prescribed	1 (0%)	13 (0%)	0.43 (0.05 - 3.31)
Currently prescribed	15 (0%)	43 (0%)	1.83 (1.01 - 3.32)
Glaucoma			
Never prescribed	9057 (94%)	49063 (94%)	1.00
Ever prescribed	625 (6%)	3037 (6%)	1.04 (0.95 - 1.14)
Previously prescribed	130 (1%)	610 (1%)	1.09 (0.90 - 1.33)
Recently prescribed	39 (0%)	170 (0%)	1.18 (0.82 - 1.68)
Currently prescribed	456 (5%)	2257 (4%)	1.02 (0.92 - 1.13)
Miscellaneous ophthalmic preparations			
Never prescribed	7944 (82%)	45364 (87%)	1.00
Ever prescribed	1738 (18%)	6738 (13%)	1.46 (1.37 - 1.55)
Previously prescribed	1100 (11%)	4230 (8%)	1.47 (1.37 - 1.58)
Recently prescribed	130 (1%)	515 (1%)	1.43 (1.18 - 1.74)
Currently prescribed	508 (5%)	1991 (4%)	1.43 (1.29 - 1.59)

More than 20% of older people have ever been prescribed anti-infective eye preparations in primary care (Table 7-9). The corresponding prevalence for corticosteroids, for miscellaneous opthalmic preparations, and for glaucoma is 16% and 13% and 6% respectively. Only for glaucoma (4%) and miscellaneous ophthalmic preparations (4%) is current prescribing greater than 1%.

The odds ratio of first fall for older people who have ever been prescribed medications for glaucoma or corticosteroids for eye conditions in primary care is not different to 1. For the other subclasses, the odds ratio of first fall for people ever prescribed ranges from 1.24 (1.17 - 1.31) for corticosteroids and other anti-inflammatory medication, to 1.44 (1.16 - 1.77) for mydriatics and cycloplegics, and 1.46 (1.37 - 1.55) for miscellaneous ophthalmic preparations.

For people currently prescribed in primary care, the odds ratio of first fall for mydriatics and cycloplegics is highest OR 1.83 (1.01 - 3.32), then for anti-infective eye preparations OR 1.53 (1.27 - 1.85).

Table 7-10 Association between first fall and prescribing in primary care of medications for ear, nose and oropharynx, THIN 2003-6

Exposure	*Cases n=9682*	*Controls n=52100*	*Odds ratio (95% confidence intervals) Unadjusted*
Ear			
Never prescribed	5727 (59%)	34988 (67%)	1.00
Ever prescribed	3955 (41%)	17112 (33%)	1.43 (1.36 - 1.49)
Previously prescribed	3498 (36%)	15329 (29%)	1.41 (1.34 - 1.48)
Recently prescribed	193 (2%)	726 (1%)	1.63 (1.39 - 1.92)
Currently prescribed	264 (3%)	1057 (2%)	1.51 (1.31 - 1.73)
Nose			
Never prescribed	7128 (74%)	41058 (79%)	1.00
Ever prescribed	2554 (26%)	11042 (21%)	1.38 (1.32 - 1.46)
Previously prescribed	2056 (21%)	8939 (17%)	1.38 (1.30 - 1.46)
Recently prescribed	154 (2%)	652 (1%)	1.41 (1.18 - 1.69)
Currently prescribed	344 (4%)	1451 (3%)	1.42 (1.26 - 1.60)
Oropharynx			
Never prescribed	7860 (81%)	1822 (3%)	1.00
Ever prescribed	1822 (19%)	7011 (13%)	1.52 (1.43 - 1.61)
Previously prescribed	1543 (16%)	6181 (12%)	1.46 (1.37 - 1.56)
Recently prescribed	91 (1%)	315 (1%)	1.71 (1.35 - 2.17)
Currently prescribed	188 (2%)	515 (1%)	2.11 (1.78 - 2.50)

Although the prevalence of current prescribing of medications for ear, nose and oropharynx ranges from between 1 – 3 %, between 13% (medications for oropharynx) and about 33% (for ear) of older people have ever been prescribed.

In all three subclasses the odds ratio of ever prescribed is positive and ranges between 1.38 (1.32 - 1.46) for medications for the nose, to 1.52 (1.43 - 1.61) for medications for the oropharynx. Amongst people currently prescribed medications for the oropharynx, the odds ratio is 2.11 (1.78 - 2.50) and is greater than amongst those previously prescribed. For medications for the ear and nose, the point estimate of the odds ratio for current prescribing is close to that for ever prescribed.

Table 7-11 Association between first fall and prescribing in primary care of medications for the skin, THIN 2003-6

Exposure	*Cases n=9682*	*Controls n=52100*	*Odds ratio (95% confidence intervals) Unadjusted*
Skin conditions			
Never prescribed	9523 (98%)	51474 (99%)	1.00
Ever prescribed	159 (2%)	626 (1%)	1.34 (1.12 - 1.60)
Previously prescribed	140 (1%)	535 (1%)	1.38 (1.14 - 1.67)
Recently prescribed	8 (0%)	37 (0%)	1.19 (0.55 - 2.59)
Currently prescribed	11 (0%)	54 (0%)	1.03 (0.53 - 1.99)
Emollient & barrier preparations			
Never prescribed	6057 (63%)	37740 (72%)	1.00
Ever prescribed	3625 (37%)	14360 (28%)	1.53 (1.46 - 1.61)
Previously prescribed	2475 (26%)	10252 (20%)	1.48 (1.41 - 1.57)
Recently prescribed	340 (4%)	1353 (3%)	1.52 (1.34 - 1.72)
Currently prescribed	810 (8%)	2755 (5%)	1.73 (1.59 - 1.88)
Topical local anaesthetics & antipruritics			
Never prescribed	9317 (96%)	50692 (97%)	1.00
Ever prescribed	365 (4%)	1408 (3%)	1.38 (1.22 - 1.55)
Previously prescribed	320 (3%)	1273 (2%)	1.34 (1.18 - 1.53)
Recently prescribed	15 (0%)	54 (0%)	1.36 (0.76 - 2.44)
Currently prescribed	30 (0%)	81 (0%)	1.95 (1.27 - 2.99)
Topical corticosteroids			
Never prescribed	4073 (42%)	26098 (50%)	1.00
Ever prescribed	5609 (58%)	26002 (50%)	1.41 (1.35 - 1.48)
Previously prescribed	4464 (46%)	21303 (41%)	1.38 (1.31 - 1.44)
Recently prescribed	404 (4%)	1825 (4%)	1.45 (1.29 - 1.62)
Currently prescribed	741 (8%)	2874 (6%)	1.64 (1.50 - 1.80)
Eczema & psoriasis			
Never prescribed	9015 (93%)	49376 (95%)	1.00
Ever prescribed	667 (7%)	2724 (5%)	1.38 (1.26 - 1.51)
Previously prescribed	499 (5%)	2067 (4%)	1.35 (1.22 - 1.49)
Recently prescribed	38 (0%)	156 (0%)	1.42 (0.99 - 2.02)
Currently prescribed	130 (1%)	501 (1%)	1.52 (1.25 - 1.85)
Acne & rosacea			
Never prescribed	6324 (65%)	36975 (71%)	1.00
Ever prescribed	3358 (35%)	15125 (29%)	1.36 (1.30 - 1.43)
Previously prescribed	3011 (31%)	13906 (27%)	1.33 (1.26 - 1.40)
Recently prescribed	128 (1%)	490 (1%)	1.59 (1.30 - 1.94)
Currently prescribed	219 (2%)	729 (1%)	1.80 (1.54 - 2.11)

Table 7-11 (continued)

Warts & calluses						
Never prescribed	9474	(98%)	51321	(99%)	1.00	
Ever prescribed	208	(2%)	779	(1%)	1.48	(1.27 - 1.74)
Previously prescribed	192	(2%)	726	(1%)	1.47	(1.25 - 1.73)
Recently prescribed	4	(0%)	21	(0%)	1.00	(0.33 - 2.99)
Currently prescribed	12	(0%)	32	(0%)	2.03	(1.03 - 4.00)
Sunscreens & camoflagers						
Never prescribed	9565	(99%)	51683	(99%)	1.00	
Ever prescribed	117	(1%)	417	(1%)	1.53	(1.24 - 1.88)
Previously prescribed	95	(1%)	350	(1%)	1.48	(1.17 - 1.86)
Recently prescribed	6	(0%)	24	(0%)	1.31	(0.53 - 3.26)
Currently prescribed	16	(0%)	43	(0%)	2.10	(1.18 - 3.74)
Shampoos & scalp preparations						
Never prescribed	8936	(92%)	49070	(94%)	1.00	
Ever prescribed	746	(8%)	3030	(6%)	1.34	(1.23 - 1.46)
Previously prescribed	624	(6%)	2550	(5%)	1.33	(1.21 - 1.45)
Recently prescribed	38	(0%)	176	(0%)	1.16	(0.82 - 1.66)
Currently prescribed	84	(1%)	304	(1%)	1.59	(1.25 - 2.03)
Anti-infective skin preparations						
Never prescribed	5064	(52%)	31891	(61%)	1.00	
Ever prescribed	4618	(48%)	20209	(39%)	1.48	(1.41 - 1.55)
Previously prescribed	3902	(40%)	17582	(34%)	1.44	(1.37 - 1.51)
Recently prescribed	282	(3%)	1067	(2%)	1.68	(1.47 - 1.93)
Currently prescribed	434	(4%)	1560	(3%)	1.78	(1.60 - 2.00)
Skin cleansers & antiseptics						
Never prescribed	8508	(88%)	48243	(93%)	1.00	
Ever prescribed	1174	(12%)	3857	(7%)	1.67	(1.55 - 1.79)
Previously prescribed	972	(10%)	3338	(6%)	1.60	(1.48 - 1.74)
Recently prescribed	68	(1%)	187	(0%)	2.00	(1.50 - 2.66)
Currently prescribed	134	(1%)	332	(1%)	2.09	(1.70 - 2.57)
Antiperspirants						
Never prescribed	9664	(100%)	52039	(100%)	1.00	
Ever prescribed	18	(0%)	61	(0%)	1.69	(0.99 - 2.86)
Previously prescribed	17	(0%)	55	(0%)	1.76	(1.02 - 3.04)
Recently prescribed	1	(0%)	4	(0%)	1.50	(0.17 - ###)
Currently prescribed	0	(0%)	2	(0%)		(-)
Topical circulatory preparations						
Never prescribed	9320	(96%)	50882	(98%)	1.00	
Ever prescribed	362	(4%)	1218	(2%)	1.66	(1.46 - 1.87)
Previously prescribed	311	(3%)	1129	(2%)	1.53	(1.35 - 1.75)
Recently prescribed	9	(0%)	32	(0%)	1.51	(0.71 - 3.22)
Currently prescribed	42	(0%)	57	(0%)	4.13	(2.76 - 6.19)

