Understanding multiple medication use in people with dementia. A pharmacoepidemiology study of prevalence, intervention and associated harms.

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Abstract

Background: Around 70% of people with dementia live with comorbidities and are subsequently prescribed multiple medications (polypharmacy). Some medicines are considered 'potentially inappropriate' when prescribed to older and cognitively impaired adults. Cognitive impairment, dementia and frailty may influence the prevalence and associated effects of polypharmacy and potentially inappropriate medicines (PIMs).

Aims: To estimate prevalence trends of polypharmacy and PIMs (antipsychotics, antidepressants, benzodiazepines, anticholinergics and proton pump inhibitors) among people with dementia. To identify associated factors, including the impact of care and medication reviews and to understand the impact of polypharmacy, PIMs and frailty on health in people with cognitive impairment.

Methods: Two cohorts were analysed, including primary care electronic medical records (Clinical Practice Research Datalink, 2015-2017) (n=22,448) and the Cognitive Function and Ageing Study (2008-2011) (n=1,154).

Results: Polypharmacy and PIMs were prevalent in people with dementia and cognitive impairment. On average, people with dementia were prescribed 8 medications, 30% were prescribed inappropriate PPIs, 17% anticholinergics, 8% antipsychotics, 7% tricyclics and 4% of people with cognitive impairment were prescribed benzodiazepines. Dementia annual reviews and medication reviews were associated with medicines optimisation. Prevalence of PIM was greater in care homes and a medication review in a care home was associated with reduced use of PIMs. Polypharmacy was associated with worse survival. PIMs were not associated with worse survival, with the exception of antipsychotics (adjusted HR=3.24, 95% CI=1.83-5.73). Being cognitively impaired and frail was associated with worse survival overall but frailty was not found to moderate the relationship between polypharmacy, PIMs and survival.

Conclusions: Few prescribing guidelines specifically address medicines use in people with cognitive impairment or dementia, despite the prevalence of polypharmacy and PIMs. The number of medicines prescribed should be carefully monitored to reduce harm. Incorporating medication reviews into annual dementia care reviews may optimise prescribing and identify people at increased risk of adverse effects. The findings from this thesis will improve understanding and support the optimisation of medicines for people living with dementia.

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Table of Abbreviations

Abbreviation	Elaboration
UK	United Kingdom
NHS	National Health Service
QOF	Quality and Outcomes Framework
MCI	Mild Cognitive Impairment
CHS	Cardiovascular Health Study
FI	Frailty Index
GMS	General Medical Services
COPD	Chronic Obtrusive Pulmonary Disease
NICE	National Institute for Health and Care Excellence
PIM	Potentially Inappropriate Medication
START	Screen Tool to Alert doctors to Right Treatment
STOPP	Screening Tool for Older Person's Prescriptions
Beers	Beers criteria for potentially inappropriate medication use in older adults
CFAS	Cognitive Function and Ageing Studies
PRISMA-ScR	Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews
RCT	Randomised Controlled Trial
MAI	Medication Appropriateness Index
NSAIDs	Nonsteroidal anti-inflammatory drugs
PPI	Proton Pump Inhibitors
PEACE	Palliative Excellence in Alzheimer's Care Efforts
REAL.FR	*REseau sur la maladie ALzheimer FRançais*
NIA	National Institute of Ageing
UDS	Uniform Data Set
EVIDEM- EoL	Evidem End of Life Studies
SSRI	Selective-Serotonin Re-uptake Inhibitors
MAOIs	Monoamine Oxidase Inhibitors
GP	General Practitioner
CPRD	Clinical Practice Research Datalink
MRC	Medical Research Council
IMD	Index of Multiple Deprivation
DAR	Dementia Annual Review
ATC	Anatomical Therapeutic Chemical Classification System
ACB	Anticholinergic Cognitive Burden
CCI	Charlson Comorbidity Index
ICD	International Classification of Diseases
MR	Medication Review
MMSE	Mini-Mental State Examination
CAMCOG	Cambridge Cognitive Examination
GMS-AGECAT	Geriatric Mental State -AGECAT computerised diagnostic system
CI	Confidence Interval
KM	Kaplan-Meier survival curve
HAS	History and Aetiological Schedule
SD	Standard Deviation
HR	Hazard Ratio
RTPC	Right Time Place Care
MEPS	Medical Expenditure Panel Surveys
ADS	Anticholinergic Drug Scale
SHELTER	Services and Health for Elderly in Long-Term Care

Publications arising from this research

Porter B, Arthur A, Savva GM (2019) How do potentially inappropriate medications and polypharmacy affect mortality in frail and non-frail cognitively impaired older adults? A cohort study. *BMJ Open*;9:e026171. doi: 10.1136/bmjopen-2018-026171

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"…It got me thinking how people in the late stages must feel when medication is added or changed. They might not know or understand why they're feeling rubbish from the side effects. Why their head feels so different. Why their body feels so strange. Why they feel so rough. They might not be able to articulate how they're feeling so lash out or simply sleep all day. I read of one supporter recently who was glad when their loved one slept all day as then they didn't have to cope with the challenges. But what sort of existence is that for either one?

Side effects can be different for everyone but I don't think enough is known about the impact on the brain for people with dementia. So more research needs to take place to understand the impact of medication on people with dementia."

A quote from Wendy Mitchell, who lives with a diagnosis of dementia, from the blog 'Which Me am I Today' July 2017.

I.   Chapter 1: Background and Introduction

In the United Kingdom (UK) there are over 850,000 people over the age of 65 living with dementia [1] and there are more than 200,000 new cases of dementia every year [2]. Around 70% of people living with dementia also live with other health conditions and are subsequently prescribed multiple medications [3]. Multiple medication use is common in this increasingly large population, who are vulnerable to a range of associated side effects and adverse effects of potentially inappropriate prescribing practices.

1.01   Dementia

More than 44 million people live with dementia worldwide and there are an estimated 4.6 million new cases annually [4, 5]. Dementia is clinically defined as the broad term of major neurocognitive disorder. Dementia is a progressive neurodegenerative syndrome, largely characterised by memory deficits but also affects an individual's communication, language, attention, perception, executive and motor functions and social cognition. Dementia is an umbrella term used to define a variety of conditions affecting the brain. Alzheimer's disease is the most frequent cause of dementia, accounting for two-thirds of cases, followed by vascular dementia (20%), Lewy body dementia (15%), frontotemporal dementia (5%), Parkinson's, Creutzfeldt-Jakob disease and other rarer forms of dementia. Each person's experience of dementia is different. It is common for an individual to be living with a combination of dementia disease types. Each condition is characterised by a different set of symptoms, and associated with ongoing disease progression over time. In general, dementia is more common in women than men [1, 5] and the prevalence of dementia increases as people age, with one in fourteen adults over 65 years old at risk of dementia, increasing to one in six in adults over 80 years [1, 4, 6].

1.02   Global burden of disease

In 2015, the global cost of dementia was estimated at £631 billion (US $818 billion). Around 80% of the financial burden falls on health and social care services and informal carers, in comparison to costs directly associated with use of medical services [7]. In 2016, dementia was one of the highest causes of death globally after ischaemic heart disease, chronic obtrusive pulmonary

disease, intracerebral haemorrhage and ischaemic stroke, accounting for 2.2 million deaths worldwide [8].

1.03   Burden of disease in United Kingdom

By 2030, it is predicted that there will be over 1 million people living with dementia in the UK and over 1.2 million by 2040 [9]. Currently, dementia costs the UK economy £26 billion annually and the overall economic burden is expected to increase to £55 billion by 2040. Dementia costs the National Health Service (NHS) £4.3 billion each year and the cost of unpaid care is £11.6 billion [10]. Dementia is now the leading cause of death in adults over 80 years old in England and Wales, accounting for 20% of all deaths, ahead of ischemic heart disease and cerebrovascular disease [11].

Improving the quality of life for people with dementia and their carers is a national priority. In England, the National Dementia Strategy (2009) and subsequent Dementia Challenge (2012), were launched by the government. Central to their aims was diagnosis, improving awareness, early interventions and quality of care. Similar strategies were launched in Scotland in 2010 and Wales in 2011 [12, 13]. Since 2006, general practitioners have been financially incentivised through the Quality and Outcomes Framework (QOF) to record dementia prevalence on dementia registers and to conduct annual care reviews for people with dementia. After the launch of the National Dementia Strategy in 2009, dementia diagnosis rates increased by 4% in 2010 and 12% in 2011 [14].

1.04   Cognitive impairment

Cognitive function is the process of knowledge acquisition and understanding through thought, experiences and the senses. There are multiple cognitive functions that are integral for our day-to-day lives. Cognitive functioning encompasses our response to emotional and social situations, decision making, memory, attention, reasoning, processing and response to people, our environment and experiences. Many older adults live with impairments across cognitive functions. Mild cognitive impairment (MCI) or mild neurocognitive disorder is the clinical term used to define a recognisable decline in cognition from previous level of functioning. Mild cognitive impairment is a recognisable decline, but does not significantly impact on the ability to

conduct day-to-day activities, and so does not meet the criteria to be formally labelled as dementia. In some cases, MCI reflects the early stages of dementia. However, longitudinal studies demonstrate that whilst some people with MCI go on to develop dementia, a significant proportion revert to normal cognition or remain stable [15]. Most commonly, MCI that is largely characterised by memory impairment is associated with progression to dementia [16]. Up to 36% of adults over 60 years old live with MCI [17] and around 60% of people with MCI progress to dementia [18]. For the purposes of this research, mild cognitive impairment, mild neurocognitive disorder and cognitive impairment that is not diagnosed as dementia, will be referred to as cognitive impairment.

1.05   Risk factors

There are a number of risk factors associated with dementia. This includes a number of comorbid health conditions that increase a person's risk of developing the disease, as well as genetic and lifestyle factors [19]. Cerebrovascular disease and cerebral damage from haemorrhage and ischemic cortical infarcts associated with stroke are associated with an increased risk of dementia. Around 8% of people who have a stroke subsequently develop post-stroke dementia [20]. Cerebrovascular disease is most strongly associated with vascular dementia, which is largely characterised by reduced blood flow to the brain.

Other physical comorbidities have been associated with an increased risk of dementia, including high blood pressure, high cholesterol and diabetes. High blood pressure in middle-aged adults has been associated with an increased risk of cognitive impairment, Alzheimer's disease and dementia [21–23]. Unhealthy cholesterol levels are associated with cerebrovascular disease, increasing the risk of dementia. Observational studies have also shown that Type 2 diabetes is associated with twice the increased risk of Alzheimer's disease [24–26]. A meta-analysis of longitudinal studies found an increased risk of 54% associated with Type 2 diabetes [27]. In addition, obesity, a risk factor for high blood pressure, cholesterol and diabetes, is associated with an estimated 59% increased risk of dementia [27]. Age is the greatest risk factor for dementia and older age is also associated with increased comorbidities and health complications [1, 4, 6]. Although, approximately 5% of cases of dementia are considered 'early-onset' when the disease is diagnosed in people under the age of 65 [28].

A number of psychosocial factors are also associated with increased risk of dementia. Evidence suggests that fewer years in education is associated with an increased risk of dementia, although

this is not conclusive [29]. Previous studies have also found an association between social isolation and cognitive impairment in older adults [30]. Depression is prevalent in people with dementia [31]. However it is difficult to determine the causal relationship between depression and dementia, particularly in the prodromal stages of disease presentation [32]. Many psychosocial factors, including social isolation and depression for example, are intrinsically linked with one another and often linked with physical comorbidity. Collectively, these factors contribute to increased vulnerability to the impact of risk factors associated with dementia. However, many of these risk factors are modifiable through lifestyle changes, psychological and pharmacological therapy. A recent report reported that modifiable risk factors could account for up to 35% of dementia burden [33].

1.06   Pharmacological approaches to managing dementia

There is no cure or disease modifying treatment for dementia. There are a small selection of medications prescribed to manage symptoms of the disease. The most commonly used medications are acetylcholinesterase inhibitors (donepezil, rivastigmine and galantamine), which inhibit the transmission of the neurotransmitter acetylcholine. These are used to manage symptoms of mild to moderate Alzheimer's disease. Donepezil can be prescribed in people with severe Alzheimer's disease. Memantine, which acts on the glutamatergic system, can be prescribed to people with moderate-severe Alzheimer's disease, Lewy body dementia and mixed dementia. Overall, the symptom management options for dementia are limited [34] and with more clinical trials resulting in negative outcomes than successes, at a ratio of 100:1 compared with a 14.6:1 average across the pharmaceutical industry [35, 36].

Since there are no disease modifying treatments, improving the quality of life for the individual and carers is a priority. Enabling the person to live-well and within their own priorities for care, for as long as possible. Symptom and comorbidity management is associated with medication use. Comorbidities associated with the risk of dementia are usually treated with medicines. Managing the symptoms associated with cardiovascular disease, cerebrovascular disease, diabetes, high blood pressure, high cholesterol, and depression, for example. Additionally, medications are often prescribed to manage behavioural and psychological symptoms of dementia.

1.07   Care for people with dementia

With two thirds of people with dementia living in the community, familial carers are a cornerstone for the provision of support and care of people living with dementia. For many carers, the experience can be associated with psychological, physical, emotional and economic strain. Many carers will experience caregiver burden, which is affected by the multiple dimensions of their role as a carers. Defined as a multidimensional response to physical, psychological, emotional, social and financial stressors associated with the caregiving experience [37]. Carers will often play a key role in the management of medicines for people with dementia, including responsibility for taking medicines and involvement in decisions around prescribing [38]. The demands and time providing care increases as the disease progresses. Health and social care services need to find ways to support both the person with dementia and their carer across the disease progression [39].

People with dementia live across the community and within institutional settings, including a high proportion of people with dementia in care, residential or nursing homes. In the UK, around one third of people with dementia live in a care home [28], often at later stages of the disease, are more frail and in need of more assistance in activities of daily living. People with dementia may live for a long time in their own home and often transition into a care home as the disease progresses, physical and cognitive capacity declines and need for support in conducting day-to-day activities, such as washing, dressing and eating requires additional support. The experiences, patient preferences and health priorities will change across the progression of the disease. It is important to factor this variation into the development of patient-centred and individualised care plans.

1.08   Frailty and dementia

'Frailty' refers to the condition of being 'frail' that is commonly recognised in many older people. A person who is frail is typically but not exclusively less mobile, may have difficulty getting up from a chair, walk slowly, is easily tired or exhausted from small amounts of activity, and is generally less active on a daily basis. More formally, frailty is a term used to describe a state of age-related decline in functioning across multiple organ systems. Frailty is associated with an increased vulnerability to and diminished ability to cope, and recover from acute and everyday life events, also referred to as reduced physiological reserve. Frailty is now a recognised, multifactorial clinical state that affects health outcomes for older adults, although it is not

exclusively a gerontological issue. A change in medication, minor infection, change of residence, bereavements, falls, hospital admission and operations are examples of potentially destabilising events. These events could significantly impact a frail adult and their ability to return to the same level of function as before the event. The consequences of these destabilising events in frail older adults may result in drastic change, such as from independent to dependent, lucid to delirious and stable to at risk of falls [40].

There is some evidence of an association between frailty and cognitive impairment and dementia. Frailty and dementia share some common aetiologies and overlapping clinical features, including factors associated with increased dementia risk, such as diet, cardiovascular risk factors and depression [41]. Age is strongly associated with dementia and it is thought that there is an association between the age-related processes associated with frailty and cognitive impairment and dementia [41]. In the Rush Memory and Ageing Project, a longitudinal study of ageing, baseline frailty and annual frailty change was associated with incident dementia and MCI [42]. An ongoing debate centres on distinguishing frailty as a clinical syndrome distinct from comorbidity and disability. Frailty, disability and comorbidity are not mutually exclusive but there are features that do distinguish them, including decreased physiological reserve, impairment across multiple organ systems and capacity to recover after a stressful event [43]. Fried et al (2001) investigated the overlap between frailty, disability and comorbidity using the Cardiovascular Health Study, in 21.5% of the sample frailty, disability and comorbidity were present. However, in 26.6% frailty was present without comorbidity or disability, supporting the argument that frailty is related to, but distinct from comorbidity and disability. On the other hand, frailty has been considered as a representation of an accumulation of comorbidities, disability, cognitive decline and any other age-associated deficits [44]. Through the operationalisation of frailty definitions in large epidemiological studies, frailty has been recognised as predictive of a number of adverse outcomes which include, increased risk of falls [45, 46], disability [45, 46], hospitalisation [47], admittance to a care home [48, 49] and mortality [45, 46, 48, 49]. More recently, frailty has started to be operationalised for use in clinical practice. Although, the concept of a 'frail' older adult has been recognised for a long time. More research is needed to validate the concept of frailty for use in clinical practice compared to translating findings from observational studies.

The concept of frailty is continually under debate and other approaches to understanding variation in ageing have been proposed. As an alternative, the concept of intrinsic capacity, which has a capacity rather than disease focus has been proposed. Particularly for monitoring trajectories from independence to dependence in older populations [50]. Regardless of the concept used, the concepts must be validated to predict adverse outcomes. Further research is

needed to validate the constructs of frailty. Moreover, in clinical practice the concept that will be able to be of most practical utility, feasibility, and able to identify those at risk of harm or who will benefit from intervention is of the utmost importance.

(a) Defining frailty

There are two dominant but very different frailty measurements that are most commonly used in research and clinical practice, the Frailty Phenotype [47] and the Frailty Index (FI) [44]. The phenotype is characterised as a syndrome with specific pathophysiological processes that are part of a cycle of frailty, whereas the FI characterises frailty much more broadly as a marker of the number of age-associated deficits that are predictive of adverse outcomes.

(i) Frailty Phenotype

Fried and colleagues initially developed a core set of frailty criteria in 2001 and operationalised these into the frailty phenotype, which was validated in the Cardiovascular Health Study [47]. The frailty phenotype is a pre-defined set of five criteria capturing a range of signs or symptoms (involuntary weight loss, exhaustion, slow gait speed, poor handgrip strength and sedentary behaviour). The frailty phenotype is dominated by physical factors that contribute to a syndrome of frailty. In the original development of the phenotype, people with cognitive impairment, Parkinson's disease, previous stroke or depression were excluded from the sample. Furthermore, the concept does not directly account for changes in cognition or mental health. This challenges the validity of some of the criteria since mental health, particularly depression may be intrinsically linked to physical health. It is of debate whether frailty assessment should include a mental health assessment too. The relationship could be argued to be bi-directional too since people who are depressed are less physically active, and people who are less physically active are more likely to become isolated and depressed [51]. Although, it can be argued that mental health may be reflected within the manifestation of the criteria, such as exhaustion. The exhaustion questions often translates from depression scales and as such could be argued to account for mental health in the criteria.

Although the frailty phenotype has since been validated in older, multimorbid populations [52], there are concerns about the predictive validity of specific criteria. According to the Fried

phenotype, obese people would not be considered frail. The criteria is characterised by rapid weight loss, even though people who are obese are less physically active and more likely to report exhaustion [53]. The overall phenotype construct is predictive of adverse outcomes, further research is required to evaluate the predictive validity of individual frailty criterion [54]. Furthermore, whether or not frailty is a useful predictor of vulnerability to adverse outcomes from another predictor, and therefore whether frailty moderates susceptibility to adverse outcomes is unknown.

(ii) Frailty Index

The Frailty Index (FI) is based on the characterisation of frailty as an accumulation of age-related deficits, with more deficits indicative of a frailer individual. To initially operationalise this concept, Rockwood and colleagues created the FI in 2005 using the Canadian Study of Health and Ageing to develop and validate the FI [44]. The FI is a clinical condition and disease checklist of up to 70 items or deficits (as originally proposed). Symptoms, signs and diseases are classified as deficits [55] which therefore may include, clinical signs (e.g. tremor), symptoms (e.g. vision problems), diseases, disabilities and abnormal test values and are used to generate a cumulative FI score. The FI score is based on each item being present or absent as a proportion of the total number of items. This score has an advantage of being useful as a continuous measure or dichotomised variable classifying non-frail, pre-frail or frail and could be more sensitive to identifying change across frailty status [56] [57]. This approach includes cognitive and physiological vulnerabilities which are not accounted for in the phenotype. Some have argued that frailty should also account for social connections and relationships which when lacking can increase vulnerability to life events [58]. However, in applying a deficit accumulation approach, all potential age-related vulnerabilities that a person has are grouped together. No distinction can be made to understand individual contribution of comorbidity, cognitive impairment or physical frailty. The frailty phenotype is more suited to understanding the individual contributory risk associated with physical frailty, distinct from comorbidity and cognitive impairment.

The clinical application of frailty has recently spiked further interest in the validity of the constructs. The routine identification of frailty has been included in the General Medical Services (GMS) General Practitioners contracts [59]. In practice, the identification of people who are frail can assist in recognising those who are most vulnerable to stressors and with complex care needs. Frailty is a good predictor of adverse outcomes and in practice will be more informative than age when assessing patients. However, much of the evidence is based on observational studies where

frailty is measured at a single time point, failing to account for the transitional nature of frailty. Both concepts of frailty have been widely replicated and adapted in observational studies and clinical settings meaning there has been little standardisation [60]. Moreover, there is a lack of a consensus on definition and measurement of frailty. This means that depending on the definition of frailty, different individuals may be identified as frail according to different definitions. This will continue to be a challenge in practice as there is limited guidance on the type of frailty measure that should be used. Standard definitions of frailty, particularly across different practices, will vary considerably [61].

Through identifying frailty, there may be opportunities for interventions to improve factors contributing to frailty. Frailty assessments can provide useful information to help practitioners and patients in developing care plans and opportunities for interventions. This may include, exercise, caloric and protein support, vitamin D supplements and reducing polypharmacy [62]. However, for the individual the concept or label of frailty can negatively affect their self-identity and the way in which other people view them as the term is loaded with negative connotations [63]. Frailty can help in delineating the heterogeneity of physical and cognitive decline associated with ageing. However, further research is required to assess the predictive validity of individual frailty criteria. From a clinical perspective, this is important as identifying frailty is more readily incorporated into clinical practice.

1.09   Comorbidity and dementia

Comorbidity, the concomitant presence of more than one health condition in an individual, is common in up to 70% of people living with dementia [3]. The presence of multiple comorbidities (multimorbidity) is associated with adverse health outcomes, decreased quality of life, complex care regimes, increased use of health care services, and subsequent health costs [64]. In a study of over 10,000 people with dementia in UK primary care, people with dementia had on average 2.9 physical comorbidities compared with 2.4 in age-matched controls [65]. A US study of over 3,000 older adults with and without dementia estimated that people with dementia had 2.4 chronic conditions. This was comparable to older adults without dementia in this population (2.3 chronic medical conditions). As expected, there is considerable overlap between the comorbidities that are risk factors for dementia and those most commonly occurring in people with dementia. An estimated 41% of people living with dementia have high blood pressure, 32% depression, 27% heart disease, 18% cerebrovascular disease and 13% diabetes [66]. A scoping

review of the literature of comorbidities in people with dementia found that the prevalence of diabetes in people with dementia was as high as 39%. Thirty four percent of people with dementia had also had a stroke [67].

Psychiatric comorbidities are also common in people with dementia but symptoms can be difficult to differentiate from dementia symptoms. Depression is a risk factor associated with dementia and is prevalent in people with dementia [31]. Anxiety is also common in around 5% to 25% of people living with dementia and is associated with restlessness, fatigue, difficulty concentrating and worry [68]. Behavioural and psychological symptoms of dementia, including psychosis, hallucinations and wandering also impact on individual experience of living with and caring for someone with dementia [69]. Medications are commonly prescribed to manage behavioural and psychological symptoms and comorbidities.

While the number of comorbidities may be similar across people with and without dementia, it is likely that managing comorbidities is more challenging in this population. People with dementia and comorbidity are particularly affected by a lack of care continuity, integration or communication across primary and secondary care and multiple specialists [67]. Many comorbidities are associated with an increased risk of dementia or are associated with consequential outcomes of dementia, such as depression in dementia. In clinical settings such as hospitals and care homes, dementia can affect and complicate care, including how the person's individual needs are understood and the way in which services are used [70].

As a direct consequence of comorbidity, many people with dementia are prescribed multiple medications, which is discussed further in the next section and is the motivating problem underlying the work presented in this research study.

1.10   Polypharmacy

Polypharmacy is the commonly used term to describe the prescription of multiple medications [71]. There are many different definitions of polypharmacy. A commonly used definition is five or more medications [72]. There is no consensus on whether polypharmacy refers to the concomitant use of multiple medications at the same time, or whether it refers to medications prescribed long-term, such as through a repeated prescription system [72]. Older adults are the largest consumers of medications compared with other groups of the population. Around one fifth of the UK population is over 60 years old, and this group receives around 60% of all

prescriptions, accounting for more than half of NHS prescribing costs [73, 74]. The increased use of symptom managing and treating medicines has been fundamental in improving the quality of health care provision, quality of life, recovery from illness, reducing disability, and increased longevity amongst the population [75]. In the past century, life expectancy in the UK has steadily increased. In 1910, male life expectancy was 51 and 55 for females. This has increased to 80 for males and 83 for females in 2012 [76]. Other factors such as improved nutrition, hygiene, housing and sanitation are important, but improvements in medicine and the introduction of the National Health Service (NHS) in 1948 has significantly contributed. Through improved control of infectious diseases, reduced mortality at birth and improvements in treatments, more and more people are able to live-well for longer.

(a) Challenges of polypharmacy

There are a number of challenges associated with polypharmacy for people with dementia with multimorbidity, for whom medicines are an integral part of everyday life. Appropriate and evidence based use of multiple medicines is made more difficult by the single disease focus of prescribing guidelines, limited external validity and generalisability of clinical trials, prescribing cascades, adherence, medication errors, a lack of guidelines for prescribing and increased susceptibility to adverse effects. Each associated challenge may also multiplicatively increase the potential for harm in a population who are already increasingly vulnerable to medication-related adverse effects and the subsequent consequences. More research is required to improve the quality of life for people with dementia and those managing multimorbidity and polypharmacy.

(i) Prescribing guidelines take a single disease focus

By taking a single disease focus, guidelines often fail to account for multimorbidity, drug-disease and drug-drug interactions that may increase the patient's susceptibility to adverse effects and ineffective treatment. Previous research has found a lack of consistency in the way in which guidelines will account for comorbid health conditions and identified few disease-specific recommendations for prescribers [77]. Multiple medications are likely to be prescribed for a patient with multiple comorbidities. For example, a patient with five mild-to-moderate comorbidities such as, previous myocardial infarction, type-2 diabetes, osteoarthritis, chronic obstructive pulmonary disease (COPD) and depression, could be prescribed a minimum of 11

medications [77]. The patient could also be prescribed up to 10 additional medications depending upon the disease progression, side effects and outcomes. In addition, managing a complex medication regime can increase treatment burden to an individual. Additional treatment burden from multiple appointments, other recommended interventions and referrals, also recommended through the guidelines would accumulate to considerable treatment burden for the individual [77]. The single disease focus approach to guidelines can negatively affect the individual. Recent years have seen some improvement in the provision of guidelines that account for multimorbidity. The National Institute for Health and Care Excellence (NICE) have published guidelines for the clinical assessment and optimisation of care for people with multimorbidity, which includes optimising medicines and assessing frailty [78]. Furthermore, the Royal Pharmaceutical Society have published good practice guides for optimising medicines for pharmacists to support patients [79]. For a person living with dementia or cognitive impairment, managing medications can be increasingly difficult, however it is unclear the extent of harm that may be associated with multiple medication use in people with dementia and there is little research into prescribing in people with dementia in primary care [80].

(ii) External validity and generalisability of clinical trials

The evidence for the safety and efficacy of medicines may not be applicable to people with cognitive impairment and dementia. For a number of reasons, people with cognitive impairment are excluded from clinical trials. It would be unethical to conduct a trial in a sample where there was a potential for increased risk of harm. In addition, people with cognitive impairment or dementia may also be excluded from trials due to difficulties in recruitment and retainment in studies. It may also be more difficult to detect outcomes due to the complexities associated with dementia and comorbidities. Controlled clinical trials are generally conducted in younger and healthy populations, representing a population with a lower-risk profile. The impact of this is that older adults, adults with comorbidities, cognitive impairment, dementia, frailty and polypharmacy are excluded. Given this, it is unsurprising that older adults are often underrepresented in clinical trials [81, 82]. One study reviewing over 280 randomised controlled trials (RCT) over a 10 year period, found 81% of RCTs excluded participants because of comorbidities and 39% excluded people based on their age. Drug intervention trials often exclude participants because of other medication use [83].

While reporting is mandatory, often adverse events go unrecognised or unreported. A recent review of the reporting of adverse events in published RCTs identified that of 184 trial studies,

30% reported methods to identify adverse event data during the trial. Therefore, only a small proportion of the trials reported using a mechanism through which an adverse event could be reported by a participant, meaning adverse events may have gone unrecognised. Moreover, 35% of the studies reported whether a withdrawal from the trial was due to an adverse event and may therefore be under reporting the incidence of adverse events [84]. In addition, a discussion of both the benefits and harms of a medication is often missing from findings in published trial studies [85]. Finally, the controlled environment of an RCT alongside selective sampling also limits the external validity, and consequently the clinical implications of prescribing in populations with high-risk profiles in an uncontrolled environment [86].

(iii) Prescribing cascade

Prescribing cascades can occur in people with dementia, particularly if the individual has difficulty communicating adverse effects of medicines. Prescribing cascades occur when cumulative prescriptions for medication related adverse effects are prescribed. Prescribing cascades can occur inappropriately. Although, side effects of medicines can also be appropriately recognised and treated with another medicine to counteract the effect. Previous studies have found that people with dementia can be at an increased risk of being inappropriately prescribed anticholinergic medications to manage urinary incontinence [87]. In people with dementia, a side effect of acetylcholinesterase inhibitors is urinary incontinence, which is commonly associated with dementia and is often misinterpreted as a symptom of the disease, when in some cases it is representative of a medication-related adverse effect [87]. Inappropriately prescribing anticholinergic medication to a person with dementia could also accumulate subsequent adverse effects particularly as anticholinergics are associated with adverse cognitive effects [88]. Anticholinergic medications block the action of the neurotransmitter acetylcholine and are a broad drug class with a diverse range of indications across the central and peripheral nervous system. It is proposed that adverse cognitive effects arise through anticholinergic effects on the parasympathetic nervous system and cholinergic pathways associated with memory, perception and attention, contra to the indication of the medicine [89]. If a medication related side effect is inappropriately misinterpreted as a comorbidity and additional medications are prescribed, the risk of adverse effects increases and subsequently increases the risk of both inappropriate and unnecessary prescribing [90].

(iv) Adherence

Adherence to medication regimes is important in enabling the best possible outcomes of medication use. However, often medications are not taken as intended and increasing treatment burden and complex medication regimes from polypharmacy is associated with non-adherence [91, 92]. Between 30% and 50% of prescribed medications are not taken as intended [92]. For people with dementia, increasing cognitive impairment and multiple medication use is associated with up to 59% non-adherence to regimes [91]. Adherence to medicines is complex and there are a range of barriers associated with adherence. Barriers include a lack of knowledge about medicines, physical and cognitive ability to take medicines as prescribed, confidence in managing complex regimes, beliefs and doubt about the efficacy of medicines, motivation, memory, attention and decision making capacity and relationship with prescriber [93]. Increasing the number of prescribed medications may be counterproductive if this is associated with reduced adherence, increased burden and potential for adverse effects.

(v) Medication errors

The risk of a medication error increases with increasing medication use. There is potential for error to occur across the process of prescribing, dispensing, administration and monitoring and across primary and secondary care and in care homes [94]. While many medication errors have little or no potential for harm or are picked up before they reach the patient, it is estimated that 66 million clinically significant errors occur each year across the NHS in England. When they do occur, medication errors are associated with considerable economic and patient burden. Costing an estimated £98.5 million each year, consuming over 180,000 hospital-bed days, are associated with 712 deaths and contribution to 1,708 deaths each year [94]. Increasing use of medications is associated with increased risk of medication errors. This can have clinically significant effects in patients, particularly in older adults who are vulnerable to such effects.

(vi) Prescribing in people with dementia

Medication management in people with dementia can be increasingly complicated as the disease progresses and decision making and cognitive capacity decreases [67]. Carers (formal and familial) will increasingly become integral in managing medicines, priorities for care will change, and medicines will need to be regularly reviewed to reflect this [95]. However, research into managing

comorbidities in people with dementia is limited [96] and there are few clinical guidelines to support prescribing for comorbidities in people with dementia. Clinical guidelines inform practice and assist health professionals to make informed decisions around prescribing and care provision for their patients.

(vii) Vulnerability to adverse effects of medications

An adverse drug reaction or adverse effect is defined as *"a harmful or unpleasant reaction, resulting from medicinal intervention, which predicts hazard from future administration and requires prevention or specific treatment, or dose alteration or withdrawal"* [97]. Physiological changes occur as a natural part of ageing and affects the way in which individuals respond to medications, including susceptibility to adverse effects [98]. There is limited research into specific physiological changes in people with dementia. Changes across different biological systems as a natural part of ageing also contribute to altered pharmacokinetics and pharmacodynamics in older adults and people with dementia [99]. Pharmacokinetic changes include changes in the absorption, distribution, metabolism and excretion of medications [100]. Evidence suggests that changes in the body composition associated with ageing, such as increased body fat and decrease lean body mass, can alter the distribution of medicines. Increased distribution is most commonly associated with medicines that are fat soluble and distributed via fatty tissues. Decreased distribution is associated with medicines that are largely water-soluble [101]. Moreover, metabolism of medicines, which largely occurs in the liver is often reduced. Reduced renal functions associated with advanced age affects the excretion or clearance of many medicines [98, 99].

Age-related changes in pharmacodynamics alter the way in which a medication has its effect within the body. Understanding of these factors is integral for effective medication management within older adults and people with dementia [102]. A systematic review of studies using biochemical or imaging techniques to examine blood brain permeability, found that older age was associated with significantly increased permeability. As was dementia, compared to age-matched controls without dementia in pooled estimates, although causality is unclear [103]. Collectively, age-related and potentially disease-related changes in response to medications are thought to underlie an increased susceptibility to adverse effects of medications in older adults and people with dementia [104].

(viii) Potentially Inappropriate Medications

Potentially inappropriate medication (PIM) is the term used when the potential harm of a medication outweighs the potential benefit, in patients with specific diseases or conditions. Criteria have been developed to identify PIMs in older adults and are used to identify PIM in specific patient groups, interactions and overuse of medicines that may increase the risk of adverse effects. In the US, Beers criteria for potentially inappropriate medication use in older adults are most commonly used. Beers lists medications or medication classes that should be avoided where possible for specific populations and specific disease-drug interactions that may cause more harm than good [105]. The Beer's criteria are less helpful for UK and European healthcare practice as a large proportion of the medications in Beers are unavailable in these regions [106]. Hence, the Screening Tool for Older Person's Prescriptions (STOPP) and the Screening Tool to Alert doctors to Right Treatment (START) physiological systems-based criteria were developed and are validated in the UK and Europe. The criteria identify potentially inappropriate prescribing and omissions. STOPP is categorised into 80 physiological systems-based criteria to screen medications or classes of medications that are potentially inappropriate in older people [107].

1.11   Medication reviews

Recently, NICE published guidelines for medicines optimisation in the general population and recommended that a medication review is integral in this process [108]. A structured medication review is a critical examination of medicines. The objective of a review is to work with the patient to make decisions about treatment, optimise medicines, minimise the number of medication related problems and reduce unnecessary medicines use. A review can help to identify medications that could be stopped, dosages reduced or new medications that are needed. The NICE guidelines recommend that people taking medicines for long-term conditions and people taking multiple medications would benefit from a review. A medication review should be a shared decision-making process that involves the patients preferences, values and needs [109, 110]. While guidelines recommend a person-centred approach, practical application and outcomes of this approach in practice is unclear. Moreover, the guidelines are unclear on how to support medicines optimisation in people with cognitive impairment, dementia or people without capacity and understanding the role of the caregiver will be important.

1.12   Dementia annual review

National initiatives to improve the quality and standardisation of primary care provided to people with dementia have been introduced. In 2004 the Quality and Outcomes Framework (QOF) was introduced in the UK and is one of the largest pay-for-performance schemes in the world. The QOF consists of financial incentives, computerised decision supports and the promotion of structured and cohesive care for patients with the aim of achieving evidence-based targets. Since 2006, QOF has included an annual review for every patient with dementia [111][112]. A dementia annual review should include a comprehensive physical, psychological and social care review, a carers assessment and assessment of access to secondary care services [111]. Previous research suggests that the quality and comprehensiveness of the reviews is varied [113]. Variation in implementation means that somewhere between 50% and 86% of people with dementia receive an annual review [114]. Whilst a medication review is not explicitly included, the annual review provides a vital opportunity to review medications as part of the comprehensive assessment, potentially reducing inappropriate polypharmacy and PIMs. There is little understanding of the impact of these annual reviews on the quality of care provided to patients. Further research is needed to understand the role of financial incentive schemes such as the QOF on the quality of patient care afforded to people with dementia, a key marker of which is appropriate medication optimisation.

1.13   Observational studies

A large number of studies understanding polypharmacy and potentially inappropriate medication use have applied observational methods to understand prescribing in a range of cohorts of older adults. Observational studies can be particularly informative in providing evidence to determine the implications of a medication in real-world, representative settings. This can include patient populations that are heterogeneous and representative of the general population. [115]. Electronic health records, for example have been widely used to inform research into prescribing [116], health care utilization, health economics [117], disease prevalence and incidence and risk factors. Using electronic health records to inform research is particularly useful for patient populations where disease cases are rare, and in situations where clinical trials are not ethical or feasible. Patient records can be used to assess how implementing national policy initiatives changes clinical practice. This approach provides an opportunity to analyse a rich and large source of important patient data to inform clinical practice. Observational cohort studies, such as the Cognitive Function and Ageing Studies or the English Longitudinal Studies of Ageing are integral to

our current understanding of the prevalence and incidence of diseases. This includes our understanding of dementia and associated risk and protective factors [1, 118].

However, there are limitations to observational studies. Compared to a trial, the uncontrolled nature of an observational study means that causal relationships are difficult to ascertain. The relationship between a variable (e.g. a medication) and an outcome (e.g. mortality) can be understood in terms of an association. Although a range of factors can be adjusted for to more accurately understanding the relationship, residual confounding that is not accounted for can lead to biased findings [119]. Additionally, observational studies can be limited by the data that is collected or available. Increasingly, large, electronic patient medical records are used to understand prevalence and outcomes of prescribing in a patients. However, these datasets will generally be limited in the availability of key lifestyle factors such as diet, smoking, alcohol intake and socio-economic status [120]. Furthermore, data may be missing or unstandardized in studies using questionnaires as participants choose to omit responses within the survey or recording of data is not standardised across data collection methods. This could increase the risk of inaccurate recording of exposures, outcomes and covariates.

1.14   Summary

Cognitive impairment and dementia are prevalent in the older population and have a significant impact upon individuals, their family, carers, health professionals, healthcare service provision and the economy, in the UK and globally. Many people are also living with comorbidities and take multiple medications to manage these comorbidities, diseases and behavioural and psychological symptoms of dementia. However, we do not know the impact of prescribing in people with cognitive impairment or dementia and clinical guidelines are needed to support prescribers in making evidence-based, informed decisions around prescribing in this population. It is the aim of this research study to improve understanding of the challenges of multiple medication use in people with dementia and cognitive impairment and how this might be addressed.

1.15   Outline of thesis

The remaining chapters of this thesis report and discuss the studies I completed to understand the challenges of multiple medication use in people with dementia and cognitive impairment. My studies included a scoping review of the literature to understand the current evidence base and

motivate the subsequent research. The subsequent studies analyse two existing data sources, an electronic primary care health record dataset and the Cognitive Function and Ageing Studies. The remaining chapters are outlined.

Chapter two outlines further contextual grounding for this study through a scoping review of research into potentially inappropriate prescribing and strategies for optimising medications in older adults and people with dementia. This review explores the prevalence of inappropriate prescribing, potential for adverse effects and the heterogeneity of the older population. Comprised of a huge variety of people with varying levels of physical, cognitive and psychological disability, disease and frailty. The gaps in understanding of inappropriate prescribing amongst people with dementia are identified and discussed, motivating the subsequent work. Chapter three outlines the aims and objectives of my study based within the findings of the review of the literature and the identified research and knowledge gaps. The pharmacoepidemiological approach used in this study and the existing data sources that are used to conduct the studies are introduced and set out in terms of the aims and objectives.

Chapter four presents the methods and statistical approaches used to analyse a primary care cohort of patients with dementia in primary care in England (Clinical Practice Research Datalink, CPRD). This chapter describes the methods used to address two aims of my study, to estimate the prevalence of potentially inappropriate prescribing in people with dementia and to understand the factors associated, including the potential impact of primary care reviews on prescribing. Chapter five describes the results of my analysis of the CPRD cohort study, reporting prevalence estimates and the change in medication use associated with medication review and annual dementia care review.

Chapter six presents the methodological approach used to analyse a subsample of the Cognitive Function and Ageing Studies (CFAS) cohort. This is a sample of older, cognitively impaired adults and the methods used address two aims of this research. First, estimating the prevalence of polypharmacy and potentially inappropriate medication use. Second, to understand the impact of polypharmacy and potentially inappropriate medication use on health and the potential role of frailty on this relationship. Chapter seven reports the findings of the analyses applied to the CFAS II subsample. Chapter eight and the final chapter in this study is a discussion of the findings, methodological approaches and implications of this research.

II.   Chapter 2: Polypharmacy and Potentially Inappropriate Medication Use. A Scoping Review of Reviews

(a)   Objectives

Polypharmacy and PIM are significant in the care of older adults with comorbid health conditions. Polypharmacy is associated with an increased risk of being prescribed a medication that is potentially inappropriate. Both polypharmacy and PIM are associated with increased risk of adverse effects including hospitalisation and mortality [121, 122]. Optimising medications for people with dementia may prevent exposure to medication related harm [123]. A large body of literature has estimated the effect of polypharmacy and PIM use in older adults, however the nature of polypharmacy and its impact among people with cognitive impairment are likely to be different [123]. To develop research questions to help optimise medication use for people with dementia, first it is necessary to survey the available literature surrounding polypharmacy and PIM in older adults generally and people with dementia specifically, hence identifying pressing gaps in knowledge in this area. With this in mind, a scoping review of the literature was conducted with four key objectives:

(1) To describe the range and nature of research into polypharmacy and PIM use in people with dementia and older adults

(2) To assess the evidence of harm associated with inappropriate medication use in people with dementia

(3) To identify gaps in the evidence base, including stated areas of future research

(4) To inform the development of specific research questions for this study.

2.02   Methods

(a)   Scoping review

To review the current literature, I conducted a scoping review of review studies. A scoping review is one of many methodologies for reviewing and synthesising research and evidence. Arksey and O'Malley (2005) proposed the original framework and defined the aim of a scoping review as to: *"map rapidly the key concepts underpinning a research area and the main sources and types of evidence available"* [124]. Since then definitions have varied, but whilst there is no established definition, the concept is underpinned by mapping and understanding a wide range of literature and evidence [125].

(i) Why a scoping review?

Scoping reviews describe the breadth of evidence across a given field, rather than answering a specific question. This is contrary to a systematic review which reviews evidence on the effectiveness of an intervention on specific outcomes, in a specific population, for example. Scoping reviews do not quantitatively synthesise evidence using meta-analysis. However like systematic reviews, scoping reviews have guidelines and frameworks such that they are replicable and adhere to specific standards. Frameworks for scoping reviews continue to be developed. Recently, reporting guidelines have been developed for scoping reviews. The process of a scoping review is becoming more established as an approach with clear advantages over a systematic review, in appropriate contexts.

(i) Why a review of reviews?

Multiple systematic reviews now exist that synthesise evidence from across many studies addressing similar research questions in polypharmacy and PIM among older people. As multiple reviews exist, there becomes a need to reintroduce clarity and understanding of the research area. A review of reviews enables synthesis across different research questions on similar areas, to understand levels of consensus or disagreement and nuances around this. Moreover, a review of reviews can include evidence from different types of interventions or from reviews of the same intervention with different outcome measures, for example. In addition, a number of reviews can be summarised addressing different problems or populations [126]. Although primary literature and studies that have not yet been included in a review may be missed, in applying this to the desired outcomes of conducting a review for this study, a review of reviews appeared to show considerable benefit. In particular, in understanding the research around different problems, such as polypharmacy and potentially inappropriate medication. As well as the effectiveness of different interventions and different outcomes. And, in different populations and settings, including older adults and people with dementia across primary and secondary care.

(ii) Scoping review framework

A scoping review framework was originally proposed by Arksey and O'Malley in 2005. Since then, it has been extended, developed and refined by Levac et al (2010) and by Peters et al (2015) [124, 125, 127]. The framework was used to direct the review and is described in Table 1.