A large number of subclasses of medication for skin conditions are prescribed in primary care (Table 7-11). For some subclasses, large numbers of older people have ever been prescribed (e.g. about one half for topical corticosteroids; about one third for anti-infective skin preparations). In most subclasses, not more than about 1% of older people are currently prescribed. Exceptions to this are topical corticosteroids (6%), emollient and barriers (5%), and anti-infective skin preparations (3%).

With the exception of antiperspirants (which is borderline significant), the odds ratio of first fall for all subclasses of medication prescribed in primary care is significant and positive for all patients who have been ever prescribed in primary care. The odds ratio of first fall for ever prescribed is highest for skin cleansers OR 1.67 (1.55 - 1.79) and topical circulatory preparations OR 1.66 (1.46 - 1.87). It is lowest for shampoos and scalp preparations OR 1.34 (1.23 - 1.46).

For current prescribing, the risk of first fall is highest for topical circulatory preparations OR 4.13 (2.76 - 6.19), sunscreens and camouflages OR 2.10 (1.18 - 2.74), skin cleansers and antiseptics OR 2.09 (1.70 - 2.57), and warts and calluses 2.03 (1.03 - 4.00). In most other subclasses the odds ratio is positive and significant and in the case of the following medications it is also higher than for the people previously prescribed: acne and rosacea 1.80 (1.54 - 2.11), emollients 1.73 (1.59 - 1.88), topical corticosteroids 1.64 (1.50 - 1.80), and anti-infective skin preparations 1.78 (1.60 - 2.00). The odds ratio of first fall for current prescribing of medication for skin conditions is not significantly different from 1.

Table 7-12 Association between first fall and prescribing in primary care of immunological products and vaccines, THIN 2003-6

Exposure	*Cases n=9682*	*Controls n=52100*	*Odds ratio (95% confidence intervals) Unadjusted*
Vaccines & antisera			
Never prescribed	4724 (49%)	27173 (52%)	1.00
Ever prescribed	4958 (51%)	24927 (48%)	1.26 (1.19 - 1.33)
Previously prescribed	4303 (44%)	21794 (42%)	1.24 (1.17 - 1.31)
Recently prescribed	301 (3%)	1485 (3%)	1.44 (1.20 - 1.72)
Currently prescribed	354 (4%)	1648 (3%)	1.55 (1.31 - 1.84)
Immunoglobulins			
Never prescribed	9484 (98%)	50856 (98%)	1.00
Ever prescribed	198 (2%)	1244 (2%)	0.91 (0.78 - 1.06)
Previously prescribed	198 (2%)	1244 (2%)	0.91 (0.78 - 1.06)
Recently prescribed	0 (0%)	0 (0%)	(-)
Currently prescribed	0 (0%)	0 (0%)	(-)

About one half of the older people are recorded as having ever been prescribed vaccine or antisera in primary care. Amongst these only 3% are currently prescribed. 2% of older people have been prescribed immunoglobulins, but none of these are being currently prescribed.

The odds ratio of first fall for immunoglobulins is not significantly different to 1. For current prescribing of vaccines and sera the odds ratio of first fall is 1.55 (1.31 - 1.84).

It should be noted that the pattern of prescribing and of concordance for a vaccine is very different to that of a medication for the management of a chronic condition. As a result, the universal definition of current prescribing used in this study may not be relevant to vaccines. Therefore, despite the fact that odds ratio is nearer to one than it is in many other subclasses, the high prevalence of vaccine prescribing suggests that the risk profile is worthy of further study.

Table 7-13 Association between recorded first fall and prescribing in primary care of anaesthesia, THIN 2003-6

Exposure	*Cases n=9682*	*Controls n=52100*	*Odds ratio (95% confidence intervals) Unadjusted*
General anaesthesia			
Never prescribed	8051 (83%)	46235 (89%)	1.00
Ever prescribed	1631 (17%)	5865 (11%)	1.58 (1.49 - 1.68)
Previously prescribed	1112 (11%)	4187 (8%)	1.53 (1.42 - 1.64)
Recently prescribed	67 (1%)	214 (0%)	1.86 (1.41 - 2.46)
Currently prescribed	452 (5%)	1464 (3%)	1.68 (1.51 - 1.88)
Local anaesthesia			
Never prescribed	8397 (87%)	46335 (89%)	1.00
Ever prescribed	1285 (13%)	5765 (11%)	1.29 (1.21 - 1.39)
Previously prescribed	1151 (12%)	5347 (10%)	1.25 (1.16 - 1.34)
Recently prescribed	57 (1%)	181 (0%)	1.80 (1.33 - 2.43)
Currently prescribed	77 (1%)	237 (0%)	1.85 (1.42 - 2.41)

12% of older people are recorded as having been prescribed general anaesthesia in primary care, and a similar proportion have been prescribed for local anaesthesia. The corresponding prevalence of current prescribing is about 3% and less than 1%, respectively.

The odds ratio of first fall for older people currently prescribed local anaesthesia is 1.85 (1.42 - 2.41) which is higher than the risk among people previously prescribed. The odds ratio is also positive and significant for people currently prescribed general anaesthesia OR 1.68 (1.51 -1.88), and among people recently prescribed OR 1.86 (1.41 - 2.46).

7.3 Discussion

In this hypothesis-generating study of medications which were not included in recent meta-analyses, for almost all subclasses of medication prescribed in primary care to older people, there was a significant positive association between ever-prescribed and first fall. Age and sex adjusted odds ratios for current prescribing ranged from not significantly different from 1, to 4.13 (2.76 – 6.19). For most subclasses, the point estimate of the age-sex adjusted odds ratio was between 1.3 and 1.7. Subclasses in which there was a statistically significant association and in which the point estimate of the odds ratio for current prescribing was higher than this include antispasmodics 1.79 (1.58 – 2.03), acute diarrhoea 2.50 (2.21 – 2.84), laxatives 2.02 (1.89 – 2.16), intestinal secretions 1.73 (1.14 – 2.64), oxygen 2.71 (2.00 – 3.68), mucolytics 1.94 (1.20 – 3.15), antibacterials 2.75 (2.54 – 2.98), antifungals 1.86 (1.43 – 2.43), antivirals 3.03 (2.07 – 4.42), antiprotozoals 1.80 (1.61 – 2.02), corticosteroids 2.03 (1.84 – 2.25), other endocrine 2.58 (1.81 – 3.68), oral nutrition 1.93 (1.64 – 2.27), minerals 1.74 (1.60 – 1.90), vitamins 1.87 (1.72 – 2.04), rheumatic diseases and gout 2.04 (1.92 – 2.17), neuromuscular disorders 1.99 (1.82 – 2.18), soft tissue inflammation 2.59 (2.37 – 2.83), mydriatics and cycloplegics 1.83 (1.01 – 3.32), oropharynx 2.11 (1.78 – 2.50), emollient and barrier preparations 1.73 (1.59 – 1.88), topical local anaesthetics 1.95 (1.27 – 2.99), acne and rosacea 1.80 (1.54 – 2.11), warts and calluses 2.03 (1.03 – 4.00), sunscreens and camouflages 2.10 (1.18 – 3.74), anti-infective skin preparations 1.78 (1.60 – 2.00), skin cleansers 2.09 (1.70 – 2.57), topical circulatory preparations 4.13 (2.76 – 6.19), and local anaesthesia 1.85 (1.42 – 2.41).

7.3.1 Study strengths and weaknesses

The main strengths and weaknesses of the study are similar to those already documented in preceeding chapters. Strengths include the large number of cases and the fact that the data were collected prospectively, which means that recall of medication exposures and of falls is not a source of bias. Medications were differentiated according to standard classifications in the British National Formulary[191].

The main potential weakness of the study is the validity of the reporting and recording of fall events, which are a subset of the falls self-reported in surveys. The significance of falls recorded in primary care in terms of subsequent mortality has been evidenced in earlier chapters of the thesis. Nevertheless, it is acknowledged that incomplete recording of falls raises the possibility of differential ascertainment of falls for patients receiving prescribed medication. Such a bias would have led to an overestimation of odds ratios. However, it should be noted that the day of the prescription was excluded from the exposure time, which avoided ascertainment bias of falls recorded at the time of initial prescribing.

As this study is intended to generate hypotheses across a wide range of medications, no attempt has been made to assess the impact of or to control for confounding by other specific medications, polypharmacy in general, or co-morbidity. For the same reason, no attempt has been made to correct for the likelihood that in a study like this which involves a high number of comparisons, some of the observed associations will be attributable to chance.