Tocca and colleagues recently re-developed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist for application to scoping reviews. The reporting of this scoping review is therefore guided by the PRISMA Extension for Scoping Reviews (PRISMA-ScR) checklist [128] (Appendix 1 Section 10.01).

Table 1 Framework used to inform the scoping review for this research study, based on the original framework proposed by Arksey and O'Malley (2005) and developed by Levac et al., (2010) and Peters et al., (2015)

Step	Detail
Step 1: Identify the research question	Because the aim of the scoping review was to map the literature, the research question should be adequately broad to encompass this.
Step 2: Identify relevant studies	Including which sources were to be studied, the type of literature included in the review and restrictions that were influenced by time and resource capabilities.
Step 3: Study selection	Inclusion and exclusion criteria were refined to guide the systematic process of selecting relevant studies.
Step 4: Charting the data or data extraction	Key information from studies was extracted, charted and sorted to synthesise and interpret the studies. Charting extraction tools were pre-defined to agree on the data to be extracted from the studies that addresses the objectives of the review.
Step 5: Collating, summarizing and reporting the results	The collated data was summarised. A descriptive or narrative approach was taken rather than a synthesis of effectiveness or weight of the evidence. Possible gaps in the literature were identified.

(b) Eligibility criteria

To be included in the review, reviews needed to include studies of older adults (primarily defined as over the age of 65 years) or people with a diagnosis of dementia. Studies needed to address polypharmacy (the use of multiple medications) according to any definition, or PIM use as identified through validated criteria. Reviews of studies addressing interventions were included if the purpose of the intervention was to address polypharmacy or medication appropriateness. Peer-reviewed journal publications were included if they were written in English, involved human participants and were review studies. Review studies were included if they were systematic or applied a systematic approach (literature search terms and methods for identifying literature were identifiable).

Studies were excluded if they focused on older adults with comorbid health conditions other than cognitive impairment or dementia. Studies addressing end of life or palliative care and studies on medication adherence were excluded. Non-systematic literature review, opinion pieces and reviews of policy or industry documents were also excluded.

(c) Information sources and selection of studies

To identify potentially relevant review articles three databases were searched, MEDLINE, EMBASE and Cochrane Library for Systematic Reviews. Search terms included 'polypharmacy', 'inappropriate prescribing', 'potentially inappropriate medication' and 'older adults' or 'dementia'. The full search strategy and terms for each database can be found in Appendix section 10.02. I conducted all titles and abstract screening and full text reviews, the final search results were exported into Mendeley and duplicates were removed.

(d) Data charting

A data-charting form was used to extract relevant information from the reviews. Data from eligible studies were charted in the extraction tool in Excel, capturing relevant information on key study characteristics, including the number and type of studies included in the review, participant group and setting. Key findings were extracted along with descriptive estimates of polypharmacy and how polypharmacy was defined, and descriptive estimates and definitions of PIM. If relevant, interventions and outcomes, adverse effects associated with polypharmacy and PIM and key drug

classes were extracted. Suggestions for future research explicitly identified by the review authors were also extracted. An example of the data charting form exemplified with one review is provided in Table 2.

Table 2 Example of completed data charting form used for extracting relevant information from the reviews included in the scoping review

Data extraction	Review details
Bibliographic information (Authors, year, title)	Alldred, D. P., Kennedy, M. C., Hughes, C., Chen, T. F., & Miller, P. (2016). Interventions to optimise prescribing for older people in care homes.
Countries of included studies	Australia, Finland, Israel, Netherlands, New Zealand, Spain, Sweden, UK, USA, Canada
Aims of review	Evaluate evidence for interventions to address suboptimal prescribing in care homes to identify how care can be improved in this frail and vulnerable population.
Review design	Systematic review
Types of studies included (n)	RCTs (n=12)
Study samples *n,* **age group, care setting**	Older adults; n= 10,953; 65+ years; Care homes
Key findings	Due to the quality of the evidence robust conclusions could not be drawn. The outcomes showed no evidence of effect of interventions on adverse drug events or mortality. Uncertain whether medication review reduces hospital admissions or improves quality of life. Medication review may lead to improvement in medication appropriateness and may lead to identification and resolution of medication related problems. Unclear about impact of medication review on decreasing medication costs.
Descriptive statistics of PIM / polypharmacy	Not assessed
Definition of PIM	5/12 studies addressed medication appropriateness using: Medication Appropriateness Index (MAI), STOPP-START, and composite criteria of

Data extraction	Review details
	Beers, Anticholinergic Risk Scale, >2 psychotropic drugs, NSAIDs and proton pump inhibitors
Intervention	Medication review was included in 10/12 studies. Otherwise the interventions were multifaceted and diverse, included education of care home staff, clinical decision support technology and multi-disciplinary case conferencing, pharmacist evaluation of medications (pharmacist conduct medication review)
Purpose of intervention	To optimise prescribing and reduce suboptimal prescribing in care homes
Outcomes of intervention	Primary outcomes: adverse drug events, hospital admissions, mortality. Secondary outcomes: quality of life, medication related problems, medication appropriateness, medicine costs
Key drug classes	Appropriateness measured using tools but specifically also included anticholinergics, psychotropic drugs, NSAIDs and PPIs
Harm associated with PIM / polypharmacy	Not assessed
Suggestions for future research	High quality and powered RCTs needed to identify effective interventions to optimise prescribing in care homes. Effectiveness of clinical decision support systems and multidisciplinary interventions in this context is needed. Further work needed to develop consensus on identifying, defining, measuring, reporting and analysing important resident related outcomes, including quality of life to enable meta-analyses to be conducted on future RCTs

(e) Synthesis of results

Review study characteristics were summarised, including setting, population and study types included in the review. The results from the reviews were grouped and summarised by the various definitions of polypharmacy, prevalence of polypharmacy and PIMs in older adults and people with dementia. Criteria used to identify PIMs, PIMs in older adults and people with dementia were summarised. The adverse effects associated with polypharmacy and PIMs and key medication classes identified across the reviews were reported. Finally interventions and suggestions for future research identified from the reviews were summarised. For the purpose of this chapter, the findings from this scoping review are reported in an integrated synthesis and discussion.

2.03 Synthesis and discussion of review findings

(a) Selection of sources of evidence

Database searches were run to include review studies published until December 2018. An initial search was conducted in 2015 and the search and search terms were updated to include reviews published until December 2018. This scoping review covers reviews published from 2003-2018. A total of 54 review articles were eligible to be included, see Figure 1 for selection of sources flow diagram. Across the electronic databases searched 4,779 articles were initially identified (Cochrane n=556, Medline n=3,215, Embase n= 1,098). Based on the title and abstract 4,495 were excluded, 19 duplicates removed, 236 studies excluded because they were not review studies and 119 full text articles were subsequently retrieved and assessed for inclusion. Of these 65 were excluded; reasons for exclusion included review focusing on medication adherence or palliative care (n=10), study design was not a systematic review (n=9), review focus was on other health conditions (n=13), pharmacological treatments evaluation (n=11), polypharmacy or PIM were not defined by criteria (n=10), or the purpose of the intervention did not meet the inclusion criteria by not addressing medication appropriateness (n=12). The authors of three studies were contacted for access to full-text manuscripts however they did not respond and therefore the final total of included studies was 51.
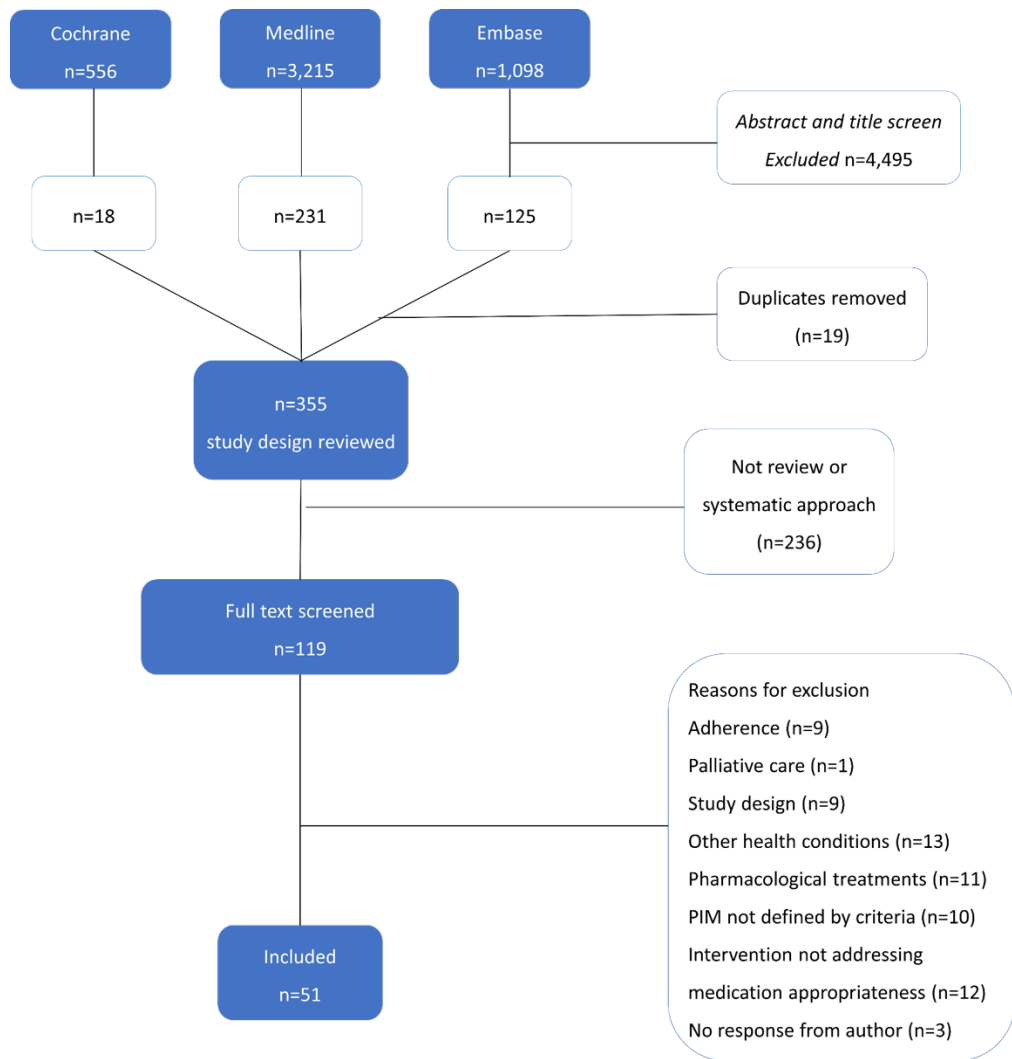
Figure 1 Selection of sources of review studies included in the scoping review flow diagram

(b) Characteristics of Reviews

Of the 51 reviews included, 8 were systematic reviews with meta-analyses [129–136]; others were systematic reviews without meta-analysis or literature reviews applying an identifiable systematic approach. An overview of review characteristics is in Table 3. A total of 1,391 primary studies were included across the 51 reviews. Although, this includes duplication of studies due to some studies being relevant to more than one review. Seven reviews specifically focused on care homes (including nursing and long-term residential care), four reviews included studies with exclusively community dwelling participants and four reviews included studies in hospital settings.

There were eleven reviews of polypharmacy or PIM prevalence across community, care home and hospital settings [137–147]. Eight reviews of the outcomes of polypharmacy or PIM, including economic impact, risk of adverse reactions such as mortality, hospitalisation and physical function [141, 142, 148–153]. Fourteen were reviews of studies defining polypharmacy and PIMs, such as reviews of PIM criteria [154–167]. There were 21 reviews focused on or including studies of medicines optimisation interventions in older adults and people with dementia, across primary and secondary care [130–132, 134, 140, 145, 167–180]. There were two reviews of qualitative studies of prescriber and patient perspectives on prescribing PIMs and polypharmacy [181, 182].

Of the reviews identified, eight included studies of people with dementia [136, 137, 142, 146, 156, 165, 166, 169]. These reviews were largely conducted in nursing homes or long-term care facilities [156, 165, 169], hospitals [146] or in a variety of settings that included hospitals, care homes as well as community based studies [136, 137, 142, 166]. One systematic review focused on the identification of potentially inappropriate prescribing in advanced dementia or palliative care [156] and found evidence for a programme to support appropriate medicines in palliative care of people with advanced dementia. A second review sought to identify criteria for medication appropriateness and evidence for interventions to improve appropriateness in nursing home residents with advanced dementia [177]. The findings from this review were also used in a multidisciplinary Delphi panel consultation to identify categories of medication appropriateness in advanced dementia (generally, sometimes and rarely appropriate). A third review was of studies of polypharmacy and PIM prevalence in people with and without cognitive impairment in hospitals. This review indicated a high prevalence in both people with and without cognitive impairment (including people with dementia) [146]. One review included studies of interventions to reduce polypharmacy in people with dementia. The results from the meta-analysis of findings from five studies did not indicate any association with reduced mortality [171]. Another was a systematic review of studies of PIM use in people with cognitive impairment and dementia,

including evidence about the association of cognitive impairment or dementia with PIMs [142]. This review found that PIM prevalence ranged from 10.2% to 56.4% in people with cognitive impairment or dementia, and was higher in nursing homes than community settings. This review also found no evidence of a positive association between cognitive impairment or dementia and PIM exposure [142].

Table 3 Characteristics of review studies included in scoping review of reviews

Reference	Review type	Type of studies included	Review topic	Studies (n)	Participants	Setting
Bokhof & Junius-Walker (2016).	Synthesis of qualitative studies	focus groups, semi-structured or in-depth interviews, Delphi approach	Reducing polypharmacy from prescriber and patient perspective	14	Older adults	Community, primary care
Chang & Chan (2010)	Systematic review	Criteria for identifying PIM	Defining PIM	-	Older adults	Mixed
Corsonello et al., (2012)	literature review	-	Defining PIM	59	Older adults	Mixed
Corsonello et al., (2009).	literature review	Reviews and observational studies	Defining PIM	-	Older adults	Hospital
Cullinan et al., (2014).	Systematic review and meta-synthesis	Qualitative	Understanding PIM prescribing from prescriber and patient perspective	7	Older adults	Mixed
Ćurković et al., (2016)	Literature review	-	PIM prevalence and risk factors	138	Older adults	Care home, community
Dimitrow et al., (2011)	Systematic review	Criteria for identifying PIM	Defining PIM	16	Older adults	Mixed
Disalvo et al (2016)	Systematic review	Cohort (longitudinal and cross-sectional), prospective cohort, , Delphi consensus, factorial survey design	Defining PIM	8	People with dementia	Nursing home, long-term care, hospice, community
Fulton et al., (2005).	Systematic review	Observational: Descriptive, cohort, cross-sectional, longitudinal, prospective, retrospective. Delphi survey	Definition of polypharmacy, interventions	16	Older adults	Primary care
Gallagher et al., (2007)	Literature review	-	Prevalence, outcomes, criteria	-	Older adults	Mixed
Guaraldo et al., (2011).	Systematic review	Studies of secondary source data i.e. insurance company and social security administrative data.	Prevalence and risk factors	19	Older adults	Community
Hajjar et al., (2007)	Literature review	Observational and RCTs	Prevalence and interventions	58	Older adults	Mixed
Hill-Taylor et al,. (2013)	Systematic review	RCTs and observational studies	Prevalence and outcomes	13	Older adults	Community, acute care, long-term care
Hyttinen et al., (2016)	Systematic review	Cohort	Outcomes (health care costs)	39	Older adults	Mixed
Johnell (2015)	Systematic review	Observational and RCTs	Prevalence and adverse effects	22	People with dementia and cognitive impairment	Community, nursing home, hospital
Kouladjian et al., (2014).	Literature review	-	Defining PIM	-	Older adults	Mixed
Kroger et al., (2015).	Scoping review	-	Defining PIM and interventions	79	People with dementia	Nursing home

Levy et al., (2010).	Literature review	Criteria for identifying PIM	Defining PIM	8	Older adults	Community, nursing home, primary care
Matanović et al., (2012).	Literature review	Criteria for identifying PIM	Defining PIM	11	Older adults	Mixed
Morin et al., (2016)	Systematic review	Observational, cross-sectional	Prevalence	48	Older adults	Nursing home
Motter et al., (2018).	Systematic review	Criteria for identifying PIM	Defining PIM	36	Older adults	Primary care, nursing home, hospital
Muhlack et al., (2017).	Systematic review and meta-analysis	Prospective, retrospective cohort	Adverse effects	16	Older adults	Community, nursing home, hospital
Opondo et al., (2012).	Systematic review	Cohort, observational	Prevalence	19	Older adults	Primary care
Pérez-Jover et al., (2018).	Systematic review	Empirical studies	Prevalence and interventions	80	Older adults	Mixed
Peron et al., (2011).	Narrative review	Observational or intervention	Adverse effects	19	Older adults	Mixed
Redston et al., (2018)	Systematic review	Observational studies	Prevalence	47	Older adults with and without cognitive impairment	Hospital
Rodrigues et al.,(2016).	Integrative review	Prospective, retrospective, case-control, cross-sectional, cohort study, RCT, longitudinal, survey, intervention, single blind controlled study,	Adverse effects	47	Older adults	Mixed
Salahudeen et al., (2015).	Systematic review	Criteria for identifying PIM	Defining PIM	7	Older adults	
Santos et al,. (2015).	Systematic review	Criteria for identifying PIM	Defining PIM	119	Older adults	Mixed
Skinner (2015).	Literature review	Criteria for identifying polypharmacy	Polypharmacy	16	Older adults	Primary care
Storms et al,. (2017)	Systematic review	-	Prevalence	21	Older adults	Long-term care facilities
Tommelein, et al,. (2015).	Systematic literature review	Observational studies	Prevalence	52	Older adults	Community
Villalba-Moreno, et al., (2016)	Systematic review	Systematic review, cross-sectional, cohort, experimental, longitudinal	Defining PIM	25	Older adults	Mixed
Wang et al,. (2018).	Systematic review	RCTs, cohort studies, case-control and case-cross over	Adverse effects	32	Older adults	Care and nursing home
Intervention reviews						
Alldred et al., (2016)	Systematic review	RCTs	Interventions	12	Older adults	Care home
Christensen & Lundh (2016)	Systematic review	RCTs	Interventions	10	Older adults	Hospital
Clyne et al., (2012)	Literature review	Cluster-RCTs, RCTs, interrupted time series, cohort studies	Interventions	14	Older adults	Ambulatory care, nursing home, hospital
Clyne et al., (2016).	Systematic review	RCTs	Interventions	12	Older adults	Community
Cooper et al., (2015)	Systematic review	RCTs, cluster RCTs, controlled before-and-after studies	Interventions	12	Older adults	Mixed

Forsetlund et al., (2011)	Systematic review	RCTs	Interventions	20	Older adults	Nursing homes
Johansson et al., (2016)	Systematic review and meta-analysis	Controlled trials	Interventions	25	Older adults	Primary care, community, nursing home
Kaur et al., (2009)	Systematic review	-	Interventions	24	Older adults	Mixed
Page et al., (2016)	Systematic review and meta-analysis	Experimental and observational	Interventions	116	Older adults and people with dementia	Mixed
Page et al., (2016)	Narrative review	-	Interventions	-	Older adults	Mixed
Rankin et al., (2018)	Systematic review	RCTs, non-randomised RCTs, controlled before-and-after, interrupted time series	Interventions	32	Older adults	Hospital, primary care, nursing home
Rollason & Vogt (2003)	Systematic review	RCTs, controlled trials	Interventions	14	Older adults	Outpatient settings, hospital
Thillainadesan (2018)	Systematic review	RCTs	Interventions	9	Older adults	Hospital
Thiruchelvam et al., (2017).	Systematic review	RCTs and observational studies	Interventions	22	Older adults	Care home
Tjia et al., (2013)	Systematic review	Controlled trials, pre-post interventions, case series	Interventions	36	Older adults	Nursing home, hospice, community
Walsh et al., (2016)	Systematic review and meta-analysis	RCTs and non-randomised trials	Interventions	4	Older adults	Hospital
Wilsdon et al., (2017)	Systematic review	RCTs and non-randomised trials	Interventions	21	Older adults	Mixed

(c)   Summary of evidence from the review findings

There was strong evidence for the high prevalence of PIM among older adults. Weighted PIM prevalence estimated around one fifth of older adults were prescribed PIM (22.6% 95% CI 19.5%-26.7%) in primary care [144, 183]. In addition, 43.2% (95% CI 37.3%-49.1%) of nursing home residents were prescribed PIM [143]. There was no consensus on a definition of polypharmacy and a range of definitions are applied across the literature [167]. There was consistent evidence that polypharmacy and PIM prevalence varied depending on the care setting, with variation in the use of multiple medicines across hospital, care home and community settings. Multimorbidity was also consistently associated with increased medicines use [132, 167].

There was some evidence that polypharmacy and PIM was associated with adverse drug reactions and drug-interactions, however these findings were not consistent across studies, quality of evidence was often not assessed and results from across studies were not statistically tested [141, 184]. The scoping review indicated that there was conflicting evidence that PIMs were associated with hospitalisation. There was also conflicting evidence that psychotropic medicines were associated with hospitalisations in one review [148]. There was some evidence that some psychotropic medicines (namely, benzodiazepines) were associated with hospitalisation. But evidence from some studies of psychotropic medicines, including antipsychotics, found no evidence of association with hospitalisation, whereas other studies (rated as high quality) found association of antipsychotic medicines with cause-specific hospitalisations [148]. However, another review identified evidence that PIMs were associated with increased hospitalisation and health care utilisation [152], although the study estimates were not pooled for statistical testing of findings across studies. The evidence of the association of PIMs with length of hospital stay or readmission to hospital was inconclusive [152]. However, the current evidence may have been biased by the predominant use of prevalent rather than incident medication user study designs. Moreover, studies often failed to consider variation in medication use over time and subsequent impact on outcomes [148].

There was conflicting evidence of the association between polypharmacy and PIMs and functional decline [150]. Some studies indicated that increased number of prescriptions, was associated with physical function decline but PIMs were not [150]. However, there was some evidence that specific PIMs, including benzodiazepines and anticholinergics were associated with worse physical function [150].

There was conflicting evidence of the association between PIM and mortality in older adults. One review found no association after combining studies in a meta-analysis [171]. Another review also

found no association in studies with high risk of bias from using prevalent user study designs. Once meta-analyses were restricted to incident-user designs (so that adverse events that occur early after the initiation of medication are accounted for), PIM was associated with significant mortality risk [151].