In the following sections, limitations specific to certain subclasses of medications are described. As a general point, it should be noted that a single definition of current, recent and previous prescribing has been applied universally across all subclasses of medication. However there may be some medications for which a different definition might be more appropriate. For example, it might be that for vaccines requiring a single dose a different definition of current is required because the pattern of prescribing and delivery of the medication is different to that for medications prescribed in the management of chronic disease. This has not been addressed in this study. The implication of this is that for some subclasses the definitions of current and recent prescribing lack specificity.

Furthermore, there are some medications which can be purchased "over the counter", i.e. without prescription. Where this applies, it is documented in the following sections. It should be noted that in such instances THIN may represent an incomplete record of exposure for some or all cases and that there may be an under-representation of people in paid employment and others whose socio-economic status means that they do not qualify to have prescription charges waived (i.e. it may be more attractive to such groups to purchase certain medications "over the counter").

7.3.2 Interpretation and consideration of other studies

Before turning to the interpretation of results for individual classes and subclasses of medication, it should be noted that for almost all medications the age and sex adjusted odds ratio of first fall is statistically significant and positive. This is interpreted as evidence of an association between the medication prescribed and first falls in older people.

Nevertheless, it could also be evidence of a general bias in ascertainment of falls amongst people who, by virtue of receiving prescribed medication, are under the management of a clinician. Such a bias could arise because increased consulting provided more opportunities to be asked about or to report previous falls, or because patients consulting a doctor for any condition are more likely to report falls or to recall them when asked (because they are readier to associate a fall with a health condition, say). It could also arise as a result of increased vigilance on the part of the clinician whose threshold for enquiring about falls may be lower for patients who are receiving any kind of prescribed medication, Any combination of these could be invoked as explanation for general association between medications prescribed and first falls. However, another hypothesis generating study of the association between hip fracture and a wide range of medication subclasses found a similar general association[213]. It is unlikely that a highly specific diagnosis like hip fracture, with its attendant implications and management, is subject to a generalised ascertainment bias. What seems more plausible is that a prescription of almost any subclass of medication is a

marker of frailty, which will be positively associated with a subsequent first fall.

7.3.2.1 Medications for the gastro-intestinal system

In this class of medication, the subclasses with the highest age and sex adjusted odds ratios are those for the treatment of acute diarrhoea, OR 2.50 (2.21 - 2.84), and irritable bowel disease and diverticular disease OR 1.79 (1.58 - 2.03), or medications which are known to cause griping or abdominal cramps, e.g. laxatives OR 2.02 (1.89 - 2.16). In these cases, an increased urge to void associated with the medication or the underlying condition provides a plausible explanation for the observed association. For some subclasses (e.g. laxatives) it has been argued that the medication may lead to dehydration, orthostatic hypotension or confusion leading to a greater propensity to fall[214]. Side effects of antimuscarinics include urinary urgency, confusion (particularly in the elderly), and giddiness[191].

In their recent meta-analysis of laxatives and falls in older people, Bloch et al found evidence of publication bias but, on the basis of a pooled odds ratio of 2.03 (1.52 - 2.72) concluded that there is also strong evidence for an association between laxative prescribing and falls in older people[214]. They also noted that it is probably not directly attributable to the medication itself but rather to co-morbidities such as Parkinsonism which confine patients to bed and are associated with constipation, and which themselves represent both a risk factor for falls and for laxative prescribing. Whilst this provides a plausible explanation, they cite no direct evidence for this from the studies in their meta-analysis. The potential role of underlying conditions such as this could be tested in THIN by undertaking self-controlled case series analysis of a group of fallers exposed to laxatives who have a diagnosis of Parkinsonism.

A search for literature relating to possible effects of anti-diarrhoeals or drugs for chronic bowel disorders and falls yielded no studies, as did searches for studies of antacids, antispasmodics, or proton pump inhibitors.

These findings suggest the need for further research to investigate the relationship between these medications and falls. Such studies would need to test for the role of confounding by indication. The high prevalence of ulcer-healing drugs in older people (more than 15%) means that it is important to understand their falls profile.

7.3.2.2 Medications for the respiratory system

The medication subclasses with the highest age and sex adjusted odds ratios are oxygen (OR 2.74) and mucolytics (OR 1.94), both of which are prescribed to patients living with Chronic Obstructive Pulmonary Disease (COPD)[191]. Roig et al's review concludes that most of the risk factors for falls in older people are common in people with COPD, and that there is evidence that lower limb weakness and impaired activities of daily living are well-established risk factors for falls in people with COPD[215]. However, the review notes the lack of epidemiological studies assessing the prevalence of falls in people with COPD which is only partially addressed in a subsequent study of 101 people with COPD[216]. The lack of larger scale epidemiological studies indicates a specific gap that can be addressed by further studies in THIN. A challenge of assessing the independent role of these medications in falls will be to differentiate the effect of newly prescribed medication from the possible impact of an exacerbation of the disease they are intended to treat. A further complication in the case of oxygen is that where this is accessed through a home-based oxygen service this may not be recorded in the patient's prescribing records. The extent of this would need to be assessed.

Other subclasses worthy of further study include antihistamines, of which the older examples are attributed with side effects including drowsiness and psychomotor impairment, blurred vision, and gastro-intestinal disturbances[191]. Other side effects include hypotension, and dizziness. Newer and non-sedating antihistamines are said to have milder side effects. There is a high prevalence of current prescribing which, together with the association observed in this study and the lack of evidence in the literature indicates the opportunity for further study. The study design would need to take account of the fact that some of these medications may be bought over

the counter, therefore primary care records may not fully reflect a patient's exposure.

7.3.2.3 Medications for infections

Acute illness is commonly cited as a medical risk factor for falls[217]. Some infections directly impact a physiological system relating to balance and stability (e.g. infection impacting vestibular functioning), but the association with falls is not strong[119]. In some (e.g. urinary tract infection) the effect may relate to an increase in activity which carries a risk of falling (mobilising to walk to the bathroom). In others, the infections may be more difficult to classify in terms of falls pathology other than that it results in a further deficit of the balance system to a point that results in instability.

The subclass with the highest adjusted odds ratio is antivirals, OR 3.03 (2.07 - 4.42). Indications for this prescribing include a range of acute and chronic infections, and for patients who are immunocompromised or considered to be at risk as a result of other co-morbidities[191]. The odds ratio for current prescribing is much higher than that for previous prescribing, and suggests that the association is not exclusively attributable to underlying co-morbidities. However, further investigation of this association will be complicated by the need to differentiate the respective possible effects of the medication itself from the indication.

Similar considerations arise for antibacterials, in which first fall is strongly associated with current prescribing, OR is 2.75 (2.54 - 2.98), but which are much more commonly prescribed than antivirals. The prevalence of antifungals is less than for antibacterials, but the association with first falls is also relatively strong, OR 1.86 (1.43 - 2.43). In this subclass, some of the indications relate to immunocompromised patients in which the association may be confounded by the condition being treated[191]. However, indications also include conditions which are less likely to represent a confounding factor (e.g. mild skin and nail infection). A study of the odds of first fall amongst older people with this diagnosis, could help establish the plausibility of the

hypothesis that this subclass of medication is independently associated with first fall in older people.

Antiprotozoal prescribing, which is also associated with first falls, OR 1.80 (1.61 - 2.02), is prescribed for the treatment for a range of infections. These include gastro-intestinal infection for which the symptoms and possible explanations are the same as those for subclasses prescribed for diarrhoea. Amongst a range of other indications, it is notable that antiprotozoals are also prescribed for prophylaxis against anti-malaria. It might be argued that the prevalence of co-morbidities in the group of older people prescribed prophylaxis for travel purposes is unlikely to be greater than that in their age-specific general population. On this basis, there may be scope for a study of the effects of the initiation of malarial prophylaxis on first fall.

7.3.2.4 Medications for the endocrine system

Amongst medications prescribed for the endocrine system, the subclass called "other endocrine drugs" has the strongest association between current prescribing and first fall OR 2.58 (1.81 - 3.68). However, the prevalence of prescribing is relatively low. Furthermore, the British National Formulary carries highlighted warnings for some drugs within this subclass regarding the sudden onset of sleepiness and other side-effects which could explain an association with first fall[191].

In comparison, more than a fifth of older people have been ever-prescribed corticosteroid, which is used as replacement therapy or for long-term suppression of a range of diseases. In many cases, the drug treats the symptoms only, and the underlying condition is not cured. The patients receiving this group of medications may be heterogeneous, and have a greater burden of disease compared to the general population comparators. In view of the heterogeneity of this group of patients, for the further exploration of the possible effect of corticosteroids it would be preferable to use a case definition which identifies a more homogeneous subset of patients and whose condition, ideally, remains fairly constant over time.

Several studies in the literature have reported an association between diabetes and falls or recurrent falls, but there is disagreement over the extent to which this may be partly or entirely attributable to insulin prescribing, polypharmacy in general, or an effect of the disease itself[218-220]. THIN provides an opportunity to study the effects of the medication itself or its initiation, using similar methods to those employed in this project.

7.3.2.5 Medications for gynaecology and urinary-tract disorders

The strength of association between each of these two subclasses and falls is weaker than for a number of classes. Nevertheless, the prevalence of prescribing (up to one fifth, in the case of medications for the genito-urinary system) warrants further consideration of their falls profile.

The subclass containing drugs for genito-urinary tract disorders includes medications for a range of conditions, including some (e.g. urinary incontinence, enuresis) for which a possible association with falls risk is already established[119]. For some medications, documented side-effects include blurred vision, diarrhoea and central nervous system stimulation leading to restlessness, disorientation or hallucination. Therefore any further study of their falls profile would need to address specific medications and conditions, and to address the potentially confounding effect of the indication.

7.3.2.6 Medications for malignant disease and immuno-suppression

The associations with subclasses of medication in this group are relatively weak, involve relatively small numbers of people, many of whom are likely to be subject to serious co-morbidities and may be receiving a range of other medication. Therefore developing a more detailed understanding of their falls profile will be more complex, and is less likely to be of utility compared to other groups of medication.

7.3.2.7 Medications for nutrition and blood disorders

More than 5% of older people are currently prescribed vitamins or minerals, and there is an association with subsequent first fall, and in both subclasses the association amongst people currently prescribed is stronger than

amongst those previously prescribed. Further study of their falls risk profile would need to adjust for possible confounding by indication (indications include a wide range of deficiencies arising directly from other treatments, diet, or underlying disease) and to consider whether the effect varies between different minerals and supplements. For example, vitamin supplements are more prevalent amongst residents in institutional settings who are prescribed corticosteroid therapy[221].

Vitamin and minerals are available "over the counter", therefore the prescribing record may not represent a complete record of exposure. The likely impact of this is that the size of any effect attributable to the exposure will be diluted.

There is weak evidence that the falls risk for people recently prescribed fluids and electrolytes is less than that for people currently prescribed suggesting that the first fall might be associated with the discontinuation of the medication rather than by the medication itself. It is not clear from the data in this study how much of this medication is prescribed to people who have diarrhoeal symptoms which may be independently associated with an increased falls risk (as discussed earlier).

7.3.2.8 Medications for musculoskeletal and joint disorders

Lord et al summarise evidence of an association between arthritis and other markers of musculoskeletal disease (e.g. restricted mobility, walking aid use) and falls[119], therefore it is unsurprising that this study finds a clear association with prescribing of medications for these and similar disorders. Similarly, there is an established association with deficits in neuromuscular functioning[119] which explains, fully or in part, the observed association between prescribing for neuromuscular disorders and falls.

Given, the large number of people who are prescribed the medications it would be valuable to understand their falls risk profile. However, this will be confounded by the underlying diseases and this may be difficult to separate

out due to the progressive nature of the diseases for which one would wish to control.

7.3.2.9 Medications for the eye

There is evidence of a strong association with falls in older people for several measures of vision including poor visual contrast sensitivity, decreased depth perception and poor visual acuity[119], and evidence of weaker associations for some other indicators. However, the indications for the medications prescribed in primary care appear not to be closely associated with these measures of vision[191]. Furthermore, for the more commonly prescribed subclasses of medication the association with falls is weak or absent.

In comparison with anti-infective and anti-inflammatory medications, fewer older people are prescribed mydriatics and cycloplegics (which are used to dilate the pupil prior to refractive procedures). It is possible that the increased risk of falls in people recently prescribed this subclass is a result of temporary impairment of vision following an eye procedure. However, as antimuscarinics, their side effects may include urinary urgency, confusion (particularly in the elderly), and giddiness[191].

7.3.2.10 Medications for the ear, nose and oropharynx

Many of the medications in this group are for the treatment of infection and also exhibit a relatively high odds ratio for first fall, e.g. current prescribing for oropharynx, OR 2.11 (1.78 - 2.50). As noted earlier, acute illness is commonly cited as a medical risk factor for falls[217]. Therefore investigation of the extent to which these are due to the independent effect of the medication itself may be confounded by the indication.

7.3.2.11 Medications for skin

This subclass includes a wide range of medications for skin conditions; for some of these the prevalence of prescribing is high and there is evidence of an association with first fall. This is strongest for topical circulatory preparations, sunscreens and camouflages, skin cleansers and antiseptics, and warts and calluses. Searches in the literature failed to identify any

studies looking at an association between these medications and falls. Neither were any studies identified for other medications such as emollients, and shampoos and scalp preparations.

There is evidence of a higher risk of falls for patients with psoriatic arthritis[222]. Evidence of the association between arthritis and falls has already been noted[119] and it may be this which accounts for the observed association with psoriasis.

Within the subclass of medications for the treatment of acne, there is at least one medication (isotretinoin) which has severe side-effects including joint pain[191]. However, this would normally be prescribed only under the supervision of a dermatologist and it seems unlikely that a medication for this indication explains the very high prevalence of prescribing of the subclass. It should also be noted that acne is a documented side-effect of potent topical corticosteroids[191], which itself may be associated with falls.

These observed associations suggests the need for further investigation, especially in medications where the prevalence of prescribing is high. It should be noted that shampoos are available "over the counter", therefore the prescribing record may not represent a complete record of exposure. The likely impact of this is that the size of any effect attributable to the exposure will be diluted.

7.3.2.12 Immunological products and vaccines

In this class of medication, only vaccines and sera have a positive association with first fall. It should be noted that in the UK there is an annual influenza vaccine campaign. It is likely that this comprises a large part of the prescribing. The campaign is targeted towards at-risk groups who, by definition, will have co-morbidities not shared by their general population controls. Further investigation is required to differentiate the falls risk profile of the most commonly prescribed vaccines.

7.3.2.13 Anaesthesia

This study was not designed to determine the indication for which a medication was used but, given the high prevalence of prescribing, it seems likely that at least some of the prescribing ascribed to this subclass will have been for pain relief, perhaps post-operatively. To the extent that this is the case, the group receiving this medication have a burden of morbidity beyond that of their general population controls. This would need to be taken into account in any further investigation of the observed association.

7.4 Implications

The results of this hypothesis-generating study, together with the lack of evidence regarding their falls profile, indicate that further study is warranted across a range of medication subclasses. Those which, on the basis of their indications and side-effects, are thought to be most easily addressed in THIN are listed below. In each case, further study should address the possibility that any association with falls may be confounded by the indication or other comorbidity.

Subclass of medication	Rationale for further study and other considerations
Laxatives	Gap in the evidence regarding the possible confounding effect of comorbidities which cause constipation, esp. Parkinson's disease
Antifungals	The lack of an obvious causal link between the indication (mild skin and nail infection) and falls provides an opportunity for studying the possible effect of the medication itself. About one tenth of older people have ever been prescribed antifungals (but current prescribing is less than 1%)
Corticosteroids	Corticosteroids are used in the treatment of a wide range of disease. Differentiating the risk

	associated with the drug itself requires a case definition which includes only patients whose condition is similar and for which the symptoms are fairly constant over time
Insulin	Disagreement in the literature about the extent to which the known association of diabetes with falls is due to insulin prescribing, polypharmacy, or an effect of the disease itself. High and increasing prevalence of insulin prescribing
Antibiotics for mild to moderate acne	Opportunity to study effect of treatment in a condition which is less likely to be associated with falls than many acute bacterial infections. In general, acute bacterial infection is associated with falls, and it is difficult to separate the effect of infections from the effect of their treatment.
Influenza or other vaccines	High prevalence of prescribing. Prevalence will be highest in groups at risk due to underlying disease. Making allowance for this is essential. Definition of current prescribing needs to be specific to how vaccine is administered.
Cohort study of the incidence of falls in people with COPD	Sparsity of evidence about the incidence of falls in people with COPD

8 Conclusions and recommendations

This chapter brings together the implications arising out of the studies described in previous chapters into a set of conclusions and recommendations. These are organised according to the specific aims of each study in the project, and some more general recommendations about the utility and potential of the methods used in this project.

8.1 The overall incidence of recorded falls among older people in primary care in the UK, and its variation over recent years and by socio-demographic attributes

The crude incidence rate of falls recorded in primary care was approximately 3.6 per 100 person years which, in a typical general practice with an all-age population of 10,000, represents about 78 recorded fall events per year amongst its 2113 people aged 60 or over. The rate remained unchanged in period 2003-2006. This rate is considerably lower than the incidence of primary care consultations amongst older people. The public health implication of this is that the National Institute for Health and Clinical Excellence's guideline that health professionals should routinely ask patients if they have fallen in the last year appears not to have been followed during the study period. Furthermore, the gap between the falls incidence observed in this study and the actual number of people attending falls clinics in 2006 suggests that opportunities to intervene were being missed.

The rate of falls is higher in women and in older age groups. The fact that it is also strongly associated with social disadvantage suggests the need to target the design and delivery of interventions accordingly.

Given the potentially costly consequences of falls for individuals, their carers and family, and the wider health and social care system, greater priority should be given to systematically identify older people who fall, to apply interventions, and to target these according to need.

8.2 The risk of death associated with falls in older people in primary care

People who fell experienced a substantial increase in mortality (two-fold increase for recurrent fallers, and more than five-fold for those aged 60-74 years) which was independent of fractures recorded at the time of the fall or subsequently. Furthermore people who fall have an increased rate of subsequent fracture (approximately three-fold and, for recurrent fallers aged 60-74 years more than eight-fold).

The public health implication of this is that older people with a recorded fall represent a group who are at increased risk of death. Furthermore these results suggest that this vulnerability is not simply a function of subsequent risk of fracture. Identifying people who fall, and especially those who fall recurrently, provides an opportunity to intervene on a group who are vulnerable irrespective of whether they have a subsequent fracture.

8.3 The falls risk profile of serotonin noradrenalin reuptake inhibitors compared to selective serotonin reuptake inhibitors

The risk of first fall was increased almost 2-fold in people currently prescribed an SNRI, and this increase in risk was apparent in the first month after the first prescription. The sizes of effect were similar to those seen for SSRIs and TCAs. The clinical and public health implications of this relate to the suggestion by some that SNRIs should be regarded as the antidepressant of choice for the elderly because of their low potential for drug interactions and possible favourable effect on pain associated with depression. The results of this study show that clinicians initiating prescribing of SNRIs should also be alert to the increased risk of falls.

8.4 The extent to which prescribing of antihypertensive medication modifies the risk of falling in older people

Prescribing of thiazides is associated with an increased risk of first falls. The size of the observed association with thiazides is small over the long term but represents an almost three-fold risk during the first three weeks of first exposure. The study is a further reminder to clinicians initiating prescribing of thiazides in older people, which has generally been considered a 'safe' option for older patients, to be alert to the possibility of an increased risk of falls in the first three weeks of prescribing.