There was strong evidence for the role of specialists such as pharmacists in interventions to improve medication appropriateness, particularly in care home settings [173, 177]. Furthermore, there was strong evidence for the effect of medication review to reduce polypharmacy and PIM use. However, there is limited evidence of the effect of a review on clinical and patient outcomes including on adverse drug events [129], mortality [129, 133, 169], falls [169] and hospital admission [133, 169], quality of life and medicine costs [129]. Although, there was some evidence that interventions were not associated with increase in drug withdrawal events [171].

(d)   Summary of evidence from reviews of studies of people with dementia and cognitive impairment

Evidence from the scoping review indicated that the importance of medicines optimisation is a topical issue, when prescribing to people with advanced dementia, particularly in nursing homes. The evidence from the scoping review suggested that polypharmacy was common in people with dementia in hospitals and nursing homes [146, 156, 177]. There was some evidence that polypharmacy was prevalent in 53.2% to 89.8% of people with cognitive impairment in hospital settings [146]. Polypharmacy prevalence was slightly higher in people with dementia (56.7%-83.7%) compared to people without dementia in hospital settings (51.5%-76.8%) [146]. Furthermore, PIM prevalence in people with cognitive impairment ranged from 20.6%to 80.5% (Beers criteria) and 39.3% to 88.5% (STOPP criteria) [146]. Whilst PIM use was prevalent in people with cognitive impairment, one review argued that there was no evidence of positive association between cognitive impairment and PIMs [142].

From the reviews, it is clear that there are a number of medications that are considered potentially inappropriate for use in people with dementia. The findings from this scoping review suggested that there were few criteria that had been reviewed focusing on prescribing in this population. One system for appropriate prescribing in palliative care of people with advanced dementia was reviewed. The Palliative Excellence in Alzheimer Care Efforts (PEACE) program was applied in five studies included in one systematic review [156, 185]. A second criteria for identifying PIM in moderate or severe dementia was also identified in another review [165].

From one review, there was little evidence to suggest that dementia or cognitive impairment were associated with an increased likelihood of PIM prescription and in a number of studies, were associated with decreased likelihood of PIM [142]. One systematic review and meta-analysis included a sub-group analysis of intervention studies among people with dementia. This review found no evidence that interventions to reduce polypharmacy in people with dementia (and in older adults) were associated with reduced mortality [171]. The findings from the scoping review are discussed in the following sections.

(e)   Polypharmacy and PIM prevalence in older adults and people with dementia

My scoping review found that polypharmacy and PIM use is prevalent in older adults and in people with dementia. Estimates of polypharmacy prevalence ranged from 5% to 78% in primary care [167] and around 50% in nursing home residents [137]. However, the review also highlighted the variety of definitions of polypharmacy used. There was conflicting evidence across the reviews on defining polypharmacy. Generally, more than four medications or more than five medications was considered as a cut-off for polypharmacy [130, 131, 134, 168, 180]. One review argued that five or more medications was established from animal and epidemiological studies and is predictive of clinically relevant adverse effects [136]. Without a consensus on a definition, comparable prevalence estimates are difficult to ascertain and estimates will vary widely.

Polypharmacy and hyper-polypharmacy (>10 medications) were also recognised as key challenges among people with dementia. In hospital settings, prevalence of polypharmacy in people with dementia ranged from 30% to 97% [146]. A systematic review of PIM in people with dementia in hospitals was published after the searches for this review were completed. This review found that polypharmacy prevalence (defined as five or more medications) ranged from 25% to 98% in acute care settings [186]. Whilst estimates do vary, primary studies among people with dementia in the community also estimate relatively high prevalence of polypharmacy. A study conducted among French community dwelling cohort of people with dementia in the REAL.FR study, estimated that 43% were prescribed polypharmacy (defined as five or more medications) [187]. In another study of 2,665 community dwelling people with dementia from the National Institute of Aging (NIA)-funded National Alzheimer's Coordinating Centre Uniform Data Set (UDS) (United States, 2005-2007), polypharmacy was prevalent in over 50% of people with dementia [188]. In addition, evidence from people with dementia in primary care in Northern Ireland, estimates the

prevalence higher, with 85% exposed to 4 or more regular repeat medications [189]. Estimates will vary depending on the cohort, setting and definition of polypharmacy, and this will change with time. In view of this, it is important that we understand the prevalence of polypharmacy amongst people with dementia, particularly in primary care in the United Kingdom, where much prescribing occurs. Up-to-date and population representative estimates from large cohort studies are informative in understanding the extent of the problem. These studies can help inform the development of service priorities for prescribing to people with dementia.

Exposure to PIMs varies across care settings, with around 20% of older adults in primary care and 40% in care homes exposed to PIMs [143, 144, 183]. Three reviews estimated prevalence of PIMs in people with dementia (See Table 4). In nursing homes, prevalence of PIM use amongst people with advanced dementia was estimated as 29% to 54% [156] and from 39% to 88% among people with dementia in hospitals [146]. The recent review of PIM in people with dementia, estimated PIM prevalence as ranging from 14% to 74% across 26 studies [186]. Primary studies of PIM use amongst people with cognitive impairment or dementia in the UK are limited. As identified through this review, will often focus on people with dementia in care homes [190], hospital [146] and advanced dementia [156]. The impact of PIM on people with dementia is increasingly recognised and specific criteria have been developed for medicines management in people with advanced dementia and palliative care [191]. Priorities for care, including the persons and their carers priorities will change as the disease progresses and the management of medications as part of care planning will also change overtime [95]. We need to better understand the impact and predictors of polypharmacy and PIMs among people with dementia across the disease trajectory is valuable as more people are diagnosed, and efforts to reduce unnecessary hospital admissions, such as through medication error, are increased [94].

There was some indication that people with dementia may be exposed to a greater number of PIMs and primary studies provide similar indications. In Denmark, a cross-sectional study (2014) of people with dementia (n=35,376) estimated around twice as many people with dementia (62%) compared to people without dementia (n= 994,231) (35%) were exposed to PIM [192]. Similar estimates were found across eight European countries involved in the 'RightTimePlaceCare' study including over 2,000 people with dementia, with around 60% prescribed at least one PIM and 26% at least two [193]. However, this sample included people with dementia if they were in long-term care or at risk of admission and therefore does not represent the majority of people with dementia living in the community. Previous primary studies of PIM use among people with dementia estimated around one fifth of people with dementia were prescribed one PIM (23%, 95% CI 22.0-24.0) and one quarter were prescribed three PIMs (24.6% 95% CI 23.6-25.7%) [189].

These findings may underestimate the extent of PIM prescriptions since only people prescribed medication for mild to moderate Alzheimer's disease were sampled. The prescription of PIMs has also been estimated as higher among people with dementia who are living in care homes. A study estimating PIM use of people with dementia in care homes in England as part of the longitudinal EVIDEM – End of Life (EoL) study (n=133), found 46% of people with dementia were prescribed at least one PIM, nearly twice as high as those in the community [190]. However, these findings are from a small and unrepresentative sample. Further research is required to understand what individual and external characteristics, such as primary care prescribing practices, increase the risk of exposure to PIMs in people with dementia.

Table 4 PIM prevalence estimates amongst older adults, people with dementia or cognitive impairment from reviews

Setting, Authors	PIM prevalence (%)	PIM prevalence (%) by criteria
Community-dwelling older adults		
Muhlack et al (2017)	5.2- 48.7	
Tommelein et al (2015)	22.6 (95% CI 19.2-26.7)	Beers (1997) 2.2 - 38.7 Beers (2003) 5.8 - 38.5 STOPP (2008) 5.8 - 42.0
Clyne et al (2016)1	18 - 100	
Chang et al (2010)		Beers (2003) 18.3-41.9 STOPP 21.4
Guaraldo et al (2011)	11.5-62.5	Beers (1997) 14.3- 24.4 Beers (2002) 18 - 62.5
Primary care		
Opondo et al (2012)	20.0 (range 2.9-38.5)	Beers (1997) 4.5-21.0 (median 12.7) Beers (2003) 2.9-38.5 (median 23.6)
Care, nursing or long-term residential home		
Muhlack et al (2017)	2.3 -50.3	
Morin et al (2016)	43.2 (95% CI 37.3 - 49.1)	
Chang et al (2010)		Beers (2003) 18-34.9
Storms et al (2017)		Beers (2003) 21.3-63.0 (median 35.1) STOPP 23.7 - 79.8 (median 61.1)
Hospital		
Muhlack et al (2017)	14.8 – 23.7	
Corsonello et al (2009)		Beers 16-49
Chang et al (2010)		Beers (2003) 14-44.1 STOPP 35.0
Mixed settings		
Hill-Taylor et al (2013)		STOPP 21.4-79
People with dementia or cognitive impairment		
Care home		
Disalvo et al (2016)	29-53.9	
Hospital		
Redston et al (2018)	53.2-89.8	Beers 20.6-80.5 STOPP 39.3-88.5
Mixed settings		
Johnell (2015)	10.2-56.4	Beers 10.2-56.4 STOPP 46.2
Baseline prevalence estimate from random and non-random trial studies		

(f) Heterogeneity of the older adult population

The scoping review has highlighted the importance of accounting for heterogeneity in the older population, particularly when it comes to prescribing. Older adults encompass a huge proportion of the population and whilst age is important, it is increasingly recognised that frailty and morbidity contribute more significantly to physical and mental health, quality of life and disability [47]. One review identified that research is needed to understand polypharmacy and PIM across the diverse population of older people to identify vulnerable, high-risk groups within this population [154].

(i) Stratifying risk using frailty

One means of stratifying the older population is through frailty classification. Increasing frailty is associated with decreased physiological reserve and greater vulnerability to adverse outcomes (such as morbidity and hospitalisation) compared to older adults of the same age [47]. The use of frailty to stratify the older population has been used widely across epidemiological studies and is increasingly applied in clinical settings [194, 195]. Frailty assessments are now incorporated into primary care practice to support the identification of people who are at increased susceptibility to adverse health outcomes [59]. A useful application of frailty assessments is to identify people who are at increased risk of adverse effects. Frailty is predictive of increased disability [45, 46], falls [45, 46], hospitalisation [47], care home admission [48, 49] and mortality [45, 46, 48, 49]. Frailty is an increasingly important way of understanding ageing. We need to know what role frailty may play in understanding the relationship between prescribing and adverse outcomes.

(ii) Validity of frailty criteria

The validity of frailty measures is tested through the ability to predict adverse outcomes and identify resilience or susceptibility to other possible risk factors [196]. Polypharmacy is associated with incident frailty [197] and frail older adults may be at increased susceptibility to adverse effects associated with polypharmacy and PIMs [101]. Previous research suggests that polypharmacy is associated with frailty and both frailty and polypharmacy are predictive of mortality [198]. In addition, in a French cross-sectional study of adults over 70 years old (n=2,350), it was estimated that people who were prescribed 10 or more medications (hyper-polypharmacy) and frail, were six times more likely to die over the follow-up period (mean 2.6

years) than people who were not frail and without polypharmacy [198]. This study suggested that frailty and polypharmacy were prevalent and frailty may be important in understanding the relationship between inappropriate medication use, including PIMs, and adverse effects. However, whether frailty moderates the relationship between inappropriate medication use and adverse outcomes, and therefore whether frailty is a useful means of identifying those at particular risk from inappropriate medication use is unknown. Furthermore, whilst the overall frailty phenotype is predictive of adverse outcomes, more research is needed to evaluate the predictive validity of individual criteria [54]. Research to understand the implications of polypharmacy and PIM among frail, multimorbid and cognitively impaired older adults will improve evidence-based prescribing guidelines, to account for specific diseases and make specific recommendations [77].

(g) Prioritising PIMs

This scoping review identified a number of adverse effects associated with PIM use including, hospitalization [148, 153], urinary incontinence [140] and falls [139]. In a study including people with dementia, from eight European countries also found an association between PIM use and increased risk of falls and hospitalisation in people with dementia [193]. There was some evidence to suggest that polypharmacy but not PIM (identified using Beer's criteria) was associated with worse physical functioning [140, 150, 171]. The evidence associating polypharmacy and PIM with mortality was conflicting [140, 171]. One review pooled estimates from studies of the association of PIM and mortality in people with dementia and found no association [199]. One review of the association of PIM in older adults with mortality found that the association with mortality depended on the study design. In studies with prevalent PIM users, PIM was not significantly associated with mortality. However, in a meta-analysis of new-user design studies, which recorded adverse events proximal to the start of PIMs, PIMs were associated with a statistically significant increased risk of mortality (RR 1.59 95% CI 1.45-1.75) [135].

However, findings in the reviews were often limited by low quality primary studies conducted. The reviews highlighted that often studies had a high risk of bias, including from failure to adjust for comorbidity appropriately, leading to increased risk of bias by indication [151]. Many studies were of prevalent user designs which are affected by survivor bias, as people who have an adverse reaction to a drug when first prescribed are likely to stop treatment and these adverse reactions are not picked up in these study designs [134]. Well-designed and adjusted studies are required to understand the clinical outcomes of polypharmacy and PIM. To support prescribers in

making informed prescribing decisions among people with dementia, we need to understand the impact of polypharmacy and PIM in this population.

Given the extent of research reviewed, it was evident that the appropriate use of medicines in older adults is important and where medicines are inappropriately prescribed there are potential adverse effects. Adverse drug reactions are a common consequence of polypharmacy and older adults are more susceptible than the general population [138, 184]. Moreover, people with dementia may be at increased susceptibility to medication related side effects, due to age-associated changes in absorption, distribution, metabolism and elimination [98]. Likewise, there is some mechanistic evidence to suggest that increased blood-brain barrier permeability associated with the disease may subsequently increase the distribution of drugs to the brain and the susceptibility to adverse effects [200]. Understanding the impact of polypharmacy and PIM in people with dementia is a research priority given the increasing size of the population and limited available evidence to guide medication use currently available [201].

My scoping review recognised the breadth of prescribing that may be considered potentially inappropriate. One included review estimated that there are over 900 medications or classes identified as PIM across more than 30 criteria used globally [162]. Despite this variety, there were a number of PIMs that repeatedly occur across criteria and across the scoping review. Given the limited research into PIM use in people with dementia, identifying priority medications of significant relevance to people with dementia and prescribers is important. This approach will direct research development and subsequently make clear recommendations for practice, based on polypharmacy and key medication classes.

Commonly identified across PIM criteria were psychotropic medications, including antipsychotics, antidepressants and benzodiazepines [150]. Psychotropic medications are medications that affect mood and behaviour of an individual. They commonly act upon the central nervous system and are individually associated with a number of adverse effects in older adults and in some cases, particularly among people with dementia.

(i) Antipsychotics

Antipsychotic medications were initially developed for the treatment of schizophrenia and have since been more widely used to manage the symptoms of people with psychoses. There are two broad groups of antipsychotics, first generation (typical) and second generation (atypical). First

generation antipsychotics were associated with a number of serious adverse effects and second generation antipsychotics are considered to be comparatively safer and associated with less serious adverse effects. Antipsychotics are prescribed to manage the behavioural and psychological symptoms (BPSD) of dementia. They may be prescribed when a person with dementia is very agitated, aggressive, hallucinating, wandering, psychotic or affected by disturbed sleep. Sometimes antipsychotics are not prescribed to treat the underlying problem that is causing the agitated and aggressive behaviour but are used to sedate the individual. This may be appropriate if the underlying problem cannot be identified or treated. Whilst antipsychotics are prescribed to manage BPSD, people with dementia are generally older, frailer and living with other comorbid health conditions. A large body of evidence has identified that the use of antipsychotic medications in people with dementia is associated with serious cerebrovascular adverse events and 1.7 times increased risk of mortality [202, 203]. It is recommended that antipsychotics are used with caution in people with dementia. They should only be prescribed when the person is at risk of causing harm to themselves or others, and when non-pharmacological approaches to managing behavioural symptoms have failed. In recent years, awareness of harms associated with antipsychotics has improved efforts to manage their use in people with dementia, including monitoring and audits. The mean prescription of antipsychotics has decreased from 19.9% to 7.4% per year among people with dementia in UK primary care (1995-2011) [204]. Although, despite improvements in the prescription of antipsychotics to people with dementia, we need to understand up-to-date prevalence of use across people with dementia in primary care and in care homes, particularly given the serious adverse effects associated with use.

(ii) Antidepressants

Antidepressants are used to treat moderate to severe depression, which affects around 15% of older community-dwelling adults [205]. Depression is associated with morbidity, decreased physical, social and cognitive function and reduced self-care [206]. In older adults, antidepressants are often prescribed to manage incontinence, pain, anxiety, irritable bowel syndrome and insomnia [207]. There are four main classes of antidepressants, tricyclic antidepressants, selective-serotonin re-uptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs) and 'other' antidepressants that do not fall within the three classes. Antidepressants have been associated with increased risk of adverse events in people with dementia [208] and increased risk of falls in older adults, across the classes of antidepressants. The increased risk of

falls may be explained by sedation, drowsiness and impaired balance as a side effect of the prescription [207]. Moreover, there is evidence that some antidepressants are not effective as first choice treatment of depression in Alzheimer's disease [209]. A recent review found little evidence for the effectiveness of antidepressants for improving depression in people with dementia and found an increase in adverse effects compared to placebo [208]. However, the quality of the available evidence was poor, including evidence of poor reporting of adverse effects (selective reporting) and negative results and risk of selection and performance bias due to inadequate blinding in studies [208]. Further research is needed to understand the effect of antidepressants in people with dementia, including potential for adverse effects.

All medications and therefore all antidepressants have the potential for adverse effects but the side effects associated with antidepressants do vary across the different types [210]. A large observational cohort study of older adults with depression (n=60,746) found all antidepressants were associated with increased risk of mortality, suicide or self-harm, falls and fractures compared to non-users. However risk varied across antidepressant class, SSRIs were associated with greatest risk of falls, MAOIs and other antidepressant medications were associated with greatest risk of mortality, suicide or self-harm, stroke, fractures and epilepsy. Tricyclics were not associated with greater risk compared to the other antidepressant classes [211]. Antidepressants have also been estimated to be associated with a small but significant increased risk of mortality in people with dementia as part of a national Veterans Health Administration registry [212]. However, this study excluded tricyclic antidepressants and MAOIs and the follow-up was over 180 days. Further studies to understand the impact of all antidepressant use in people with dementia and with follow-up periods that account for long-term use, will add to our understanding of the impact of prescribing potentially inappropriate antidepressants in people with dementia.

There is also evidence that tricyclic antidepressants are associated with sedation, orthostatic hypotension, and cognitive impairment [205–207]. The anticholinergic effects of tricyclic antidepressants are associated with detrimental effects on some cognitive domains [216]. Although, other studies observe impaired cognition at baseline in tricyclic antidepressant users, however no significant changes in decline were observed overtime in older adults [217]. Reducing exposure to medications with negative cognitive side effects is a priority for people living with cognitive impairment or dementia to reduce the potential for exacerbating the condition. This is an exemplar of the benefit compared to harm decision-making process associated with medication use in this population.

(iii)   Benzodiazepines

The findings from this review identified that benzodiazepines were among one of the most commonly identified PIM prescribed to older adults [147, 158, 180, 218]. Benzodiazepines were also prevalent in studies of populations in nursing homes [137, 219]. Benzodiazepines are a type of anxiolytic and hypnotic medication with sedative effects. Primarily benzodiazepines are indicated to relive anxiety and sleep problems in older adults. Some common side effects include drowsiness, dizziness and reduced coordination. The evidence from the review highlighted that long-term use is also associated with an increased risk of dependence, serious falls and fall-related fractures [220], cognitive impairment [221], delirium. There is some observational evidence of an increased risk of dementia, however the evidence is inconclusive and benzodiazepine use may be an early marker of the disease [222]. Many older adults are prescribed benzodiazepines for long-term use, and may be prescribed to people with dementia to manage sleep disturbances, despite a lack of clinical benefit supporting their use in this way and increased prevalence of adverse effects. Until recently, there were no guidelines to support safely stopping benzodiazepines and only since 2019 have NICE endorsed guidelines developed in the Bruyère Deprescribing Research Team [108]. A lack of guidelines for safely stopping medicines and the associated dependence and withdrawal symptoms may have also impacted on the challenges associated with prescribing and deprescribing benzodiazepine prescriptions in older adults.

(iv)   Anticholinergics

This scoping review also showed that anticholinergic medicines were included across a number of PIM criteria and are associated with particular adverse effects, including cognitive impairment, confusion, delirium, falls and hospital admission in older adults and people with cognitive impairment or dementia [129, 143, 150, 154, 161, 162, 166]. Anticholinergics work by blocking the action of acetylcholine, a neurotransmitter acting within the central nervous system, smooth muscles of the gut, some non-voluntary internal organs and the heart. Medications with anticholinergic effects account for a range of medications but includes medications used for gastro-intestinal disorders, incontinence, drugs for Parkinson's, some antidepressants and antipsychotic medications. Previous studies have found observational associations of anticholinergic drugs with a number of consequential side effects including well established detrimental effects on cognition [216] and some evidence of increased risk of dementia [223]. However, a recent case-control study found an association of some but not all anticholinergic

medications. Antidepressants and definite anticholinergic medicines were associated with incident dementia [223]. The use of anticholinergic medications in older adults has previously been associated with increased delirium, sedation, urinary retention, falls, cardiovascular disease and mortality, although the evidence is not conclusive [213, 224, 225]. Evidence of an association of anticholinergics and mortality has been conflicting and somewhat limited by short follow-up periods and small sample sizes [226–229]. Moreover, previous studies have not accounted for physical frailty beyond the presence of comorbidities, or the use of other medications [230]. Measures of frailty are predictive of mortality and accounting for frailty may improve understanding of the relationship between anticholinergic medicines and mortality in people with dementia. Furthermore, a review of studies of anticholinergic medications and the association with delirium found the majority of studies did not find an association of anticholinergics with delirium [226]. Clinical guidelines suggest that anticholinergic medications should be avoided if possible in frail older adults [231]. Tricyclic antidepressants, are one example of a medication with high anticholinergic burden and it is recommended that they should be avoided in people with dementia due to associated adverse effects [107, 232]. Anticholinergic medications are a priority medication to be managed, particularly in people with dementia due to associated adverse effects, but more evidence is needed to understand the potential for adverse effects in this population given previous limited evidence.