There is weaker evidence for a protective effect of calcium channel blockers in the first three weeks of exposure, and the observed effect could have arisen by chance or as a result of clinician or patient responses to concerns about the effect of these medications. Considering the complementary analyses together (and contrary to what might have been expected from some classes regarded as more likely to undermine homeostasis), there was no increase in falls risk for other classes of antihypertensive medication.

8.5 Identifying other medication prescribed in primary care whose falls risk warrants investigation in future studies

Further study is needed to address gaps in the evidence base regarding the falls profile of a number of medication subclasses including: laxatives, antifungals, corticosteroids, insulin, antibiotics for mild to moderate acne, and vaccines for influenza and other infections.

8.6 Utility and potential of the methods

The preceding chapters have described the methods and the results obtained, including proper consideration of specific strengths and weaknesses of each study. It is proposed that these accounts, together with the four resulting publications[196 211 223 224] in peer-reviewed journals, successfully demonstrate that the research questions have been addressed

using methods which are appropriately rigorous in their design and execution. Nevertheless, in this final chapter, some broader reflection is warranted of the overall suitability of the methods and the potential for their future application in addressing questions about falls and the role of medications.

8.6.1 THIN as a data source for falls

THIN has provided a readily available source of longitudinal information about diagnoses and medical management of older people in the community, including comprehensive records of prescribing history on which to base reliable analyses of exposure to medications. This much is in common with a growing number of studies in pharmacoepidemiology which have used data from THIN or other primary care datasets. What is more unusual in this project is the use of recorded fall as an outcome measure which, as noted in the Introduction, may occur as a random event or may be the result of a complex interaction between an individual's physical capability and a range of environmental factors.

Early observations included the fact that the number of falls recorded in primary care is much lower than the number of self-reported falls reported in a range of other studies, and that amongst older people who are recorded as having fallen there is an increased incidence rate of mortality and of fracture. These are important findings in their own right, provide a baseline against which to measure future changes, and justify the use of this outcome in the subsequent studies. Whilst care should be taken to avoid unwarranted inferences about falls in general based only on data relating to recorded falls, it should also be noted that currently (aside from primary care databases like THIN) other individual sources of data about falls in the general population are too small or too imprecise in their measurement of exposure to medications and potential confounders to provide a conclusive evidence about medications and falls in general[129]. Therefore, findings based on

analyses of falls recorded in primary care represent an important addition to the evidence base.

Another point addressed in the hypothesis generating chapter but which warrants consideration here is that in almost all medications the risk of first fall was found to be positive and statistically significant. It has been noted earlier that this could be evidence of a general bias in ascertainment. However it was also argued that the association found (for example) between hip fracture (the management of which makes it unlikely to be subject to ascertainment bias) and a wide range of medications suggests that a different explanation is more plausible; namely, that prescribing of almost any subclass of medication in older people provides a marker of frailty. The additional reflection warranted here is that the possible role of bias is commented on in the literature and few studies address this directly[125]. However, self-controlled case series does provide a means by which the role of bias may be assessed and, in the studies of antidepressants and antihypertensives described in this thesis, it has been applied for exactly that purpose. Considerations relating to its application are addressed in the following section.

8.6.2 Considerations relating to study design

The application of a cohort design to measure incidence and risk of mortality followed classic approaches, as did the nested case-control design. The complementary application of the case series method demonstrated the value of applying more than one method to an epidemiological problem, because it provided an indication of the extent of possible bias in the estimates.

One reflection on the future application of these methods relates to the selection of first fall as the event of interest (not subsequent or recurrent falling), which was critical both in the case-control study and the complementary case series analysis. In the case-control study the choice of

first fall was indicated by prior findings about the temporality of falls after first exposure and was made essential because of the possibility that prescribing behaviour is changed after a first fall (which would have been difficult to deal with if the event of interest was a recurrent fall). The case series studies were used to provide complementary analyses, so that findings arising from the case-control and case series methods could be compared directly. Therefore, it was essential that first fall remained the event of interest in the case series method. In point of fact, even if the event of interest in the case-control study had been recurrent falls, it would have been problematic to adopt this in the case series studies because the method requires that occurrence of an event should not affect the rate at which subsequent events occur. In these studies, it is quite probable that ascertainment and recording will increase subsequent to a first fall; indeed, regular review of people who are known to have fallen is very much the intention of published guidance[163]. Since completion of the analysis, Farrington et al have published an extension to the case series method to address within-individual dependence between recurrent events[225]. Further work on falls in this dataset should consider whether this extension could be applied in the case of recurrent falls.

Whitaker et al have previously identified, and provided access to Stata code for the case-series models addressed in their tutorial[195] (e.g. single and multiple periods of risk). The periodic and recurrent nature of exposures in these studies (a single period was deemed to continue until there was a break in prescribing, and this might be followed by one or more subsequent periods at a later date) required further development of these models and code to address this new combination of exposure characteristics, including the incorporation of logic to handle prevalent exposure, to ensure that risk periods are always consecutive but not overlapping, and to execute the sensitivity analyses needed to test for possible breaches of key assumptions. These will be valuable for future studies, including those needed to explore further the effects of some of the medications identified in the hypothesis-

generating study (e.g. insulin, corticosteroids) which are used in the management of long term conditions and are likely to be characterised by a prescribing history comprising periodic, recurrent exposure.

One aspect of the method which would require consideration in any future study using this design relates to the approach for dealing with the possibility that the occurrence of a fall affects the probability of subsequent exposure. If true, it would represent a violation of one of the assumptions underpinning the method: that probability of exposure is not affected by the occurrence of an outcome event. In the case of medications and falls in older people, there are two hypothetical situations in which this may be violated. The violations relate either to "disruption" of the exposure process or to the observation period. An example of the former is where the medication is thought to be contraindicated for falls, in which case prescribing may be modified subsequent to the fall. An example of the second is where follow-up is curtailed as a result of the event, thereby curtailing the exposure history. The most extreme example of this would be where patients die following a fall. The methods chapter describes the sensitivity analyses undertaken to test for each of these violations. In 2009, Farrington et al published methods for dealing with the possible impact of such "interferent" events (i.e. events on which subsequent exposure is in some way dependent)[199]. However, this extension to the method is intended for analysis of transient point exposures. This suggests that it has little potential for analysing the effect of the periodic recurrent exposures found in the prescribing histories for medications used to treat long term conditions, such as antihypertensives and antidepressants. Furthermore, the method involves ignoring post-event exposures so tends to be less efficient in situations where the event merely increases the risk of death (i.e. less curtailment) compared to those where the event often or always leads to death (i.e. frequent curtailment).

As recently as 2011, Farrington et al published a further extension of the method to deal with situations in which rare nonrecurrent events increase

mortality in the medium and longer term[226]. This latest extension addresses the possible non-random curtailment which may be associated with a critical event, but not the possibility of a shorter term disruption of exposure. Notwithstanding the special assumptions underlying each of these extensions to the standard method, it is recommended that, in future case series analysis of a rare non-recurrent event like first fall, consideration is given to their suitability for addressing the possible impact of interferent events.

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Appendix A - Search criteria used in literature reviews

The initial search of the literature was completed using the following parameters which were applied in Ovid Medline. This yielded a large number of papers which were manually sorted to identify those of most immediate relevance to the topic. These were supplemented with relevant chapters from a recently published textbook[3 7 115 121] and with key current policy documents and guidelines published in the UK. From April 2008 the same search criteria were applied on a monthly basis to new content added to Medline.

1. Accidental Falls/
2. "Wounds and Injuries"/ep [Epidemiology]
3. 1 or 2
4. falls.ab,ti.
5. 3 and 4
6. incidence.ab,ti.
7. prevalence.ab,ti.
8. mortality.ab,ti.
9. survival.ab,ti.
10. rate$.ab,ti.
11. older.ab,ti.
12. senior.ab,ti.
13. elder$.ab,ti.
14. geriatric$.ab,nw,ti.
15. 11 or 12 or 13 or 14
16. 6 or 7 or 8 or 9 or 10
17. 5 and 15 and 16
18. epidemiology of falls.m_titl.
19. 17 or 18
20. remove duplicates from 19

A different set of parameters were applied for the review of literature relating to medications (see below for example). This also required sorting to identify a small number of studies of immediate relevance to the topics

1. medication.mp.
2. drug.mp. or Pharmaceutical Preparations/
3. 1 or 2
4. Accidental Falls/ or falls.mp.
5. 3 and 4
6. Heart Diseases/
7. Hypertension/
8. 6 or 7
9. 8 and 5

Appendix B - Read codes used to identify incident falls

16D..00	Falls
16D1.00	Recurrent falls
16D2.00	Number of falls in last year
8BIG.00	Falls caused by medication
R200.12	[D] Geriatric fall
T040.00	Fall in train
T040000	Fall in train, railway employee injured
T040100	Fall in train, passenger injured
T040y00	Fall in train, other specified person injured
T040z00	Fall in train, unspecified person injured
T041.00	Fall on train
T041000	Fall on train, railway employee injured
T041100	Fall on train, passenger injured
T041200	Fall on train, pedestrian injured
T041300	Fall on train, pedal cyclist injured
T041y00	Fall on train, other specified person injured
T041z00	Fall on train, unspecified person injured
T042.00	Fall from train
T042000	Fall from train, railway employee injured
T042100	Fall from train, passenger injured
T042y00	Fall from train, other specified person injured
T042z00	Fall from train, unspecified person injured
T04z.00	Fall in, on or from train NOS
T04z000	Fall in, on or from train NOS, railway employee injured
T04z100	Fall in, on or from train NOS, passenger injured
T04z200	Fall in, on or from train NOS, pedestrian injured
T04z300	Fall in, on or from train NOS, pedal cyclist injured
T04zy00	Fall in, on or from train NOS, other spec person injured
T04zz00	Fall in, on or from train NOS, unspecified person injured
T420000	Submersion-fall from gangplank- occ small unpowered boat inj
T420100	Submersion-fall from gangplank- occ small powered boat inj
T420200	Submersion-fall from gangplank- crew other watercraft inj
T420300	Submersion-fall from gangplank- passenger oth watercraft inj
T420400	Submersion-fall from gangplank- water skier injured
T420500	Submersion-fall from gangplank- swimmer injured
T420600	Submersion-fall from gangplank- docker or stevedore injured
T420y00	Submersion-fall from gangplank- other specified person inj
T420z00	Submersion-fall from gangplank- unspecified person injured
T421.00	Submersion or drowning due to fall overboard
T421000	Submersion-fall overboard - occ small unpowered boat inj
T421100	Submersion-fall overboard - occupant small powered boat inj
T421200	Submersion-fall overboard - crew other watercraft injured
T421300	Submersion-fall overboard - passenger other watercraft inj
T421400	Submersion-fall overboard - water skier injured
T421500	Submersion-fall overboard - swimmer injured
T421600	Submersion-fall overboard - docker or stevedore injured
T421y00	Submersion-fall overboard - other specified person injured
T421z00	Submersion-fall overboard - unspecified person injured
T43..00	Fall on stairs or ladders in water transport
T430.00	Fall on stairs in water transport (WT)
T430000	Fall-stairs water transport - occ small unpowered boat inj
T430100	Fall-stairs water transport - occ small powered boat injured
T430200	Fall-stairs water transport - crew other watercraft injured
T430300	Fall-stairs water transport - passenger other watercraft inj
T430400	Fall-stairs water transport - water skier injured

T430500	Fall-stairs water transport - swimmer injured
T430600	Fall-stairs water transport - docker or stevedore injured
T430y00	Fall-stairs water transport - other specified person injured
T430z00	Fall-stairs water transport - unspecified person injured
T431.00	Fall on ladder in water transport
T431000	Fall-ladder water transport - occ small unpowered boat inj
T431100	Fall-ladder water transport - occ small powered boat injured
T431200	Fall-ladder water transport - crew other watercraft injured
T431300	Fall-ladder water transport - passenger other watercraft inj
T431400	Fall-ladder water transport - water skier injured
T431500	Fall-ladder water transport - swimmer injured
T431600	Fall-ladder water transport - docker or stevedore injured
T431y00	Fall-ladder water transport - other specified person injured
T431z00	Fall-ladder water transport - unspecified person injured
T43z.00	Fall on stairs or ladders in water transport, NOS
T43z000	Fall-stairs/ladders-WT NOS - occ small unpowered boat inj
T43z100	Fall-stairs/ladders-WT NOS - occupant small powered boat inj
T43z200	Fall-stairs/ladders-WT NOS - crew other watercraft injured
T43z300	Fall-stairs/ladders-WT NOS - passenger other watercraft inj
T43z400	Fall-stairs/ladders-WT NOS - water skier injured
T43z500	Fall-stairs/ladders-WT NOS - swimmer injured
T43z600	Fall-stairs/ladders-WT NOS - docker or stevedore injured
T43zy00	Fall-stairs/ladders-WT NOS - other specified person injured
T43zz00	Fall-stairs/ladders-WT NOS - unspecified person injured
T44..00	Other falls in water transport (WT)
T440.00	Fall from one level to another NEC in water transport
T440000	Fall to other level NEC in WT - occ small unpowered boat inj
T440100	Fall to other level NEC in WT - occ small powered boat inj
T440200	Fall to other level NEC in WT - crew other watercraft inj
T440300	Fall to other level NEC in WT - passenger oth watercraft inj
T440400	Fall to other level NEC in WT - water skier injured
T440500	Fall to other level NEC in WT - swimmer injured
T440600	Fall to other level NEC in WT - docker or stevedore injured
T440y00	Fall to other level NEC in WT - other specified person inj
T440z00	Fall to other level NEC in WT - unspecified person injured
T44z.00	Fall in water transport NOS
T44z000	Fall in water transport NOS - occ small unpowered boat inj
T44z100	Fall in water transport NOS - occ small powered boat injured
T44z200	Fall in water transport NOS - crew other watercraft injured
T44z300	Fall in water transport NOS - passenger other watercraft inj
T44z400	Fall in water transport NOS - water skier injured
T44z500	Fall in water transport NOS - swimmer injured
T44z600	Fall in water transport NOS - docker or stevedore injured
T44zy00	Fall in water transport NOS - other specified person injured
T44zz00	Fall in water transport NOS - unspecified person injured
T477.00	Hit by boat, or part thereof, after fall from boat
T477000	Hit boat after fall from boat- occ small unpowered boat inj
T477100	Hit boat after fall from boat- occ small powered boat inj
T477200	Hit boat after fall from boat- crew other watercraft injured
T477300	Hit boat after fall from boat- passenger oth watercraft inj
T477400	Hit boat after fall from boat- water skier injured
T477500	Hit boat after fall from boat- swimmer injured
T477600	Hit boat after fall from boat- docker or stevedore injured
T477y00	Hit boat after fall from boat- other specified person inj
T477z00	Hit boat after fall from boat- unspecified person injured
T53..00	Fall in, on, or from aircraft
T532.00	Fall in aircraft
T532000	Fall in aircraft - occupant of spacecraft injured
T532100	Fall in aircraft - occupant of military aircraft injured
T532200	Fall in aircraft - crew commercial aircraft surface/surf inj

T532300	Fall in aircraft - other occ comm aircraft surf/surf injured
T532400	Fall in aircraft - occupant comm surf/air aircraft injured
T532500	Fall in aircraft - occupant other powered aircraft injured
T532600	Fall in aircraft - occupant unpowered aircraft injured
T532700	Fall in aircraft - parachutist injured
T532800	Fall in aircraft - ground crew or airline employee injured
T532z00	Fall in aircraft - other person injured
T533.00	Fall on aircraft
T533000	Fall on aircraft - occupant of spacecraft injured
T533100	Fall on aircraft - occupant of military aircraft injured
T533200	Fall on aircraft - crew commercial aircraft surface/surf inj
T533300	Fall on aircraft - other occupant comm aircraft surf/s inj
T533400	Fall on aircraft - occupant comm surf/air aircraft injured
T533500	Fall on aircraft - occupant other powered aircraft injured
T533600	Fall on aircraft - occupant unpowered aircraft injured
T533700	Fall on aircraft - parachutist injured
T533800	Fall on aircraft - ground crew/airline employee injured
T533z00	Fall on aircraft - other person injured
T534.00	Fall from aircraft
T534000	Fall from aircraft - occupant of spacecraft injured
T534100	Fall from aircraft - occupant of military aircraft injured
T534200	Fall from aircraft - crew commercial aircraft surf/surf inj
T534300	Fall from aircraft - other occupant comm aircraft surf/s inj
T534400	Fall from aircraft - occupant comm surf/air aircraft injured
T534500	Fall from aircraft - occupant other powered aircraft injured
T534600	Fall from aircraft - occupant unpowered aircraft injured
T534700	Fall from aircraft - parachutist injured
T534800	Fall from aircraft - ground crew or airline employee injured
T534z00	Fall from aircraft - other person injured
T53z.00	Fall in, on or from aircraft NOS
T53z000	Aircraft fall NOS - occupant of spacecraft injured
T53z100	Aircraft fall NOS - occupant of military aircraft injured
T53z200	Aircraft fall NOS - crew comm aircraft surf/surf injured
T53z300	Aircraft fall NOS - other occ comm aircraft surf/surf inj
T53z400	Aircraft fall NOS - occupant comm surf/air aircraft injured
T53z500	Aircraft fall NOS - occupant other powered aircraft injured
T53z600	Aircraft fall NOS - occupant unpowered aircraft injured
T53z700	Aircraft fall NOS - parachutist injured
T53z800	Aircraft fall NOS - ground crew/airline employee injured
T53zz00	Aircraft fall NOS - other person injured
T60E.00	Fall from powered vehicle, industrial or commercial
T613.00	Accident involving fall from cable car, not on rails
TC...00	Accidental falls
TC...11	Fall - accidental
TC0..00	Fall on or from stairs or steps
TC00.00	Fall on or from escalator
TC00000	Fall on escalator
TC00100	Fall from escalator
TC00z00	Fall on or from escalator NOS
TC01.00	Fall on or from stairs
TC01000	Fall on stairs
TC01100	Fall from stairs
TC01z00	Fall on or from stairs NOS
TC02.00	Fall on or from steps
TC02000	Fall on steps
TC02100	Fall from steps
TC02z00	Fall on or from steps NOS
TC0z.00	Fall on or from stairs or steps NOS
TC1..00	Fall on or from ladders or scaffolding
TC10.00	Fall from ladder