(v) Proton pump inhibitors

Identified in a number of reviews was the high prevalence of inappropriately prescribed proton pump inhibitors (PPIs), which were cited as the most commonly occurring PIM [141, 168]. Used for the treatment of acid related indigestion and peptic ulcers PPIs are one of the most frequently prescribed medications globally [233]. PPIs are generally considered safe and effective and associated with few adverse effects. However, recent evidence has suggested that PPIs may be associated with hip and spine fractures [234, 235], hospital and community acquired pneumonia [236–238], *Clostridium difficile* infections [239, 240] and vitamin and mineral deficiencies [241]. However, findings are not consistent across observational studies and previous studies have been limited in their approach to adjusting for comorbidities and confounding by indication [242].

Around 23% of people with dementia are prescribed inappropriate PPIs [189]. In addition, for 27% of the older population PPIs are prescribed long-term, despite a lack of evidence supporting the efficacy and safety of their long-term use [242]. It is considered that PPIs should not be prescribed for longer than eight weeks in older adults [243]. PPIs are widely prescribed and account for

considerable prescribing costs. In England, over £100 million is spent annually on PPIs from NHS budgets [244], however as highlighted many PPIs are prescribed chronically and possibly unnecessarily. PPIs may be contributing to inappropriate polypharmacy when they are prescribed long-term and without clear indication. The implications of managing the inappropriate use of PPIs on clinical and economic outcomes are not yet known. PPIs are a useful target medication to monitor in future studies as a potential for improving patient safety, identifying inappropriate polypharmacy and medications to be deprescribed and have substantial financial implications for health care providers.

(vi)   Targets for deprescribing

The process of reducing, tapering and ceasing a medication to improve medicines is known as deprescribing [245]. Deprescribing is an integral part of optimising medicines, particularly when a medication is potentially inappropriate. The scoping review identified a number of key medications that are useful targets for improving appropriate medication use. Given the large number of PIMs identified, prioritising which medications to deprescribe has been a priority within previous studies and is integral in informing the priority direction of this research. A Delphi consensus survey study consulted over 60 physicians, pharmacists, geriatricians and nurses to identify medications commonly used by older people, for which evidence-based deprescribing guidelines would be useful for practice [246]. The highest priority medications for deprescribing were benzodiazepines, antipsychotics, antidepressants, proton pump inhibitors and anticholinergics, statins and cholinesterase inhibitors, for which over 30% of Delphi participants indicated the medication as a high priority for deprescribing evidence. Other medication classes were opioids, bisphosphonates, anticonvulsants, beta-blockers and antiplatelet medications. A number of the reviews included in my scoping review also identified the need for deprescribing guidelines to support practitioners and to be incorporated into practice [136, 173, 181]. The corroboration between the medications identified in this scoping review and those identified as priority medications for deprescribing is important and provides a useful focus for future research [246].

People with dementia may be at increased susceptibility to side effects of medications and there is evidence that people with dementia are particularly vulnerable to serious adverse effects of antipsychotic medications and detrimental cognitive effects of anticholinergic medications. From this scoping review, it is apparent that whilst there is a large body of literature investigating polypharmacy and PIM among older adults, the evidence is limited amongst people with cognitive

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impairment or dementia. This is despite the growing size of this population, who are often frail and living with multimorbidity alongside cognitive impairment or dementia.

Guidelines are limited for prescribers in making evidence-based decisions about prescribing for comorbidities in people with dementia. Consideration needs to be given to specific medication classes when developing guidelines to support prescribing and deprescribing in people with dementia. Prioritising key medication classes that people with dementia may be exposed to, which could be targets for medication management interventions and building the evidence base around these key medications, is informative for the subsequent development of guidelines to inform prescribing.

Clinical trials of medications are often conducted in younger, healthy populations, excluding frail older adults and people with dementia, comorbidity or polypharmacy and alternative approaches are needed to address this gap [81, 82]. Clinical trials have lacked external validity and generalisability but observational studies are key in addressing these shortcomings. Observational cohort studies are useful because they can include large, representative samples of people who would often be excluded from clinical trials. Incorporating samples with frailty, polypharmacy, dementia and comorbidity providing more representative sample of a heterogeneous older population, and the nuances of medication use in this population can be better understood and will inform the development of prescribing guidance in people with dementia and comorbidities.

(h)   Interventions to optimise medication use

The scoping review revealed a range of interventions to address inappropriate polypharmacy and medication use in older adults. Interventions targeted prescribing, prescribers, methods of practice and care structures to improve prescribing and patient outcomes. This included, education of prescribers, the incorporation of specialists (geriatricians and pharmacists) into interventions, application of multidisciplinary teams and technology-assisted interventions to improve prescribing. However, common across interventions was the incorporation of a review of medications. The evidence suggested that medication review was an effective intervention in improving appropriate medication use, by reducing medications no longer indicated [175], reducing polypharmacy and reducing the number of PIMs [136]. Although medication review was effective in improving the quality of prescribed medications, the impact on patient outcomes was uncertain. On one hand, there was evidence that deprescribing was not associated with an increase in the number of drug withdrawal events [171]. On the other hand, there was little

evidence that medication review reduced adverse drug events [129], or hospitalisation [169] and there was unclear evidence whether a review improved quality of life or decreased medication costs [129]. In addition, the impact on mortality was only evident in non-randomised studies [129, 169, 171]. The evidence for the impact of interventions on clinical outcomes was often low quality and susceptible to bias [130, 131, 168, 133, 135, 141, 146, 148, 150, 154, 163]. Interventions were often poorly described, particularly for complex interventions, and failed to adequately report adverse outcomes or negative findings (publication bias), no or limited blinding or randomisation methods in trials. Moreover, there was little research into the impact of medication review in community-dwelling people with dementia. Further research is needed to assess the usefulness of medication review to improve prescribing, particularly among people with dementia and the subsequent impact on patient outcomes. Moreover, a number of reviewers also identified the need for guidelines to be developed to support prescribers in deprescribing medicines [136, 181] [173].

In people with dementia, one review found that using medication review to target PIMs was effective in improving medication appropriateness. Medication review was associated with 11% to 78% reduction in PIMs and reduction of 2% to 8% in overall medication use [165]. However, this was a review of studies of care home residents with advanced dementia. In an environment where patients are being cared for consistently, staff may have a good understanding of the person with dementia, their behaviours and the day-to-day impact of medication use. Care home staff involvement in the review of medications may assist in the identification of PIMs or unnecessary medications that could be deprescribed, and monitoring potential adverse drug withdrawal events or symptom changes may be better managed. The potential for monitoring of patient safety and the controlled deprescribing of inappropriate medications may be easier to manage in a care home. In primary care, medication monitoring is much more reliant upon the patient and (if available) their carer to monitor changes day-to-day after medication review and deprescribing. From the scoping review, the impact of medication review on appropriate medication use in people with dementia was unclear and more research is needed to understand the role of medication review among people with dementia in primary care and beyond trial settings.

(i)   Patient and prescriber perspectives

A growing body of qualitative research has sought to understand the perspectives of patients, carers and prescribers in the process of medicines optimisation. The scoping review identified two

systematic reviews synthesising qualitative studies [181, 182]. On one hand, prescribers identified a number of internal factors that were associated with prescribing and medicines optimisation. This included a sense of 'powerlessness' arising from self-perceived restrictions to optimising medicines. Prescribers felt that they needed to meet the demands and desires from patients to receive medicines at a consultation. Also, prescribers identified that in some cases of prescribing in particular nursing homes or care situations, that they felt forced to prescribe by nursing home staff or carers [182]. Despite this, it was also evident that some prescribers had developed their own approaches to manage polypharmacy, given their experience and knowledge of their patients [181]. On the other hand, extrinsic factors were also identified. This included consultation time, relationships with patients and coordination of care between care homes, hospitals and GPs. Furthermore, the impact of prescribing guidelines and a lack of deprescribing guidance was identified by GPs as impacting on medicines optimisation for their patients [181].

The findings from reviews of a number of qualitative studies exploring patient perspectives of polypharmacy found a number of factors that were important to patients. The findings suggested that many patients took ownership over their medication regimes by experimenting with medicines. This would include prioritising certain medicines, taking breaks, stopping and reducing dosage. In addition, patients who had a good, trusting relationship with their GP were less worried about adverse effects and felt supported in medicines management. Like prescribers, patients felt that consultation times were too short and that there were multiple prescribers, who communicated poorly across health care systems. Of the patients who experienced adverse effects, the benefits of medicines did not outweigh the harms and they felt that medicines were less effective. Largely, patients did not want to take more medicines. There was both a resistance to taking medicines and an unwillingness to stop certain medicines [181]. These factors influence the experience of both patients and prescribers and may also influence the effectiveness of interventions to optimise medicines in practice.

(j)   Strengths and limitations of the scoping review

There are a number of strengths to this review. To ensure a broad literature search, the search strategy used three databases and a comprehensive range of search terms that were developed with the guidance of a faculty librarian. This review provided an overview of the literature into polypharmacy and PIM in older adults. This enabled a process that was grounded within the literature to discuss previous literature and identified key areas for future research that are integral to this research project. Mapping the breadth of the literature is a key strength of the

scoping review methodology compared to a systematic review [125]. This was particularly informative in understanding the extensive and clinically significant field of prescribing and medication appropriateness, particularly within older adults. The use of scoping reviews as a methodology to review the literature is growing in application across the literature and are increasingly recognised as an incredibly useful tool, particularly within health services research [247]. The consistency of scoping reviews will be improved by the development of reporting guidelines, such as the PRISMA-SR used in this review (Appendix 1 Section 10.01) [128]. Conducting a review of reviews summarised a range of reviews addressing a number of research questions across related areas and understanding the extent of research evidence of different types of studies, interventions and outcomes across different populations [126]. This approach enabled this review to cover research across medication appropriateness including polypharmacy and PIMs, understand the impact of different interventions, outcomes and across older adults and people with dementia in a range of care settings.

Limitations of the scoping review of reviews include the possibility that recent and primary literature may not have been included in a review yet, and other reviews may have been missed due to database selection, exclusion of grey literature, time and resource constraints. The studies were extracted by one reviewer which affects the validity of the extraction process. However, a scoping review differs from a systematic review in that the goal is not necessarily to identify all relevant literature to a specific question but to understand the breadth of research into an area, which in the case of this review is far reaching. Although, through this process it was necessary to rely on secondary interpretation of findings, which is additionally compounded in a review of reviews.

It was also evident from the reviews that there were well established areas of research that have identified the challenge of prescribing in older adults. Despite this, there were identifiable gaps within the evidence base particularly around the understanding of the nuances of medicines use amongst this diverse population. Understanding the variation in this population will help prescribers manage medicines appropriately. A critical quality appraisal of the reviews included was not completed and is not a requirement from Arksey and O'Malley's (2005) original framework, and is an optional addition according to the PRISMA-SR reporting system [128]. If a quality appraisal was undertaken in the included reviews, this was taken into account when evaluating the evidence. To improve the quality of the reviews included, only systematic reviews or literature reviews with a systematic approach were included. Grey literature and opinion pieces were not included to reduce author bias.

A limitation of a review is that the review inherits the limitations and quality of the studies included in the review. Across a number of the reviews, the diversity in study designs, range of measurements and outcomes made it unfeasible to pool estimates and conduct meta-analyses. It was difficult to assess comparisons across interventions because of variation in implementation. The quality of reporting about the methods and implementation of interventions in the reviews was often limited, inherited from poor quality of reporting in the primary studies, particularly when describing complex interventions. A lack of clarity when reporting within primary studies included in the reviews affects the understanding of the impact of findings. Quality appraisals reported in the reviews often reported the evidence as low quality, lacked rigour and was at high risk of bias. Often this was associated with poor blinding and randomisation procedures in clinical trials and failure to appropriately adjust for comorbidity, considerably increasing the risk of confounding by indication bias.

2.04   Summary

Medicines optimisation in older adults is a clinically significant priority for practitioners, patients and researchers. The scoping review of reviews provided a comprehensive overview of existing research in this area. Polypharmacy and PIMs are associated with adverse effects in older adults. However, given the heterogeneity of the older population, further research is needed to refine risk estimates among vulnerable groups, including frail adults and people with dementia. Interventions to reduce PIMs and polypharmacy have been trialled but there has been little research into how these actually affect prescribing quality in practice, hence further research is needed to evaluate their impact both on prescribing and patient outcomes.

For prescribers, systems that ease the process of identifying where care pathways and medication management can be optimised will be useful across care settings. This will support the routine identification and reduction of inappropriate polypharmacy and PIMs to optimise medications. A regular medication review is often included in clinical guidelines, particularly for people who are frail, taking multiple medications, or living with long-term health conditions [108]. This review has identified gaps in the current evidence base and priorities for medication optimisation in people with dementia. The older population is heterogeneous and prescribing is complex and challenging in the presence of cognitive impairment and dementia, comorbidities and frailty. Whilst there has been a large body of research into polypharmacy and PIM use in older adults, research in people with dementia (particularly at early stages) and cognitive impairment has previously been limited, largely by its focus on advanced stages of the disease and palliative care [191]. Mild cognitive impairment and mild dementia are particularly important stages for preserving function, adjusting to a diagnosis, preparing for the future and maintaining good quality of life.

Given the lack of clinical guidelines to support prescribers when making evidence-based decisions about medication use in this population, further research is required to understand polypharmacy and PIM use. Antipsychotics, benzodiazepines, anticholinergics, antidepressants and PPIs were identified as key potentially inappropriate medication classes to direct a focus of the studies conducted in this research. These medications are implicated in both Beers and STOPP criteria [107, 232] and identified by prescribers as medications where evidence to support deprescribing would be of great value [246]. These medications are specifically associated with adverse effects in people with dementia or are widely used in the older population and deprescribing could reduce the impact of inappropriate polypharmacy. However, there is limited or conflicting evidence into the extent to which they are associated with harm. To add to this growing body of

evidence, further research is required to understand the prevalence of polypharmacy and PIM in people with dementia in primary care.

It is with these findings in mind that the broad aim of this research study was established. The overarching aim was to understand the impact of polypharmacy and potentially inappropriate prescribing on people with dementia, and to understand the effectiveness of existing approaches to improving care in this patient group. The subsequent chapter outlines the specific aims and objectives that are addressed in this research study and a broad overview of the methodological approaches applied.

III. Chapter 3: Aims and Objectives

3.01 Introduction

The scoping review of reviews established that whilst there is a large body of research into polypharmacy and PIM in older adults, the research into people with dementia is limited. Further research is needed to understand the impact of inappropriate prescribing across this heterogeneous population. The central aim of this thesis was to understand the impact of potentially inappropriate prescribing in people with dementia, including the real world effectiveness of approaches to optimise medication use in this population. Applying epidemiological methods, two cohorts including people with cognitive impairment or dementia were analysed to address the aims and objectives of this thesis. This chapter provides an overview of the methodological approach, briefly introduces the two datasets that were analysed and outlines the aims and objectives addressed in the remaining chapters of this thesis.

3.02 Pharmacoepidemiology

Evidence for the efficacy and safety of medication use is often extrapolated from clinical trials that lack external validity and generalisability because they often use lower-risk samples, which would exclude older, multimorbid and frail adults, people with polypharmacy, cognitive impairment or dementia [81, 82]. Observational studies are able to mitigate these limitations through observing the effects of a disease or intervention, for example, in real-life environments and if sampled appropriately, also provide a representative sample of a population. In older populations, a truly representative sample may include a mixture of genders, care settings, ages, frailty, comorbidity, polypharmacy and cognitive impairments, representing the diversity of this population including the most vulnerable and traditionally inaccessible groups.

As the study of the use and effects of medications in large cohorts, pharmacoepidemiology lends itself as an appropriate methodology for the studies I conducted, although this approach has limitations. Observational studies using existing data are restricted by the nature and quality of the data that is collected and made available. Secondary data analysis of cohort studies is dependent upon the reliability of the reporting of responses to answers in subjective questionnaires and the recording of responses by interviewers. Some data may be inaccurate, missing or recorded at particular or single time points. While a key strength of observational

studies is the observation of behaviour in real-world environments, this inevitably increases the susceptibility to any number of unmeasured confounders that may influence estimates. Accounting for these limitations, analyses of two distinct population representative cohorts with existing data were performed from (i) primary care patient records from Clinical Practice Research Datalink (CPRD) and (ii) participants from the Cognitive Function and Ageing Study.

(a) Clinical Practice Research Datalink

One of the world's largest research databases using electronic health record data is the Clinical Practice Research Datalink (CPRD). Established in 1987 and previously known as the General Practice Research Database, CPRD is an active database of UK primary care. The CPRD has over 30 years of longitudinal data from over 11.3 million patients, including 4.4 million active patients currently registered with over 600 practices. The CPRD covers 6.9% of the UK population and is broadly representative of the population in terms of age, sex and ethnicity [248]. The dataset contains recorded data from each patient consultation with a GP. The patient record includes key demographic information, consultation details, medical history, prescriptions, diagnoses, referrals, immunisations, and tests. Accordingly, the CPRD patient record contains information on diagnoses of dementia, prescriptions and records of patient reviews, such as the QOF dementia annual review and medication reviews.

(b) Cognitive Function and Ageing Study

The Cognitive Function and Ageing Study (CFAS) is a multi-centre, population-representative cohort study of ageing in the UK, including adults over 65 years living in the community and care homes. The original CFAS study (MRC CFAS) [249] began in 1989, the second CFAS study (CFAS II) started in 2008 [2] and CFAS Wales in 2011. My analysis used data collected as part of CFAS II, which included more than 7,700 older adults who took part in the CFAS interviews between 2008-2011 from three geographical areas in England (Cambridgeshire, Nottingham and Newcastle). The CFAS interviews comprised an extensive and comprehensive collection of over 600 questions about demographics, health and lifestyle of the participant. This included cognitive assessments, medication use as well as assessments indicative of physical frailty.

3.03 Aims and objectives of this research

(a) Aims

The broad aims of this research project were to use existing data sources to understand the impact of potentially inappropriate prescribing on people living with dementia, and how effective existing approaches to improving care in this population are. Specific aims were to:

1. To estimate the prevalence of polypharmacy and of potentially inappropriate prescribing among people with dementia.
2. To estimate the factors that predict the use of PIMs and polypharmacy, in particular the effect of dementia annual review and medication review on potentially inappropriate prescribing.
3. To understand the impact of PIMs and polypharmacy on health among older cognitively impaired adults and the potential impact of frailty on this relationship.

(i) Data sources

To address the aims, two existing data sources were used (see Figure 2). To address Aim 1 and Aim 2, primary care electronic health record data were used that was extracted from the Clinical Practice Research Datalink (CPRD). Data from the second Cognitive Function and Ageing Study (CFAS II) was analysed to address Aim 1 and Aim 3. This thesis describes and discusses how each of the aims were addressed, through a series of analyses of the CPRD and CFAS II cohort addressing the subsequent specific objectives.

(b) Objectives

(i) CPRD cohort study

Objectives addressing Aim 1:

1a. To estimate the prevalence of potentially inappropriate prescribing and average number of concurrent medications prescribed among patients with dementia in primary care in England over a two-year period.

Objectives addressing Aim 2:

2a. To estimate the probability of starting or stopping a PIM, and the change in the average number of medications prescribed after a review.

2b. To estimate the association of dementia annual review and medication review (and other patient and practice level factors) associated with starting or stopping each class of PIM, and association with a change in the number of concurrent prescribed medications, in people with dementia.

(ii) CFAS II subsample study

Objectives addressing Aim 1:

1b. To estimate the prevalence of PIM use and polypharmacy in frail and non-frail older adults with cognitive impairment.

Objectives addressing Aim 3:

3a. To estimate the association between PIM and polypharmacy use at baseline and subsequent survival, as an indicator of overall health.

3b. To estimate the moderating role of baseline frailty on the relationship between polypharmacy, PIM use and mortality.

3c. To assess the predictive validity of frailty phenotype and individual criteria to predict susceptibility to mortality.
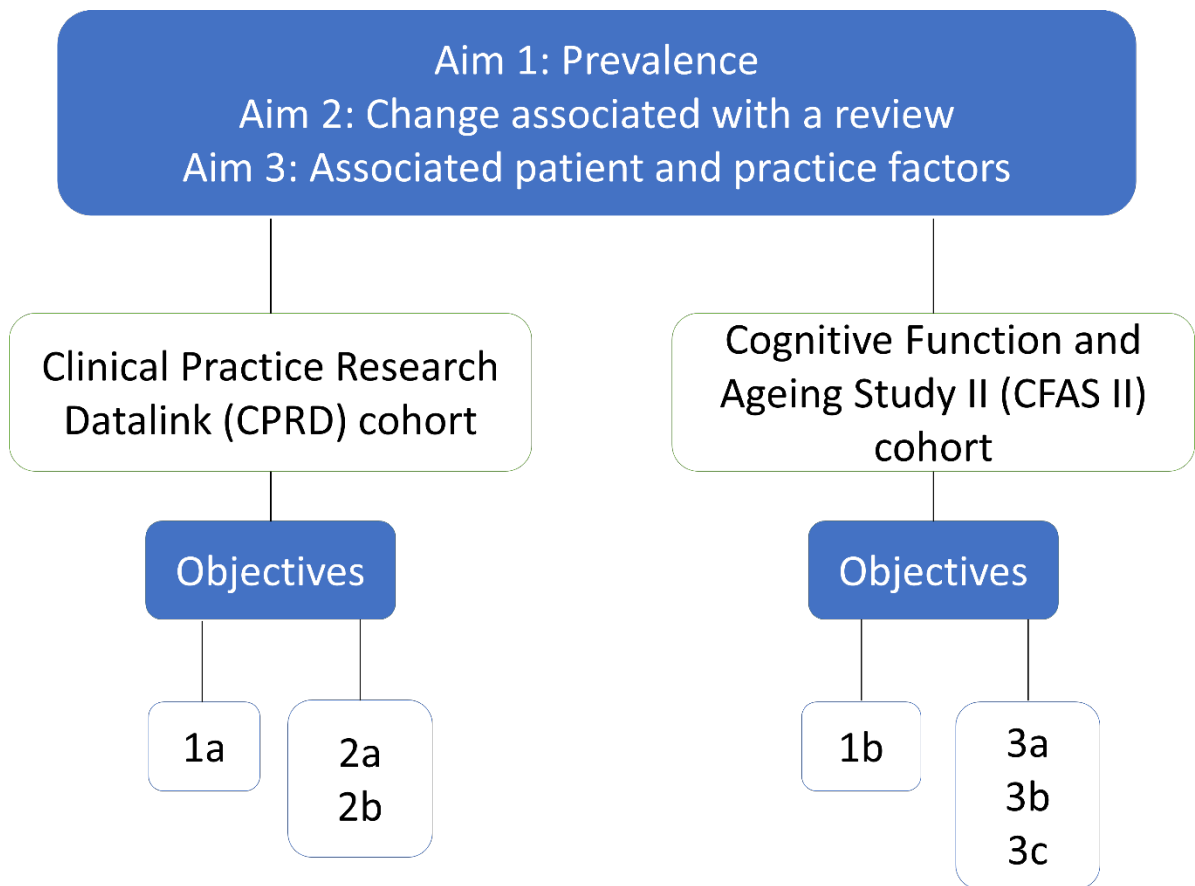
Figure 2 Describing how the three aims of this research study are addressed through a series of objectives in a CPRD cohort study using electronic health record data (n=22,448) 1st January 2015 – 30th April 2017 and a cohort study of the second Cognitive Function and Ageing Study (CFAS II) (n=1,154) 2008 – 2016

IV.   Chapter 4: CPRD cohort study Methods

4.01   Overview of chapter

This chapter presents the study design, methods and statistical approaches used to conduct the analyses of a primary care dataset of patients with dementia in England. The CPRD cohort study of people with dementia in primary care in England is described. This study addressed Aim 1 and Aim 2 and objectives 1a, 2a and 2b of this research to estimate the prevalence of and factors associated with (and changes in) polypharmacy and PIM in people with dementia. This chapter describes the study design, the dataset used, sampling approach, exposures, outcomes and covariates and statistical analyses applied. The development of a multilevel mixed effects regression models to estimate transitions in prescribing is described. This model is used to estimate the association of medication review and annual dementia reviews on starting and stopping PIMs among people with dementia in primary care.

The protocol for this study (16_240) was granted approval by an Independent Scientific Advisory Committee (ISAC) in February 2017 (Appendix Section 10.04: Appendix 4). The abstract is available online at: https://cprd.com/protocol/potentially-inappropriate-prescribing-people-dementia-england-prospective-cohort-study

4.02   Study design

This was a prospective cohort study of people with dementia in primary care in England, extracted from CPRD. The study design is summarised in Figure 3. The study period ran from 1st January 2015 until 30th April 2017. Patients with dementia diagnosis were followed from the point at which they entered the study until they left their general practice, died, the practice left CPRD or until the end of the study period (30th April 2017). Patients meeting the eligibility criteria and with a dementia diagnosis before 1st January 2015 were included at the start of the study period but patients could also subsequently enter throughout the study period, to include incident cases of patients with a dementia diagnosis, for example. This was done to ensure that at all time points, the study included a representative sample of all people with a dementia diagnosis. This included people entering the study as they were diagnosed or move to the practice and people leaving the study as they die or move.

For the purpose of the analyses, the study period was split into 14 time periods, each equivalent to two calendar months. Two month time periods were used to account for a change in a patient's prescription being applied to the patient's CPRD record.
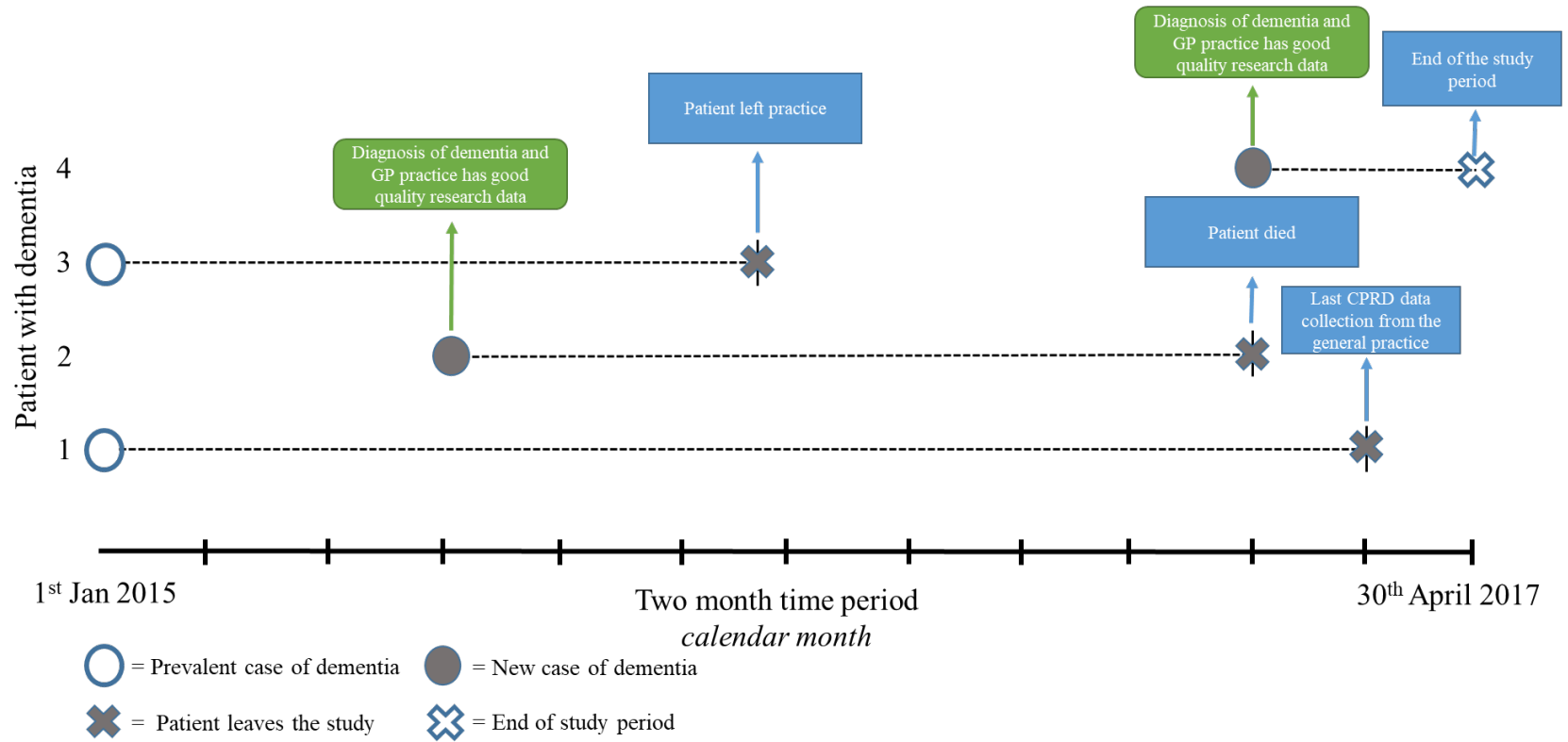
Figure 3 Example of four patients with dementia entering and leaving the study, from the sample extracted from the Clinical Practice Research Datalink.

Study period from 1st January 2015 - 30th April 2017 and is split into 14 two-month time periods. To be included, patients must have been registered at an English general practice, with a diagnosis of dementia. The patient must have been registered at a practice contributing good quality research data for at least one year to the CPRD. Patients needed to remain registered at the same practice, be alive and be included in the QOF data recording for the practice.

4.03   Setting

This study used data extracted from the Clinical Practice Research Datalink (CPRD), a research database generated from UK electronic health records. CPRD contains anonymised records of consultations, diagnoses, referrals and prescribing for more than 11.3 million patients from 674 primary care practices across the UK. In the UK, every consultation a patient has with a General Practitioner is recorded in the patient's electronic health record. A range of software systems are used by general practices and CPRD collects coded data from practices using the Vision and recently from the EMIS systems. This study used the CPRD GOLD data, containing data collected from practices using Vision in England, which is the system used in an estimated 9% of all GP practices [250] [248].

Index of Multiple Deprivation data was also linked to the CPRD dataset. This is a government measure of relative deprivation based on income, employment, education, health and disability, crime, housing and living environment, linked from the general practice postcode [251].

(i)   Structure of CPRD dataset

There are 10 separate data tables within the CPRD GOLD database, although not all tables were used for the current analyses (Figure 4)

1)   Data tables used in analyses

1. Practice data table: contained practice level details of each practice, including regional location of the practice and data collection information, including the date when the practice joined CPRD and had up-to-standard data for research purposes that was collected.
2. Patient data table: patient level demographic information.
3. Consultation data table: contained data on the type of consultation, including the consultation location.

4. Clinical data table: contained patients' medical history while registered with the practice, including clinical diagnoses and death. Coded using Read Codes.

5. Additional clinical data table: contained additional structured data associated with and linked to the clinical file events, which may include the residential status of the patients.

6. Therapy data table: contained the details of all prescriptions, including medicines and medical appliances issued by the GP, recorded using Gemscript product codes.

2) Data tables not used in analyses

7. Staff data table: included information on the practice staff.

8. Referrals data table: contained any referrals to external organisations or systems, including hospital admissions or outpatient care.

9. Immunisations data table: contained a record of any patient immunisations.

10. Tests data table: contained a record of any test data recorded by the GP
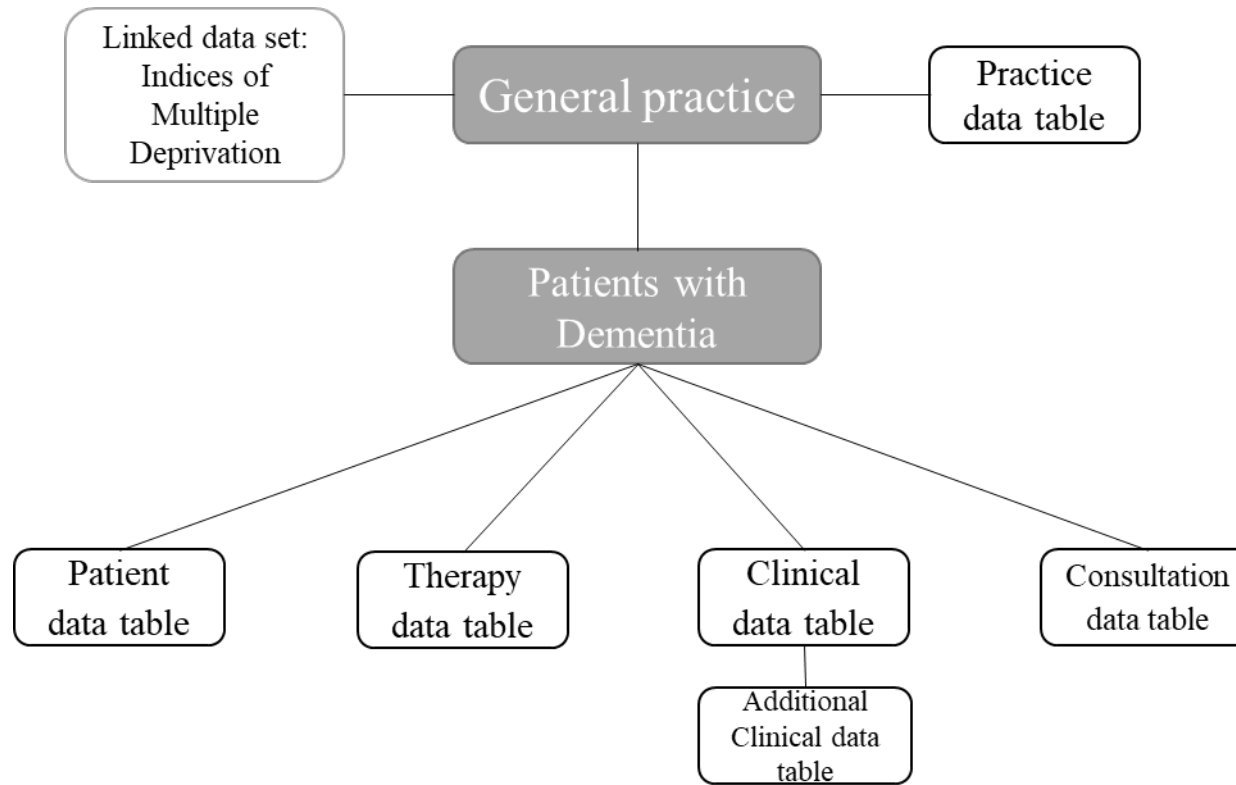
Figure 4 Hierarchal model explaining the CPRD data tables used in this study, of the 10 data tables available from CPRD, the staff, referrals immunisations and test data tables were not used for the purpose of this study.

4.04   Population and sample

The target population was all people with a diagnosis of dementia in England. The study population was patients with a diagnosis of dementia in primary care in England registered at a general practice contributing to CPRD. A series of inclusion criteria were applied to the study population to identify the eligible sample. The sample inclusion criteria are provided and justified in Table 5. A figure explaining how patients entered and exited the study is provided in Figure 3.

For a patient to enter the study, they needed to meet the inclusion criterion. In addition, the patient was required to meet a series of criterion to enter into and remain in the study, at each time period. This included:

1. The last CPRD data collection date from the practice was required to be after the end of each time period. After a general practice stopped contributing the electronic health record data to the CPRD, the patients who were registered at this practice would no longer be eligible to be remain in the study.

2. The patient must not leave the general practice until after the end of each two-month time period. If a patient leaves the general practice, there will be no future record in the CPRD of this patient. The patient might leave because they change address or move into a care home and are subsequently registered with a new general practice. It is not possible to match a patients' record from their previous general practice to the new practice and subsequently no further data on that patient can be used.

3. The patient must also be alive until the end of each time period.

Table 5 CPRD study inclusion criteria and supporting rationale.

Inclusion Criteria	Rationale
1. Diagnosis of dementia as defined by the presence of a record of a dementia diagnosis or a prescription of a cognitive enhancer (i.e. memantine, donepezil, rivastigmine, or galantamine) before the start of or during the study period (1st January 2015 – 30th April 2017).	1. New diagnoses were also included to maintain a representative sample of dementia patients throughout the duration of the study period. Identifying dementia diagnosis using similar definitions has been validated in the CPRD with a positive predictive value (PPV) of 95% [252].
2. Currently registered at an English GP practice	2. While CPRD does provide data from primary care practices across the United Kingdom, because health care provision is devolved across the four countries, clinical practice, guidelines and the use of pay-for-performance schemes can vary greatly. The use of the Quality and Outcomes Framework, for example is different between countries in the United Kingdom, with Wales and Scotland recently radically changing their approach [253]. In addition, the IMD linkage data is not comparable between countries in the UK.
3. The patient must be registered with a practice that is contributing good quality research data for at least one year before entry into the study.	3. The CPRD assess the quality of the data that is provided from primary care using an algorithm evaluating the practice recording of death and of gaps within the data. A variable is generated by CPRD to identify the date at which the practice data is of appropriate quality to be used for research purposes. For this study, I used data from patients registered with practices that had a minimum of one year of good quality data to allow for appropriate measurement of baseline confounders.
4. Patients must be included in the QOF data recording for the practice.	4. A GP can exclude patients from the QOF for example because it is deemed inappropriate to conduct the review due to significant frailty or the patient is in palliative care. Alternatively, the patient can choose to be not be included in the data collection. A patient can choose to not have a dementia annual review, for example and would therefore not count towards the QOF data recording and the practice score and practice income would not be affected.

4.05   Exposures

The primary exposures of interest were the presence of a record of a dementia annual review or a medication review in each two-month time period across the duration of the study. The CPRD clinical data table contained Read Codes that were used to extract detail for medication reviews and dementia annual reviews from the patient records from 1st January 2015 until 30th April 2017 (Figure 5). The presence of a record of a dementia annual review or a medication review, in each two-month time period was coded. Two binary variables were generated to account for a record of a dementia annual review and a medication review.

(a)   Dementia Annual Review

In-line with the QOF guidelines, a record of annual dementia care plan review should be recorded in a patient's file using one specified Read Code, in order for the practice to gain the associated income from QOF if they met the target. A record of a dementia annual review was identified as an event in the clinical data file with the Read Code 6AB..00 and was classified as a binary variable (1= dementia annual review, 0 = no dementia annual review) in each two-month time period for each patient.

(b)   Medication review

Any record of an event in the clinical file with a Read Code identifying a medication review (see Table 6) within the two-month time period was used to generate a binary variable identifying medication review in each time period (1=medication review 0=no medication review). The Read Code lists to identify the record of a review were cross-checked by a practising general practitioner with experience of QOF recording and working with CPRD.

Table 6 Read Codes used to identify Medication Review, checked by a practising GP.

Read Code	Read Term
8B31400	Medication review
8B3y.00	Medication review of medical notes
8B3x.00	Medication review with patient
8B3V.00	Medication review done
8B3S.00	Medication review
8B3h.00	Medication review without patient
8B31B00	Polypharmacy medication review
8BIC.00	Medication review done by pharmacist
8BIy.00	Medication review done by nurse
8BIH.00	Medication review done by doctor
8BMF.00	Medicine use review done by community pharmacist
8BMH.00	Medication review done by pharmacy technician
8BMY.00	Medication review done by medicines management pharmacist
8BMJ.00	Dispensing review of use of medicines
8BMX.00	Medication review done by medicines management technician
8BT..00	Medication review - additional
8BT2.00	Medication review by practice nurse
8BM0.00	Mental health medication review

4.06 Outcome variables

(a) Potentially inappropriate medications

Selected potentially inappropriate medications (anticholinergics, antipsychotics, tricyclic antidepressants and proton pump inhibitors) were defined according to the World Health Organisation Anatomical Therapeutic Chemical Classification System (ATC) codes, the Anticholinergic Cognitive Burden scale and the STOPP criteria. A binary variable was generated for each of the selected PIMs, identifying the presence of a recorded prescription within each two-month time period.

(i) Anticholinergic medication

Definite anticholinergic medications were defined as any medication with an Anticholinergic Cognitive Burden (ACB) score of three, where an ACB score of three indicates medications with definite anticholinergic activity and severe negative cognitive effects [254]. The full list of anticholinergic medications from ACB included can be found in Appendix Section 10.05: Appendix 5a.

(ii) Antipsychotic medication

Antipsychotic medications were defined using ATC code N0A5A.

(iii) Tricyclic antidepressants

Tricyclic antidepressants were defined using ATC codes. Antidepressants (ATC N06A) were grouped into tricyclic antidepressant sub-type. The ATC codes were cross-referenced with the British National Formulary (BNF) to identify those used in UK practice (ATC N06AA02, N06AA03, N06AA04, N06AA06, N06AA07, N06AA09, N06AA10, N06AA12, N06AA16, N06AX03 and N06AX05).

(iv) Proton pump inhibitors

Proton pump inhibitors are considered to be potentially inappropriate, according to STOPP criteria when they are used at maximum therapeutic dose for more than eight weeks. For this study, PPI use was classified as long-term use when there was a record of a prescription of a PPI in at least two consecutive two-month time periods. Their use was defined using ATC code A02BC, see Appendix Section 10.05: Appendix 5b for full list of codes.

(b) Total number of prescribed medications

A continuous variable for the total number of different drugs prescribed within each two-month time period per patient was generated. This variable excluded all records of devices, dressings and topical preparations. Any repeat prescriptions within each two-month time period were removed.

4.07 Covariates

Covariates were selected due to their association with dementia or prescribing practices. An explanation of how the variables were derived from the CPRD is provided (see Figure 5).

(i) Age

To ensure anonymity CPRD only records the patient year of birth. An age variable was generated from year of birth based on the assumption that all patients are born on 1st July. The patients' baseline age was included as a continuous variable. Age was included as a mean-centred variable when included as a covariate in the regression models.

(ii)   Gender

Patients were identified as male or female with a binary variable indicator from the patient file. Age and gender are associated with the prescribing and may be associated with medication reviews and dementia annual reviews, previous studies have observed gender differences and age associated increases in the use of health care services in older adults [255].

(iii)   Residence in a care home

Around 39% of people with dementia in the UK are living in a care home [28]. Living in a care home is associated with polypharmacy, prescribing errors and mortality [256, 257] and reviews of medications should occur regularly in care homes, depending on the health needs of each patient [108]. The living situation of all patients in CPRD is not explicitly coded. Therefore, whether a patient lived in a care home or their own home was ascertained from available data. Bringing together patient data from multiple files in the CPRD, a single binary variable was created that identified if a patient was expected to be living in a care or nursing home. Using the data available within the CPRD, I was able to identify from a patient's electronic health record an indication of their living situation, in particular when there was a reference to living in a care home, nursing home, in sheltered accommodation or in their own home. In the CPRD file describing some detail of each consultation with a patient for example, two Medcodes could be used to identify the location of the consultation as a care home.

For this variable, patients who were living in a care home, nursing home or sheltered accommodation were grouped into one group identified as living in a 'care home'. Therefore, the term 'care home' encompasses residential, nursing or sheltered accommodation. If there was no record of a care home in a patient's electronic health record, the patient was assumed to not be living in a care home.

The patient was identified as living in a care home from the date at which this first appears in their electronic health record, as gathered from the clinical files and consultation files. Before this date, the patient is assumed to be living in their own home and after this date, they are assumed to live in a care home. This is useful in identifying patients who move into a care home across the study period. Once the patient was considered to be living in a care home, it was assumed they did not leave the care home. In some cases this also coincided with the patient exiting the study

because they were simultaneously registered with another General Practice and CPRD cannot track patients across practices.

(iv) Comorbidity

Comorbid health conditions were defined using the Charlson Comorbidity Index (CCI) [258]. The CCI has been widely used and validated and has previously been applied to electronic health records and used in the CPRD to account for patient comorbidity [259, 260]. An adapted version of the CCI was used in this study, which translated the CCI to Read Codes that could be applied to electronic health record databases [261]. The CCI groups comorbid health conditions using the International Classification of Diseases (ICD) diagnosis codes. Comorbidities are allocated a weighted score, from one to six, based on their association with mortality. Comorbidities with the highest association with mortality and a CCI score of six includes AIDs and metastatic tumour. Cerebrovascular disease, chronic pulmonary disease, congestive heart failure and diabetes with a CCI score of one, for example. All patients in the sample have a minimum CCI score of one because of the dementia diagnosis (Appendix Section 10.06: Appendix 6). Each patient was allocated a CCI score, based on the summation of all the weighted comorbidity scores for the patient. Higher scores indicate greater comorbidity and greater associated risk of mortality.

(v) Practice level area deprivation

Deprivation is associated with health, and there is evidence to suggest that living in a deprived area is associated with worse health and mental health [262]. Previous studies have found variation in prescribing among people with dementia according to area-level deprivation [263]. Deprivation as identified from the English IMD 2015 data, linked through the General Practice postcode, provided the practice area-level deprivation. The IMD is a measure of relative deprivation and ranks every area from the most deprived to the least deprived area and are classified into deciles. The General Practices were ranked as being within the most deprived 10% up to the least deprived 10%, with higher scores meaning less deprivation. The IMD was coded in deciles and was recoded into quintiles for the purpose of analyses.