TC11.00	Fall from scaffolding
TC1z.00	Fall from ladder or scaffolding NOS
TC2..00	Fall from or out of building or other structure
TC20.00	Fall from balcony
TC21.00	Fall from bridge
TC22.00	Fall from building
TC23.00	Fall from flagpole
TC24.00	Fall from tower
TC25.00	Fall from turret
TC26.00	Fall from viaduct
TC27.00	Fall from wall
TC28.00	Fall from window
TC29.00	Fall through roof
TC2z.00	Fall from or out of building or other structure NOS
TC3..00	Fall into hole or other opening in surface
TC30500	Accident caused by fall into swimming pool
TC31.00	Accidental fall into well
TC32.00	Accidental fall into manhole
TC32000	Accidental fall into manhole, unspecified
TC32100	Accidental fall into storm drain
TC32z00	Accidental fall into manhole NOS
TC3y.00	Fall into other hole or other opening in surface
TC3y000	Fall into cavity, unspecified
TC3y100	Fall into dock
TC3y200	Fall into hole
TC3y300	Fall into pit
TC3y400	Fall into quarry
TC3y500	Fall into shaft
TC3y600	Fall into tank
TC3yz00	Fall into other hole, unspecified
TC3z.00	Fall into hole NOS
TC4..00	Other fall from one level to another
TC40.00	Fall from playground equipment
TC41.00	Fall from cliff
TC42.00	Fall from chair or bed
TC42000	Fall from chair
TC42100	Fall from bed
TC42z00	Fall from chair or bed NOS
TC4y.00	Other fall from one level to another
TC4y000	Fall from embankment
TC4y100	Fall from haystack
TC4y200	Fall from stationary vehicle
TC4y300	Fall from tree
TC4yz00	Other fall from one level to another NOS
TC4z.00	Fall from one level to another NOS
TC5..00	Fall on same level from slipping, tripping or stumbling
TC50.00	Fall on same level from slipping
TC51.00	Fall on same level from tripping
TC52.00	Fall on same level from stumbling
TC53.00	Fall on moving sidewalk
TC5z.00	Fall on same level from slipping, tripping or stumbling NOS
TCy..00	Other falls
TCy0.00	Fall from bump against object
TCyz.00	Other accidental fall NOS
TCz..00	Accidental falls NOS
TG30700	Accident caused by fall into moving part of machinery
TG30800	Accident caused by fall from moving part of machinery
TH03.00	Late effects of accidental fall
TN7..00	Injury ?accidental, fall from high place
TN70.00	Injury ?accidental, fall from residential premises

TN71.00	Injury ?accidental, fall from other man-made structure
TN72.00	Injury ?accidental, fall from natural site
TN7z.00	Injury ?accidental, fall from high place NOS
U018411	[X]Fall from pedal cycle without collision
U10..00	[X]Falls
U100.00	[X]Fall on same level involving ice and snow
U100000	[X]Fall on same level involving ice and snow occurrn home
U100100	[X]Fall same level involv ice / snow occurrn resid instit'n
U100200	[X]Fall sam lvl inv ice/snw occ sch oth inst/pub admin area
U100300	[X]Fall same levl involv ice/snow, occ sport/athlet area
U100400	[X]Fall same levl inv ice and snow, occ street / highway
U100500	[X]Fall same levl inv ice / snow, occ trade / service area
U100600	[X]Fall same levl inv ice/snow, occ indust / construct area
U100700	[X]Fall on same levl involving ice and snow occurrn on farm
U100y00	[X]Fall same levl inv ice / snow, occ at other specif place
U100z00	[X]Fall same levl inv ice / snow, occ at unspecified place
U101.00	[X]Fall on same level from slipping, tripping and stumbling
U101000	[X]Fall same levl frm slip trip + stumb, occurrence at home
U101100	[X]Fall same level from slip trip + stumb occ resid instit
U101200	[X]Fall sme levl slp trp+stmb occ sch, oth inst/pub adm area
U101300	[X]Fall sme levl frm slip trip+stumb, occ sport/athlet area
U101400	[X]Fall same level from slip trip+stumb, occ street/highway
U101500	[X]Fall sme lvl frm slip trip+stumb, occ trade/service area
U101600	[X]Fall same levl, slip trip+stumb occ indust/construct area
U101700	[X]Fall same level from slip trip+stumbling, occur on farm
U101y00	[X]Fall same level, slip trip+stumb, occ other specif place
U101z00	[X]Fall same levl frm slip trip+stumbling, occ unspec place
U102.00	[X]Fall involv ice-skates skis roller-skates or skateboards
U102000	[X]Fall inv ice-skate skis roll-skate/skateboard, occ home
U102100	[X]Fall inv ice-skat ski roll-skat/skateboard occ resid inst
U102200	[X]Fall, ice-skt ski rol-skt/skbd, sch oth inst/pub adm area
U102300	[X]Fall inv ice-skt ski rol-skt/skbrd occ sport/athlet area
U102400	[X]Fall inv ice-skat ski roll-skat/skbrd occ street/highway
U102500	[X]Fall inv ice-skt ski rol-skt/skbrd occ trade/servce area
U102600	[X]Fall inv ice-skt ski rol-skt/skbrd indust/construct area
U102700	[X]Fall inv ice-skat ski roll-skat/skatebrd, occur on farm
U102y00	[X]Fall inv ice-skt ski roll-skt/skbrd, occ oth spec place
U102z00	[X]Fall inv ice-skat ski roll-skat/skbrd occ unspecif place
U105.00	[X]Fall involving wheelchair
U105000	[X]Fall involving wheelchair, occurrence at home
U105100	[X]Fall involvng wheelchair occurrence residential instit'n
U105200	[X]Fall invlv w'chair occ school oth instit/pub admin area
U105300	[X]Fall involving wheelchair, occurrn at sport/athlet area
U105400	[X]Fall involving wheelchair, occurrence on street/highway
U105500	[X]Fall involvng wheelchair occurrnce at trade/service area
U105600	[X]Fall involv wheelchair, occurrnce at indust/constr area
U105700	[X]Fall involving wheelchair, occurrence on farm
U105y00	[X]Fall involv wheelchair, occurrnce at other specif place
U105z00	[X]Fall involving wheelchair occurrnce at unspecified place
U106.00	[X]Fall involving bed
U106000	[X]Fall involving bed, occurrence at home
U106100	[X]Fall involving bed occurrence in residential institution
U106200	[X]Fall involv bed occurrn school oth instit/pub admin area
U106300	[X]Fall involving bed occurrence at sports / athletics area
U106400	[X]Fall involving bed, occurrence on street and highway
U106500	[X]Fall involving bed, occurrence at trade and service area
U106600	[X]Fall involv bed occurrn at industrial/construction area
U106700	[X]Fall involving bed, occurrence on farm
U106y00	[X]Fall involving bed, occurrence at other specified place
U106z00	[X]Fall involving bed, occurrence at unspecified place

U107.00 [X]Fall involving chair
U107000 [X]Fall involving chair, occurrence at home
U107100 [X]Fall involving chair occurrence in residential instit'n
U107200 [X]Fall invlv chair occ at school oth instit/pub admin area
U107300 [X]Fall involving chair occurrence at sports/athletics area
U107400 [X]Fall involving chair, occurrence on street and highway
U107500 [X]Fall involv chair, occurrence at trade and service area
U107600 [X]Fall involving chair occurrence at indust/construct area
U107700 [X]Fall involving chair, occurrence on farm
U107y00 [X]Fall involving chair occurrence at other specified place
U107z00 [X]Fall involving chair, occurrence at unspecified place
U108.00 [X]Fall involving other furniture
U108000 [X]Fall involving other furniture, occurrence at home
U108100 [X]Fall involv other furniture occurrn resident institut'n
U108200 [X]Fall inv oth furnitur occ schl oth instit/pub admin area
U108300 [X]Fall involv oth furniture occurrnce at sport/athlet area
U108400 [X]Fall involv other furniture occurrnce on street/highway
U108500 [X]Fall involv oth furniture occurrnce at trade/serv area
U108600 [X]Fall involv oth furnitre occurrnce at indust/constr area
U108700 [X]Fall involving other furniture, occurrence on farm
U108y00 [X]Fall involv oth furnitur occurrnce at other specif place
U108z00 [X]Fall involv oth furniture, occurrnce at unspecif place
U109.00 [X]Fall involving playground equipment
U109000 [X]Fall involving playground equipment, occurrence at home
U109100 [X]Fall involv playgrnd equipm occurr in resident instit'n
U109200 [X]Fall inv playgrnd equip occ sch oth inst/pub admin area
U109300 [X]Fall involv playgrnd equipm occurrn at sport/athlet area
U109400 [X]Fall involv playgrnd equipm occurrnce on street/highway
U109500 [X]Fall involv playgrnd equipm occurrnce trade/service area
U109600 [X]Fall involv playgrnd equipm occurrnce indust/constr area
U109700 [X]Fall involving playground equipment, occurrence on farm
U109y00 [X]Fall involv playgrnd equip occurrnce other specif place
U109z00 [X]Fall involv playgrnd equipm occurrnce at unspecif place
U10A.00 [X]Fall on and from stairs and steps
U10A000 [X]Fall on and from stairs and steps, occurrence at home
U10A100 [X]Fall on + from stair + step occurrnce resident instit'n
U10A200 [X]Fall on + frm stair + step occ sch oth inst/pub adm area
U10A300 [X]Fall on + from stair + step occurrn at sport/athlet area
U10A400 [X]Fall on + from stairs + steps occurrn on street/highway
U10A500 [X]Fall on + from stair + step occurrn at trade/servce area
U10A511 [X]Fall on or from escalator
U10A600 [X]Fall on + from stair + step occurrnce indust/constr area
U10A700 [X]Fall on and from stairs and steps, occurrence on farm
U10Ay00 [X]Fall on + from stair + step occurrn at oth specif place
U10Az00 [X]Fall on + from stair + step occurrnce at unspecif place
U10B.00 [X]Fall on/from ladder
U10B000 [X]Fall on and from ladder, occurrence at home
U10B100 [X]Fall on + from ladder occurrn in residential institution
U10B200 [X]Fall on + from ladder, occ sch oth inst/pub admin area
U10B300 [X]Fall on + from ladder occurrnce at sports/athletics area
U10B400 [X]Fall on and from ladder occurrence on street and highway
U10B500 [X]Fall on and from ladder occurrence at trade/service area
U10B600 [X]Fall on + from ladder occurrn at industr/constructn area
U10B700 [X]Fall on and from ladder, occurrence on farm
U10By00 [X]Fall on+from ladder, occurrence at other specified place
U10Bz00 [X]Fall on and from ladder, occurrence at unspecified place
U10C.00 [X]Fall on and from scaffolding
U10C000 [X]Fall on and from scaffolding, occurrence at home
U10C100 [X]Fall on+from scaffold occurrn in residential institution
U10C200 [X]Fall on + from scaffold occ sch, oth inst/pub admin area