(vi)   Polypharmacy

A categorical variable to account for the overall number of medications prescribed was included and categorised as 0-4 medications, 5-9 (polypharmacy) and 10 or more medications (hyperpolypharmacy).

(vii)   Patient and practice random effects

Previous studies using the CPRD have identified considerable variation between general practices in prescribing appropriateness and safety, particularly among older patients and those prescribed multiple medications [116]. The effect of the patient being registered at a particular general practice was included in regression analyses to account for the possibility of within and between practice variations.
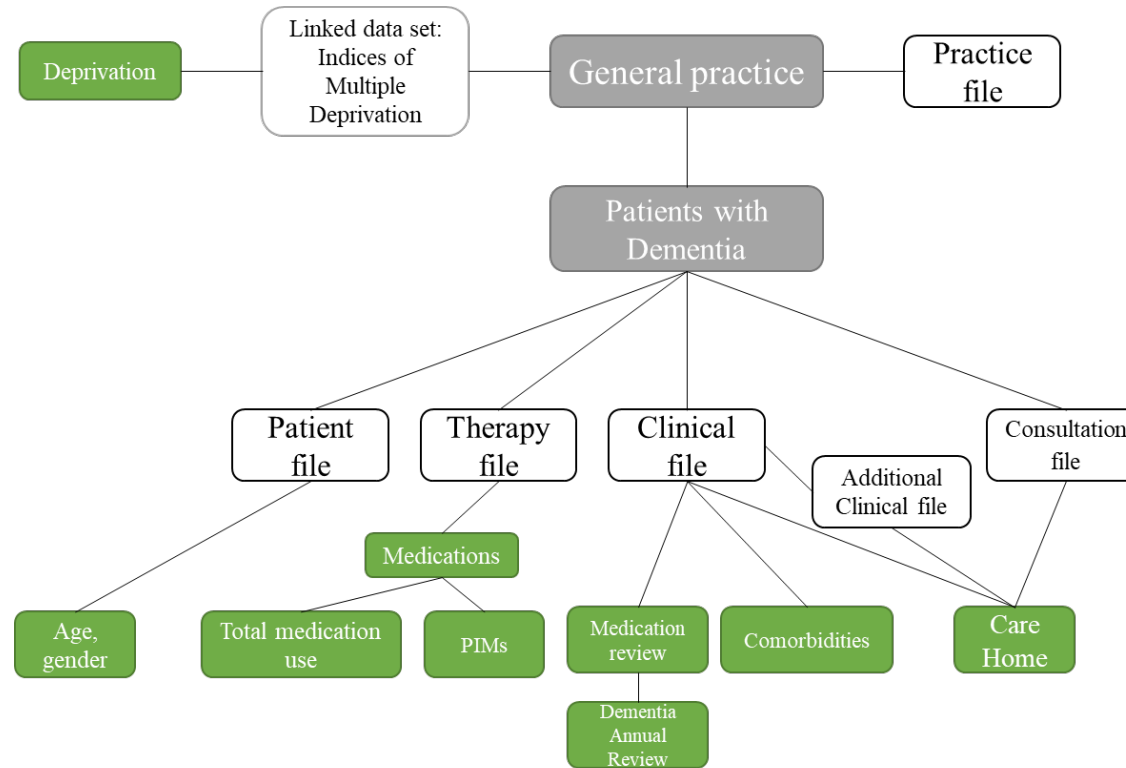
Figure 5 structure of the CPRD GOLD data set and variables. Explaining which CPRD file the variables were derived from in the CPRD cohort study.

There are 10 separate file types included with the CPRD dataset, not all of the files were used for analyses. The practice and file provided information on the practice and linked to patients who were registered with each practice, subsequently providing the sample of patients with dementia and patient age and gender variables. The therapy file contained details of patient prescriptions from which the total number of prescribed medications and PIM variables were derived. Medication review, dementia annual review and comorbidity were extracted using Read Codes from the clinical file. Residence in a care home was derived from the clinical, additional clinical and consultation files to create one care home variable. Linked data set, IMD, was linked to CPRD by the practice postcode.

4.08   Statistical analysis

(a)   Description of the sample

The CPRD cohort study sample was described in terms of the inclusion and exclusion of patients with dementia between 1st January 2015 and 30th April 2017. This included a count of the incident cases of dementia and patient and practice factors associated with reasons for exclusion from the study sample.

(b)   Sample characteristics

The patient characteristics, comorbidity, living situation and the general practice area-level deprivation were described for the sample as a whole and among patients with dementia who were living in a care home.

(c)   Prevalence of potentially inappropriate prescribing

To address objective 1a of this study, the prevalence of each class of PIM and average number of concurrent medications prescribed among patients in primary care was estimated. The prevalence of each class of PIM (anticholinergics, antipsychotics, tricyclic antidepressants and long-term PPIs) and total number of prescribed medications, was estimated in each two month time period from 1st January 2015 until 30th April 2017, by dividing the total number of people with dementia with a recorded PIM prescription by the total number of people with dementia in the study, at each time period. The prevalence of each PIM and mean number of prescribed medications was also estimated according to a patient's living situation. The proportion of patients with dementia with a record of each PIM was estimated with 95% confidence intervals.

(d)   Describing occurrence of dementia annual review and medication review

Patient age, gender, comorbidity, living situation, practice area-level deprivation and proportion of patients with a prescription of PIM were described at the point of the first medication review

and the first dementia annual review. Kaplan-Meier survival curve graphs were used to estimate the time until the first dementia annual review and medication review and to estimate the proportion of patients who had had a dementia annual review or medication at different points across the study period.

(e) Estimating the change in total medication use and the probability of being prescribed a potentially inappropriate medication before and after a review

Addressing the second aim of this thesis, objective 2a was to estimate the change in the probability of a PIM prescription and change in total number of prescribed medications after a medication review or dementia annual review. For each patient the first medication review and dementia annual review within the study period was identified. The presence of each PIM and the average number of concurrent prescribed medications before and after the period including the review was identified. The analysis of each PIM class and concurrent prescriptions were treated separately in analyses. A prescription of each PIM in the time period after a review was compared to the prescription of each PIM in the time period before the review. A figure to explain the set-up of the analysis is provided in Figure 6.
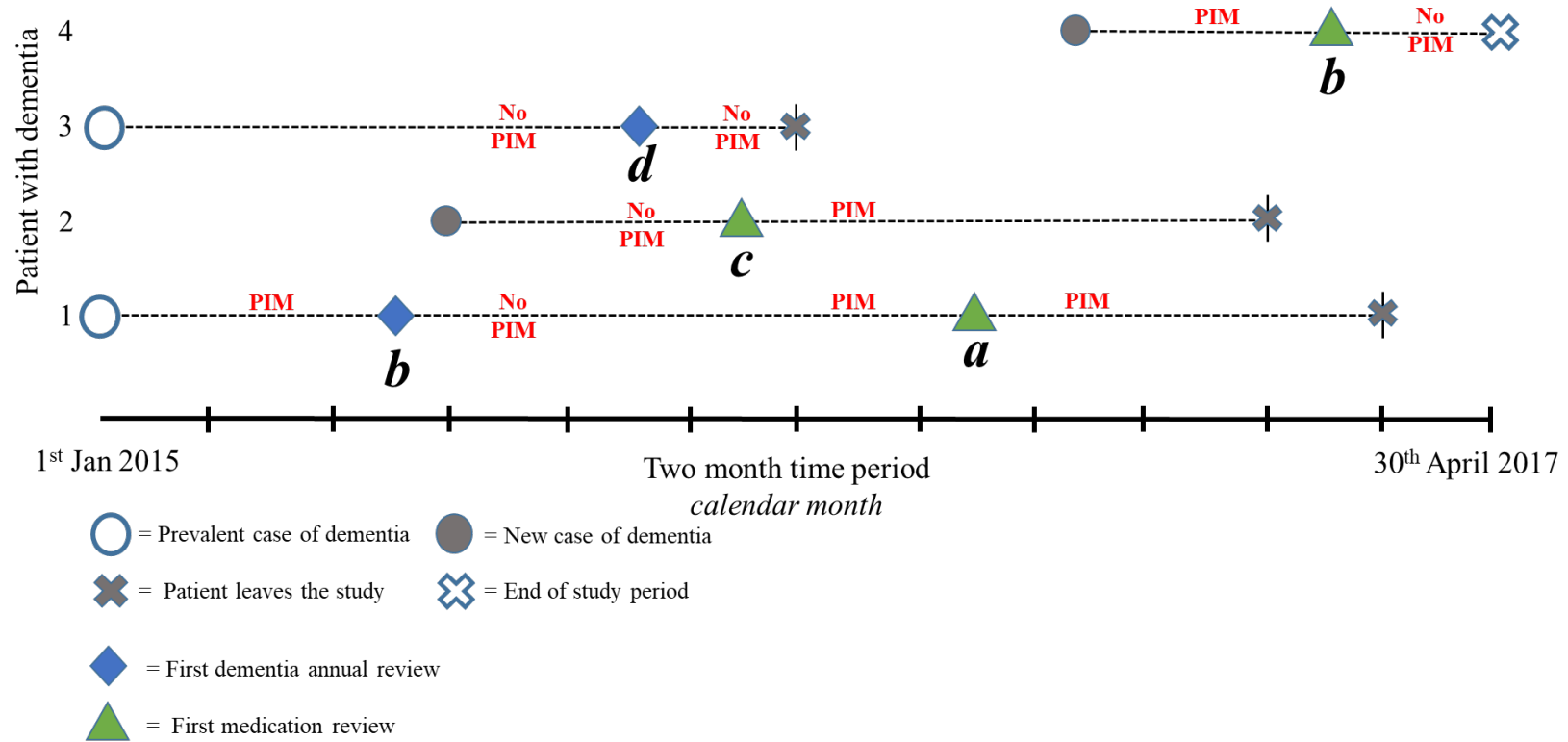
Figure 6 explaining the setup of the McNemar analysis for the CPRD cohort study estimating the change in the probability of being prescribed a PIM before and after a dementia annual review or medication review. Reviews and each PIM were analysed separately.

a = prescription before and after ie. No change; b = PIM Stopped; c = PIM Started; d = No PIM

The McNemar test compares the proportion of patients who stopped PIM (b) to the proportion of patients who started PIM (c) after a review in the previous time period. For the purpose of the analyses, a lead variable and a lagged variable were used to compare PIM prescription in the time period before and after the time period when there was a review

For the analysis of each PIM class, McNemar tests were used to test the hypothesis of no overall change in binary outcomes of PIM prescription before and after the review. The McNemar test compares the proportion of patients with dementia who have started compared to stopped a PIM, after a review. McNemar uses 2x2 contingency tables to test the proportion of disconcordant pairs, an example 2x2 table is shown in Table 7 and example of the Stata output is provided in Figure 6. The null hypothesis is $H_0 : p_b = p_c$ where the probability of starting a PIM prescription is equal to the probability of stopping a PIM after a review i.e. a person with dementia is as likely to start a antipsychotic medication as they are to stop, after a review.

To identify the presence of a PIM in 1) the next two month time period and 2) the previous two month time period, a lead variable and a lagged variable were generated using Stata's Time Series operators. These variables were used to compare the PIM prescription before and after a record of a medication review or dementia annual review. Medication review and dementia annual review were analysed separately.

A paired t-test was used to estimate the change in the average number of concurrently prescribed medications after a dementia annual review or medication review. The change in the mean number of prescribed medications in the time period after the first record of a review was compared to the mean number of medications in the time period before the review. A second t-test was used for patients who did not have a review, to compare change in medication use regardless of a review.

Table 7 Example of McNemar 2x2 contingency table to explain the McNemar analysis used to estimate change in the probability of being prescribed a PIM after a review.

	Proportion of patients with PIM after review		
Proportion of patients with PIM before review	PIM = 1	PIM = 0	Row Total
PIM = 1	a	b	a + b
PIM = 0	c	d	c + d
Column total	a + c	b + d	n

Explanation

a = prescription before and after (no change)

b = PIM Stopped

c = PIM Started

d = No PIM (no change)

b & c = discordant pairs = outcome is different

a & d = concordant = outcome is the same

The McNemar test compares the proportion of patients who stopped PIM (b) to the proportion of patients who started PIM (c) after a review in the previous time period.

Figure 7 Example of the Stata output of the McNemar analysis in CPRD cohort study. Starting and stopping antipsychotic medications after the first record of a medication review.

McNemar test in Stata is run using the mcc command. This McNemar test compares the number of patients starting an anticholinergic to the number of patients who stopped an anticholinergic at the point of the first record of a medication review. In the table, controls refers to antipsychotic prescription (exposed) or no antipsychotic prescription (unexposed) before the review. Cases refers to antipsychotic prescription (exposed) or no antipsychotic prescription (unexposed) after the first review.

(f)   Estimating the predictors of stopping and starting each PIM

The objective 2b of this thesis was to estimate the patient and practice level factors associated with stopping or starting each class of PIM and associated with a change in the number of concurrent prescribed medications. Two potential analysis approaches arose; a multistate model and a multilevel regression model. The multistate model approach provided a useful means for understanding the processes involved in prescribing, however limitations of this approach deemed it inappropriate for the needs of this analysis. A multilevel regression model was subsequently applied and accounted for these limitations outlined.

(i)   Multistate model for PIM use

A multistate model was used for initial conceptual understanding of the process of prescribing and deprescribing in primary care, in order to inform the development of the multilevel regression models used in subsequent analyses.

A multistate model can be used to describe the process of an individual moving through a series of states in continuous time. A multistate model describes a stochastic process, where at any time an individual can occupy one state, of a specified number of discrete states. The structure of the model specifies the states that are possible and the transitions from state to state which are also possible. A traditional Markov model assumes independence from previous transitions, meaning that only the current state is relevant and previous states or history are not accounted for [264].

In this study the multistate model is understood in terms of two possible 'states' and four 'transitions' that were used to develop the multilevel regression models for estimating the factors associated with PIMs and prescribing. There were two possible states that each patient could occupy in terms of the prescription of each PIM. Each patient with dementia was either taking a PIM or not taking a PIM (Figure 8).
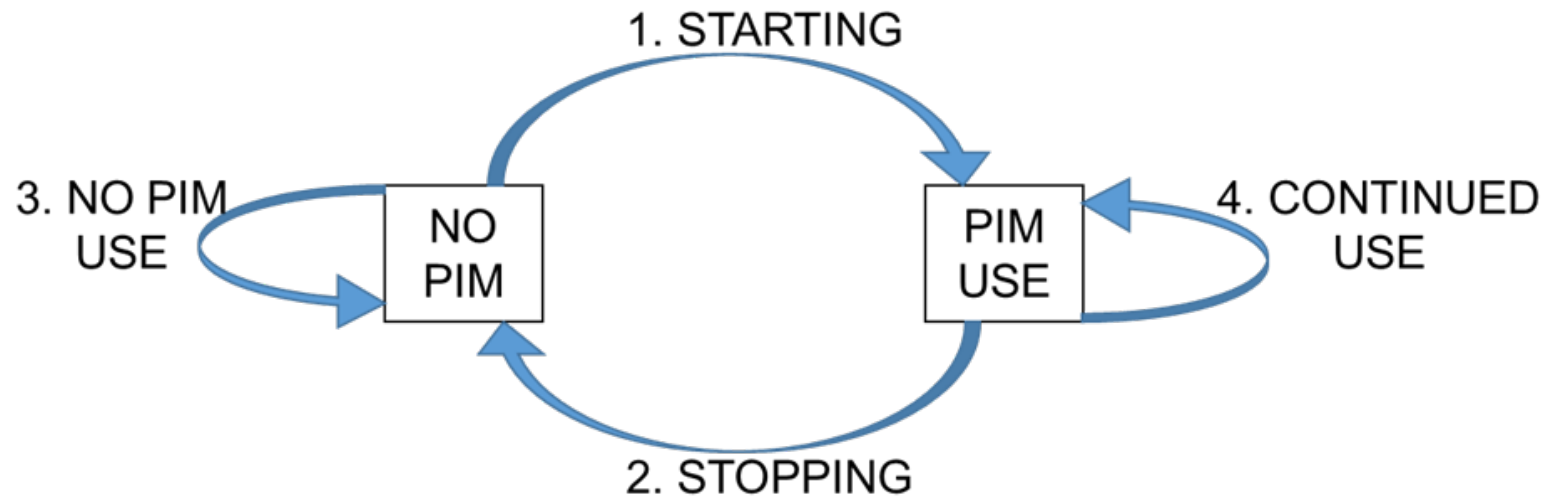
Figure 8 the two possible states of the multistate model for conceptualising the analysis of the CPRD cohort study and the four possible transitions between the two states.

1) Patients can transition from no PIM use to PIM use (the patient starts a PIM prescription), 2) Patients can transition from PIM use to no PIM use (the patient stops a PIM prescription),

3) Patients can 'transition' and remain in a state of no PIM use, 4) Patients can 'transition' and remain in a state of PIM use.

After a review, for example, at a basic level a GP would have, four options for prescribing; starting a medication, stopping a medication (if it is also assumed that the process of stopping included careful deprescribing processes such as dose reduction before cessation), continuing to prescribe a medication and continuing to not prescribe a medication.

Therefore, there were four possible transitions between the two states.

1. Starting PIM
2. Stopping PIM
3. Continued no PIM use
4. Continued PIM use

The transitions between the two states is illustrated in Figure 8. Within each two month time period all patients are within one of two possible states. Across two month time periods there are four possible transitions.

1. Patients can transition from no PIM use to PIM use (the patient starts a PIM prescription)
2. Patients can transition from PIM use to no PIM use (the patient stops a PIM prescription)
3. Patients can 'transition' and remain in a state of no PIM use
4. Patients can 'transition' and remain in a state of PIM use.

Regression models were developed to reflect these two possible states and four transitions and therefore the process of both stopping PIM and starting PIM. Mixed effects regression equations were used to model the transitions. First, the odds of starting a PIM were compared to the odds of continuing not to take a PIM (among those starting in state 1). Second, the odds of stopping a PIM were compared to the odds of continuing to take a PIM (for those starting in state 2). This was the case until either the end of the study period or until the patient left the study e.g. having died or on leaving the GP practice. Two elements make this analysis different to a typical multistate model. First, the random effects of patient and practice are included in the regression equations. Second, the process is not assumed to be memoryless, by the inclusion of a variable accounting for the previous use of medicines, which would likely predict future use.

(ii)   Estimating transition probabilities using multilevel regression

A multilevel model (also known as a hierarchal model) was used to model the relationship between an outcome variable and explanatory variables, which in this study included two

exposure variables and a set of confounding variables. Multilevel models are often used to model longitudinal data, with multiple data points on individuals over a specified time period.

Distinct from a simple regression analysis, a multilevel model also accounts for clustering between observations. In this study, the relationship with the outcome of PIM prescription was modelled accounting for individual patient factors (level one) and factors associated with the GP practice where that patient was registered (level two). A multilevel model follows a hierarchal structure, with patients nested within practices, for example (see Figure 9) [265–267]. Including practice random effects and nesting patients within practices as random effects allows for the between practice variation in prescribing practices to be accounted for. Including practice associated effects was important because patients who are registered at the same GP practice are expected to be more similar to each other than patients registered with another practice. This may be due to the patients' health being influenced by the area they live in and related to the prescribing behaviours of individual GPs or within individual practices.

A multilevel regression model is characterised by the inclusion of variables accounting for the random effect of level one and level two factors. The patient random effects (level one) go some way to accounting for individual variation across the study period that is unmeasured by the confounding variables. The nesting of patients within each practice and the subsequent inclusion of practice random effects enabled some accountability for within and between practice variations. An example of the structure of the multilevel regression model is provided in Figure 9.
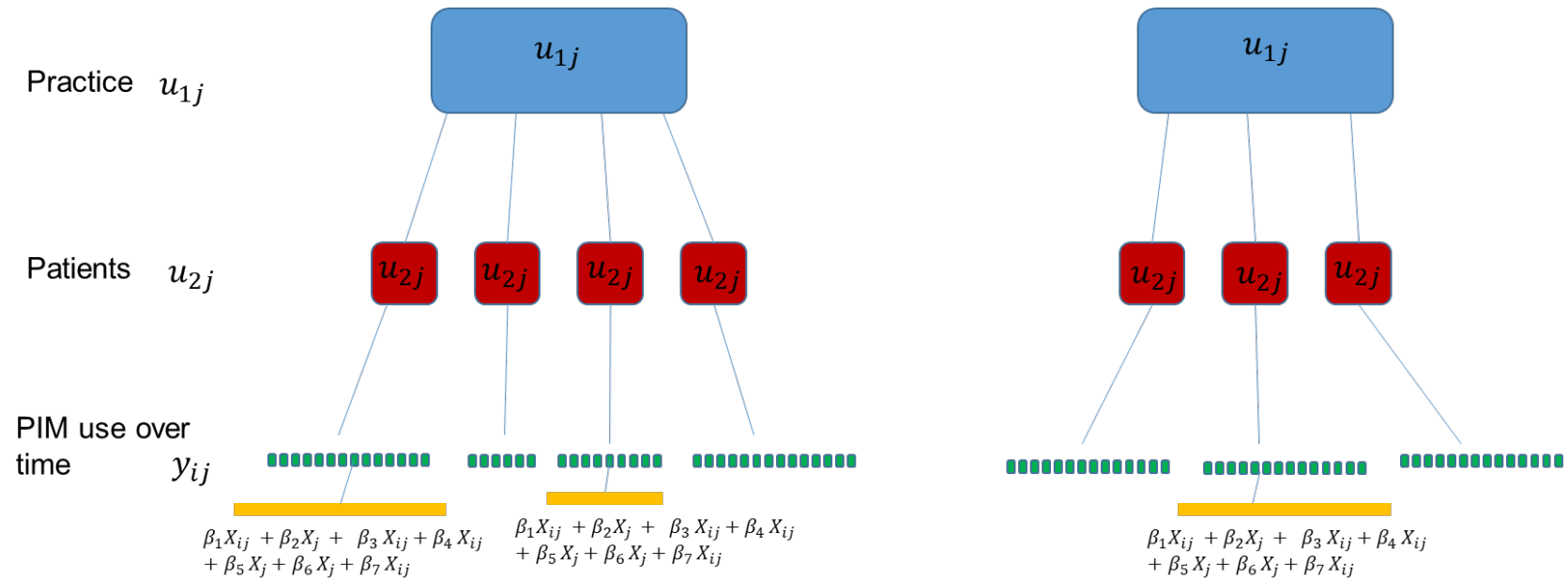
Figure 9 a visual example of the multilevel model used to estimate the factors associated with PIM and total medication use in people with dementia in primary care in England.