U10C300 [X]Fall on+from scaffold occurrnce at sports/athletics area
U10C400 [X]Fall on + from scaffolding, occurrence on street/highway
U10C500 [X]Fall on + from scaffold occurrence at trade/service area
U10C600 [X]Fall on+from scaffold occurrn at industr/constructn area
U10C700 [X]Fall on and from scaffolding, occurrence on farm
U10Cy00 [X]Fall on+from scaffold occurrnce at other specified place
U10Cz00 [X]Fall on + from scaffold, occurrence at unspecified place
U10D.00 [X]Fall from, out of or through building or structure
U10D000 [X]Fall from out of/through building/structur occurn home
U10D100 [X]Fall from out of/thro buildng/struct occ resid instit'n
U10D200 [X]Fall frm out/thr bldng/strct occ sch oth ins/pub adm area
U10D300 [X]Fall frm out/thro bldng/struct occ at sport/athlet area
U10D400 [X]Fall from out/thro buildng/struct occ on street/highway
U10D500 [X]Fall from out/thro buildng/struct occ at trade/serv area
U10D600 [X]Fall from out/thro buildng/struct occ indust/constr area
U10D700 [X]Fall from out of/through building/structur occurnce farm
U10Dy00 [X]Fall from out/thro buildng/struct occ other specif place
U10Dz00 [X]Fall from out/thro buildng/struct occurrn unspecif place
U10E.00 [X]Fall from tree
U10E000 [X]Fall from tree, occurrence at home
U10E100 [X]Fall from tree, occurrence in residential institution
U10E200 [X]Fall from tree occurrn school oth instit/pub admin area
U10E300 [X]Fall from tree, occurrence at sports and athletics area
U10E400 [X]Fall from tree, occurrence on street and highway
U10E500 [X]Fall from tree, occurrence at trade and service area
U10E600 [X]Fall from tree occurrnce at industrial/construction area
U10E700 [X]Fall from tree, occurrence on farm
U10Ey00 [X]Fall from tree, occurrence at other specified place
U10Ez00 [X]Fall from tree, occurrence at unspecified place
U10F.00 [X]Fall from cliff
U10F000 [X]Fall from cliff, occurrence at home
U10F100 [X]Fall from cliff, occurrence in residential institution
U10F200 [X]Fall from cliff occurrn school oth instit/pub admin area
U10F300 [X]Fall from cliff, occurrence at sports and athletics area
U10F400 [X]Fall from cliff, occurrence on street and highway
U10F500 [X]Fall from cliff, occurrence at trade and service area
U10F600 [X]Fall from cliff occurrn at industrial/construction area
U10F700 [X]Fall from cliff, occurrence on farm
U10Fy00 [X]Fall from cliff, occurrence at other specified place
U10Fz00 [X]Fall from cliff, occurrence at unspecified place
U10H.00 [X]Other fall from one level to another
U10H000 [X]Other fall from one level to another, occurrence at home
U10H100 [X]Othr fall frm one level to anothr occurrn in resid inst
U10H200 [X]Othr fall frm one level to anothr, sch inst/pub adm area
U10H300 [X]Othr fall from one level to anothr occ sport/athlet area
U10H400 [X]Othr fall from one level to anothr occurrn street/h'way
U10H500 [X]Other fall frm one level to anothr occ at trde/serv area
U10H600 [X]Other fall frm one level to anoth occ indust/constr area
U10H700 [X]Other fall from one level to another, occurrence on farm
U10Hy00 [X]Other fall frm one levl to anothr occ at oth specif plce
U10Hz00 [X]Othr fall frm one level to anothr occurrn at unspec plce
U10J.00 [X]Other fall on same level
U10J000 [X]Other fall on same level, occurrence at home
U10J100 [X]Other fall on same level, occurrnce in resident instit'n
U10J200 [X]Other fall on same levl occ schl oth inst/pub admin area
U10J300 [X]Other fall on same level occurrn at sports/athletic area
U10J400 [X]Other fall on same level, occurrence on street / highway
U10J500 [X]Other fall on same level occurrnce at trade/service area
U10J600 [X]Other fall on same levl, occurrn at indust/constuct area
U10J700 [X]Other fall on same level, occurrence on farm

U10Jy00 [X]Other fall on same level occurrn at oth specified place
U10Jz00 [X]Other fall on same level occurrence at unspecified place
U10z.00 [X]Unspecified fall
U10z000 [X]Unspecified fall, occurrence at home
U10z100 [X]Unspecified fall, occurrence in residential institution
U10z200 [X]Unspecif fall occurrnce school oth instit/pub admin area
U10z300 [X]Unspecified fall, occurrence at sports / athletics area
U10z400 [X]Unspecified fall, occurrence on street and highway
U10z500 [X]Unspecified fall, occurrence at trade and service area
U10z600 [X]Unspecified fall occurrn at industrial/construction area
U10z700 [X]Unspecified fall, occurrence on farm
U10zy00 [X]Unspecified fall, occurrence at other specified place
U10zz00 [X]Unspecified fall, occurrence at unspecified place
U131.00 [X]Drowning and submersion following fall into bath-tub
U131000 [X]Drowning+submersn follow fall into bath-tub occ at home
U131100 [X]Drowng+submersn foll fall into bath-tub occ resid instit
U131200 [X]Drown+subm foll fall into bath-tub sch ins/pub adm area
U131300 [X]Drown+subm foll fall into bath-tub occ sport/athlet area
U131400 [X]Drowng+submersn foll fall into bath-tub occ street/h'way
U131500 [X]Drown+subm foll fall into bath-tub occ trade/servce area
U131600 [X]Drown+subm foll fall into bth-tub occ indust/constr area
U131700 [X]Drowning+submersn follow fall into bath-tub occ on farm
U131y00 [X]Drown+subm foll fall into bath-tub occ oth specif place
U131z00 [X]Drown+subm foll fall into bath-tub occ at unspecif place
U133.00 [X]Drowning + submersion following fall into swimming-pool
U133000 [X]Drowning+submer follow fall into swim-pool occurrn home
U133100 [X]Drown+submersn foll fall into swim-pool occ resid instit
U133200 [X]Drown+subm foll fall into swim-pool sch ins/pub adm area
U133300 [X]Drown+subm foll fall into swim-pool occ sport area
U133400 [X]Drown+submersn foll fall into swim-pool occ street/h'way
U133500 [X]Drown+subm foll fall into swim-pool occ trade/serv area
U133600 [X]Drown+sub foll fall into swim-pool occ indust/constr area
U133700 [X]Drowning+submer follow fall into swim-pool occurrn farm
U133y00 [X]Drown+subm foll fall into swim-pool occ oth specif place
U133z00 [X]Drown+subm foll fall into swim-pool occ unspecif place
U135000 [X]Drowng+submersn follow fall into natural water occ home
U135100 [X]Drown+submr foll fall into naturl water occ resid instit
U135200 [X]Drown+subm foll fall into natrl watr sch ins/pub adm area
U135300 [X]Drown+subm foll fall into natrl watr occ sport/athl area
U135400 [X]Drown+submr foll fall into naturl water occ street/h'way
U135500 [X]Drown+sub foll fall into naturl watr occ trade/serv area
U135600 [X]Drwn+sub foll fall into natrl watr occ indust/constr area
U135700 [X]Drowng+submersn follow fall into natural water occ farm
U135y00 [X]Drown+sub foll fall into naturl watr occ oth specif place
U135z00 [X]Drown+subm foll fall into naturl watr occ unspecif place
U4B..00 [X]Falling jumping/pushed from high place undeterm intent
U4B0.00 [X]Falling jumpng/push frm high place undet intent occ home
U4B1.00 [X]Fall jump/push frm high place undet intent occ resid inst
U4B2.00 [X]Fall jump/push high plce undet intnt sch/ins/pub adm area
U4B3.00 [X]Fall jump/push frm high plce undt intnt sport/athlet area
U4B4.00 [X]Fall jump/push frm high place undt intnt occ street/h'way
U4B5.00 [X]Fall jump/push frm high plce undt intnt trade/servce area
U4B6.00 [X]Fall jump/push frm high plce undt intn indust/constr area
U4B7.00 [X]Falling jumpng/push frm high place undet intent occ farm
U4By.00 [X]Fall jump/push frm high plce undt intnt occ oth spec plce
U4Bz.00 [X]Fall jump/push frm high plce undt intnt occ unspecif plce
U4C..00 [X]Falling lying running befor/into moving obj undet intent
U4C0.00 [X]Falling lyng run befr/into mov obj undet intent occ home
U4C1.00 [X]Fall ly run befr/into mov obj undet intent resid instit'n
U4C2.00 [X]Fall ly run bef/into mov obj und int sch/ins/pub adm area

U4C3.00	[X]Fall ly run befr/into mov obj undet intent sprt/athl area
U4C4.00	[X]Fall ly run befr/into mov obj undet intent street/highway
U4C5.00	[X]Fall ly run befr/into mov obj undet intent trad/serv area
U4C6.00	[X]Fall ly run befr/into mov obj undet intent industr area
U4C7.00	[X]Fallng lyng run befr/into mov obj undet intent occ farm
U4Cy.00	[X]Fall ly run befr/into mov obj undet intent oth spec place
U4Cz.00	[X]Fall ly run befr/into mov obj undet intent unspecif place

Appendix C - Publications arising from PhD studies