The model includes two random effects terms, the first is a random intercept (constant only) at the practice level u_{1j} and the second is the random intercept at the patient level u_{2j}. Patients are nested within practices with estimated starting or stopping PIM at each two month time period (from 1st January 2015 until April 30th 2017). Estimates are adjusted for a range of time varying covariates X_{ij}, time-constant covariates X_j. modelled for patient i at time j. . u is randomly distributed

(iii)   Multilevel logistic regression model

Multilevel logistic regression models were used to estimate patient and practice level factors associated with stopping and starting each PIM (antipsychotic, tricyclic antidepressants, definite anticholinergics and proton pump inhibitors) across the study period (1st January 2015 until 30th April 2017).

The models included fixed effects of age, sex, comorbidities, area-level deprivation, dementia annual review in the previous period and medication review in the previous period, care home residence and polypharmacy and random effects of GP practice and within-patient variation. Conditional on these covariates the observations are assumed to follow a binomial distribution. All analyses were stratified by care home residence.

The mathematical model for this multilevel logistic regression is provided below and explained in terms of the variables included in the model.

1) Mathematical model for multilevel logistic regression model

$$y_{ij} = \beta_0 + \beta_1 X_{ij} + \beta_2 X_j + \beta_3 X_{ij} + \beta_4 X_{ij} + \beta_5 X_j + \beta_6 X_j + \beta_7 X_{ij} + u_{1j} + u_{2j}$$

where, in the multilevel logistic regression model y is the log-odds of stopping or starting a PIM and in the linear mixed effects regression y is the estimated change in total medication use.

$$\beta_1 X_{ij} + \beta_2 X_j + \beta_3 X_{ij} + \beta_4 X_{ij} + \beta_5 X_j + \beta_6 X_j + \beta_7 X_{ij}$$

represents the predictors at each time period, with time varying covariates X_{ij}, time-constant covariates X_j

$$u_{1j} + u_{2j}$$

u_{1j} and u_{2j} are randomly distributed practice and patient random effect variance components.

Log-Odds stopping antipsychotic medication = β_0 + $\beta_{1\,age}$ + $\beta_{2female}$ + $\beta_{3previous\;review}$ + $\beta_{4CCIscore}$ + $\beta_{5\,IMD}$ + $\beta_{6\,care\;home\;residence}$ + $\beta_{7\,polypharmacy}$ + u_{1j} + u_{2j}

y_{ij} = estimated log odds of starting or odds of stopping PIM for patient *j* at time *i*

β_0 = constant

$\beta_{1\,age}$ = age in years, estimates are centred on the sample mean of 82 years

$\beta_{2female}$ = participant gender 1 = female, 0 = male

$\beta_{3previous\;review}$ = record of a medication review or dementia annual review in the previous two month time period 1= record of review, 0 = no record of a review

$\beta_{4CCIscore}$ = patient total Charlson Comorbid Index score.

$\beta_{5\,IMD(1-5)}$ = relative deprivation quintiles, ranging from 1 to 5, where 1 indicated practices within the most deprived areas and 5 as practices in the least deprived areas. As a categorical variable, there were five associated $\beta_{5\,IMD}$ included in the model.

$\beta_{6\,care\;home\;residence}$ = residential status, 1 = resident in a care home and 0 = community-based residence.

$\beta_{7\,polypharmacy}$ = total mediation use, excluding PIMs in each time period. 0 = 0-4, 1 = 5-9, 2 = 10+ prescribed medications

u_{1j}= randomly distributed practice level random effect variance component

u_{2j}= randomly distributed patient level random effect variance components, with patients nested within practices

(iv) Multilevel linear regression model

As above, multilevel linear regression models were used to estimate patient and practice level factors associated with a change in total medication use across the study period. The models included fixed effects of age, sex, comorbidities, area-level deprivation, dementia annual review in the previous period and medication review in the previous period, care home residence and random effects of GP practice and within-patient variation. Analyses were stratified by care home residence.

The multilevel linear model applied the same hierarchal structure described in Figure 9. The mathematical model is outlined below.

1) Mathematical model for linear model

$$y_{ij} = \beta_0 + \beta_1 X_{ij} + \beta_2 X_j + \beta_3 X_{ij} + \beta_4 X_{ij} + \beta_5 X_j + \beta_6 X_j + u_{1j} + u_{2j} + e_{ij}$$

where, in the linear regression y is the estimated change in total medication use.

$$\beta_1 X_{ij} + \beta_2 X_j + \beta_3 X_{ij} + \beta_4 X_{ij} + \beta_5 X_j + \beta_6 X_j$$

represents the predictors at each time period, with time varying covariates X_{ij} and time-constant covariates X_j

$$u_{1j} + u_{2j} + e_{ij}$$

practice and patient random effect variance components plus the error term e_{ij}

2) Example statistical linear mixed effects model

Estimated change in total medication use = $\beta_0 + \beta_{1\,age} + \beta_{2female} + \beta_{3previous\ review} + \beta_{4CCIscore} + \beta_{5\,IMD} + \beta_{6\,care\ home\ residence} + u_{1j} + u_{2j} + e_{ij}$

y_{ij} = estimated change in total number of prescribed medications from time *t-2* to time *t*.

β_0 = constant , $\beta_{1\,age}$ = age (years), $\beta_{2female}$ = binary variable for participant gender 1 = female, 0 = male

$\beta_{3previous\ review}$ = record of a medication review or dementia annual review in the previous two month time period 1= record of review, 0 = no record of a review

$\beta_{4CCIscore}$ = Charlson Comorbid Index score.

$\beta_{5\,IMD}$ = relative deprivation quintiles. As a categorical variable, there were five associated $\beta_{5\,IMD}$ included in the model.

$\beta_{6\,care\ home\ residence}$ = residential status, 1 = resident in a care home and 0 = community-based residence.

u_{1j}= practice level random effect estimated variance components

u_{2j}= patient level random effect estimated variance components, with patients nested within practices

All analyses were completed in Stata 14. An example of the Stata commands used for the multilevel logistic regression model is described below (Figure 10), followed by an explanation of the Stata output (Figure 11).

The Stata model included a multilevel regression command, followed by the outcome (starting PIM, stopping PIM, total medication use), predictors (age, gender, previous review, Charlson Comorbidity Score, Indices of Multiple Deprivation Quintile, care home residence, previous total medication, and practice and patient random effect.

Outcome (starting or stopping PIM)   Predictors

melogit antipsychotic_stopp2 age2_centred i.gender i.medreview_previous
cciscore i.e2015_imd_5 i.carehome_variable i.totalmeds || pracid : ||patid:

Mixed effects regression command   Practice and patient random effects
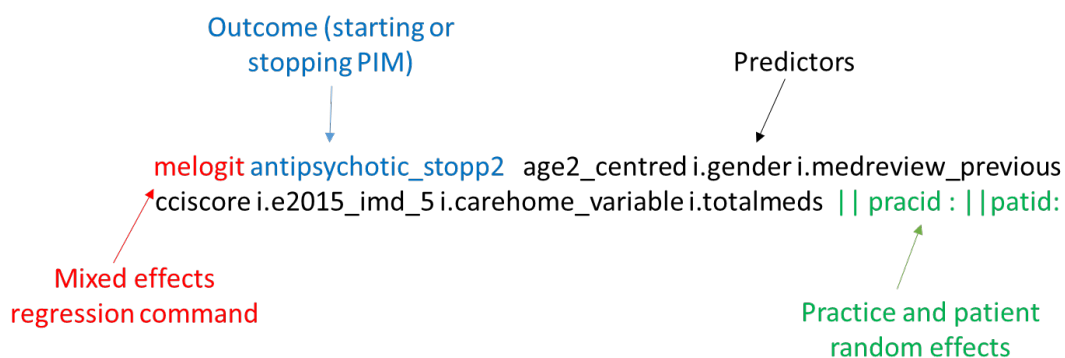
Figure 10 Stata command example for multilevel logistic regression estimated in CPRD cohort study

The model includes fixed and random effects equations, separated by | | the first is a random intercept (constant only) at the practice level, and the second is the random intercept at the patient level. The order is important as the command (*melogit)* assumes that patients are nested within practices. The order of nesting goes from right to left, from the biggest group, the patients at level one, to the smallest group, the practices at level two.

```
Mixed-effects logistic regression                    Number of obs    =    21,975

                              No. of      Observations per Group
            Group Variable    Groups   Minimum    Average    Maximum

                    pracid      268         1        82.0        413
                     patid    4,445         1         4.9         13


Integration method: mvaghermite                      Integration pts.  =         14

                                                     Wald chi2(12)     =      49.55
Log likelihood =  -7036.601                          Prob > chi2       =     0.0000

anticholinergic_stopp2_updated4  Odds Ratio   Std. Err.      z    P>|z|    [95% Conf. Interval]

                    age2_centred   1.010017   .0048087     2.09   0.036   1.000636   1.019486

                          gender
                          Female    .8153463   .0634513    -2.62   0.009   .7000039   .9496939
            1.medreview_previous    1.21199   .0800818     2.91   0.004   1.064771   1.379564
            1.demreview_previous    .582766   .0604005    -5.21   0.000   .4756329   .7140301
                        cciscore   1.000701   .0198511     0.04   0.972   .9625398   1.040374

                      e2015_imd_5
                               2   1.050039   .1475489     0.35   0.728   .7972539   1.382975
                               3    .9596984   .1341301    -0.29   0.769   .7297406   1.262121
                               4    .9027111    .130468    -0.71   0.479   .6800258   1.198318
                   least deprived   1.015555   .1418845     0.11   0.912   .7722912   1.335445

                carehome_variable
                       care home    .9870553   .0794818    -0.16   0.871   .8429449   1.155803

             totalmeds_noPIM_poly
                             5-9    .8426928   .0631075    -2.29   0.022   .7276535   .9759194
                             10+    .836216   .0754575    -1.98   0.047   .7006622   .9979947

                           _cons    .0988666    .013989   -16.35   0.000    .074922   .1304636

pracid
                      var(_cons)    .0913558   .0373994                    .0409514   .2037994

pracid>patid
                      var(_cons)   2.141267   .1507872                    1.865218   2.458171

LR test vs. logistic model: chi2(2) = 767.92              Prob > chi2 = 0.0000

Note: LR test is conservative and provided only for reference.
```

Figure 11 Example of Stata output for multilevel logistic regression model for the CPRD cohort study.

The model includes two random effects equations, the first is a random intercept (constant only) at the practice level, and the second is the random intercept at the patient level. The model includes patients nested within practices. The output shows the estimated variance components for the random effects equations.

(g) Sample size considerations

There were an estimated 33,000 patients with dementia based in English CPRD GOLD registered practices at the start of the study period (01/01/2015) (sample size estimated from October 2016 version of CPRD GOLD). There were around 14000 patients with a dementia annual review and 16000 with a medication review Read code (CPRD GOLD 2015).

The primary objective of this study was to estimate the effect of dementia annual review or medication review on changing prescription of PIM classes. Using data from a RCT of medication reviews in the general older population [268], I estimated the number of participants needed to demonstrate a change in potentially inappropriate medication (PIM) prevalence, considering a relatively rare PIM. This provided an illustrative example of the expected change in prescribing. The paired changes in PIM prescriptions before and after exposure (a medication review) are provided (Table 8).

For a relatively PIM, where baseline prevalence was around 5%, with a 2% reduction in PIM and 1% starting a PIM, to detect a difference following a exposure with 90% power (at significance level of $p = <0.05$) this would require a sample of 2600 patients (for rare PIM, such as tricyclic antidepressant medications). To reflect the multiple testing correction with a significance level of $p=<0.05$ at 90% power, this would require 4400 patients. More common PIM would require fewer participants, and this was comfortably within the 14000 patients with a dementia annual review code available in CPRD in the sample size considerations conducted prior to study initiation.

Table 8 Proportion of rare PIM prescriptions, such as tricyclic antidepressants post-medication review, based upon Milos et al. (2013)

		Post-review		Total
		PIM	**No PIM**	
Pre-review	**PIM**	0.03	0.02	0.05
	No PIM	0.01	0.94	0.95
	Total	0.04	0.96	**1**

n.b. Odds Ratio = 2, Proportion of discordant pairs = 0.03

4.09   Model checking

To check the model assumptions and fit, Pearson residuals were plotted against the predicted probabilities, any outliers were investigated and the model was run without outliers and compared using likelihood ratio test. As accuracy is increased with the number of integration points, the model quadrature was tested by modelling with varied integration points and comparing the model fit. Increasing integration increases the number of computations, and therefore a balance between speed and accuracy was considered [267]. To assess correlation between the independent variables, collinearity was assessed using Variance Inflation Factor (VIF) estimates. Dependence among responses within practice and patient clusters (random effects) were assessed using Intraclass Correlation Coefficients (ICC).

4.10   Summary

Primary care electronic health records are a rich and valuable source of existing data on large cohorts of people with dementia, including medical records and primary care practices, and including the implementation of pay-for-performance incentivising schemes. This chapter has presented the approach used to estimate the prevalence of and factors associated with potentially inappropriate prescribing in people with dementia. The following chapter presents the findings addressing Aim 1 and Aim 2 of this research.

V. Chapter 5: CPRD cohort study results

5.01 Introduction

A sample of over 22,000 people with dementia in primary care in England were included in this study, using electronic health records sampled from CPRD. This chapter reports the results of analyses using this cohort of people with dementia. First the prevalence of medication use and PIMs in people with dementia is reported. Second, the change in total number of prescribed medications and individual PIMs associated with a review is presented. Third, patient and practice factors associated with the potentially inappropriate prescribing in people with dementia is presented.

5.02 Description of the sample

There were 22,448 patients with dementia included at any point during the study period. Table 9 is an overview of patients who entered and left the study within each two-month time period. At the start of the study (1st January 2015 – 28th February 2017) there were 16,061 patients with dementia who met the inclusion criteria while 6,024 patients remained at the end of the study period (1st March 2017 - 30th April 2017). Across the study period, there were 10,911 incident cases of patients with a dementia diagnosis who were included in the study.

Around 50% of the sample were included in the study for less than one year and there were a number of possible reasons for leaving the study, as described in Table 9. There were 3,732 patients with dementia who died and 5,039 who left their GP practice. Reasons for leaving GP practice may include moving residence, transitioning into residential care and subsequently changing the GP practice they are registered with. There were 6,445 patients with dementia who left the study because the GP practice that they were registered with was no longer contributing data to CPRD after many practices changed the electronic health record system they used. Practices leaving CPRD are likely to be the major cause of the decrease in sample size over the course of the study as the study is designed so that the sample is representative of people with dementia at all of the time points.

Table 9 Description of the sample entering and leaving the study across the study period (1st January 2015 – 30th April 2018) and within each two-month time period in CPRD (n=22,448), including factors associated with the patient and factors associated with the GP practice.

	Entering study		Reasons for leaving the study (n)						
			Patient factors					Practice factors	
Time Period	Sample size (n)[1]	Incident dementia cases[6] (n)	Deaths	Cumulative Death[2]	Not included in the QOF data recording[4]	Patient leaves the practice	Cumulative n patient leaves practice[3]	Last CPRD data collection[5]	Cumulative Last CPRD data collection
2015									
1st Jan − 28th Feb	16,061	-	-	-	-	-	-	-	-
1st March − 30th April	15,519	606	469	469	103	614	614	529	529
1st May − 30th June	14,750	827	385	854	27	500	1,114	608	1,137
1st July − 31st Aug	13,128	1,115	374	1,228	31	466	1,580	1,161	2,298
1st Sept − 31st Oct	12,085	1,451	343	1,571	36	489	2,069	750	3,048
1st Nov − 31st Dec	10,869	1,280	303	1,874	58	386	2,455	706	3,754
2016									
1st Jan − 28th Feb	10,402	1,005	291	2,165	91	360	2,815	177	3,931
1st March − 30th April	9,882	452	338	2,503	95	463	3,278	165	4,096
1st May − 30th June	8,780	832	235	2,738	18	325	3,603	656	4,752
1st July − 31st Aug	7,876	1,059	185	2,923	25	284	3,887	532	5,284
1st Sept − 31st Oct	7,247	694	183	3,106	17	278	4,165	486	5,770
1st Nov − 31st Dec	6,754	731	226	3,332	32	322	4,487	176	5,946
2017									
1st Jan − 28th Feb	6,204	417	236	3,568	80	306	4,793	290	6,236
1st March − 30th April	6,024	442	164	3,732	51	246	5,039	119	6,445

n = individual patients at any point in each period,

[1] total sample n = 22,448, *n* eligible for analysis (last collection date of CPRD data from practice after period end, registered with the practice before period start, CPRD research quality data, patient leaves practice after the end of the time period and died after time period and not excluded from Dementia Annual Review), including incident inclusion into the study based on index date of dementia diagnosis (the point at which patients become eligible for the study)

[2] died after the end of the time period

[3] CPRD recorded 'transfer out', there is no longer a record of the patient at the practice due to the patient transferring out of the CPRD records before the end of time period. Transfers could occur due to the patient moving into a care home, for example, and the patient will be registered with a new practice and there will be no subsequent record in the CPRD.

[4] A practice can identify patients with dementia as exceptions to the Quality and Outcomes Framework indicators, meaning they are on the disease (dementia) register but are not included in the indicator denominator because they meet an exception criteria.

[5] The last point at which the practice uploaded data to CPRD, therefore after point the practice is no longer contributing data to CPRD and therefore will not be included in the subsequent analyses after this point.

[6] Incident cases of dementia. Also including patients with dementia joining a new practice.

5.03 Representativeness of CPRD of the population

(a) Age and sex

The age of the sample at the start of the study period was normally distributed for both men and women with dementia (see Figure 12). This is comparable to the population estimates of the age distribution of men and women living with dementia in the UK [1, 28] (see Figure 13 as example to compare the distributions).
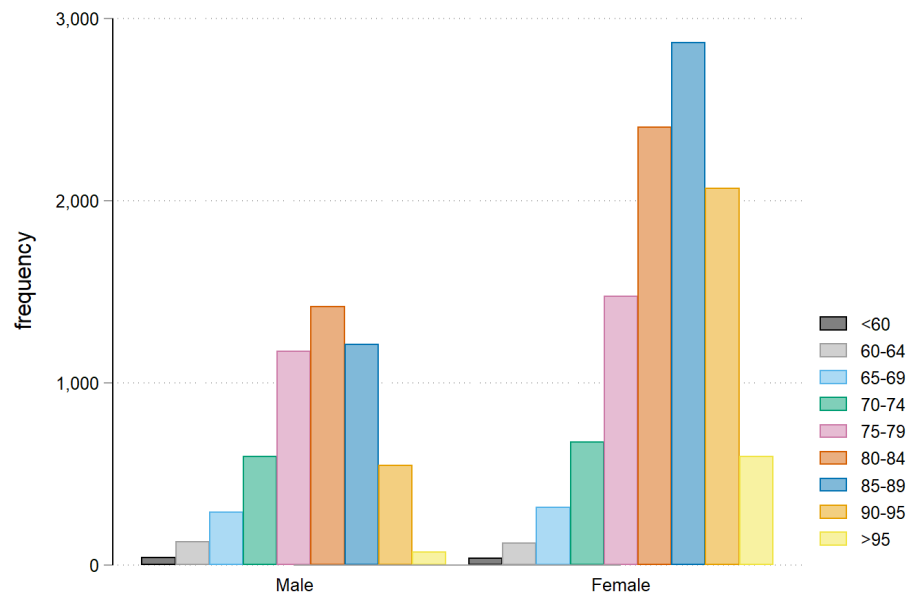
Figure 12 the distribution of patients with dementia across each age category, stratified by gender at the start of the study period (January 2015) n=16,061 in the CPRD.

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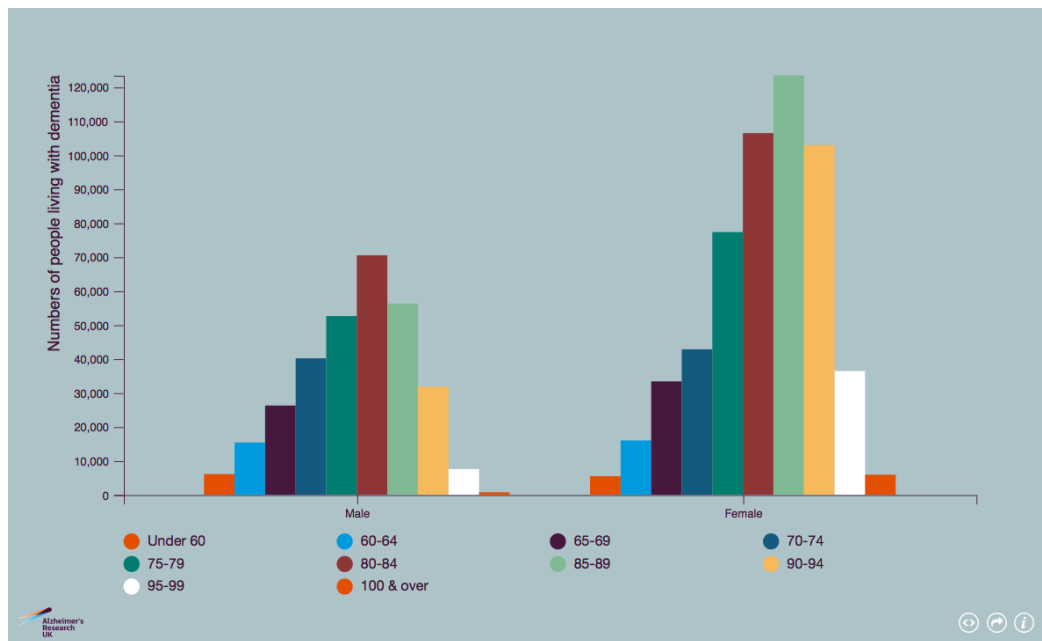
Figure 13 Frequency of people living with dementia in UK.

Source: https://www.dementiastatistics.org/statistics/prevalence-by-age-in-the-uk/

Prince et al.,(2014) Dementia UK: Update Second Edition report produced by King's College London and the London School of Economics for the Alzheimer's Society – Data from Expert Delphi Consensus of UK population-based studies of dementia prevalence, including CFAS estimates (Matthews et al., 2013)

(b) Deprivation

The area-level deprivation at practice level was broadly representative of the country as a whole (see Figure 14). The percentage of practices within each decile of IMD ranged from 8.0% to 11.7%. There were 8.0% of practices that were in the most deprived decile and 9.8% in the least deprived decile. Although the two most deprived deciles were under-represented there was no obvious trend that indicated bias.
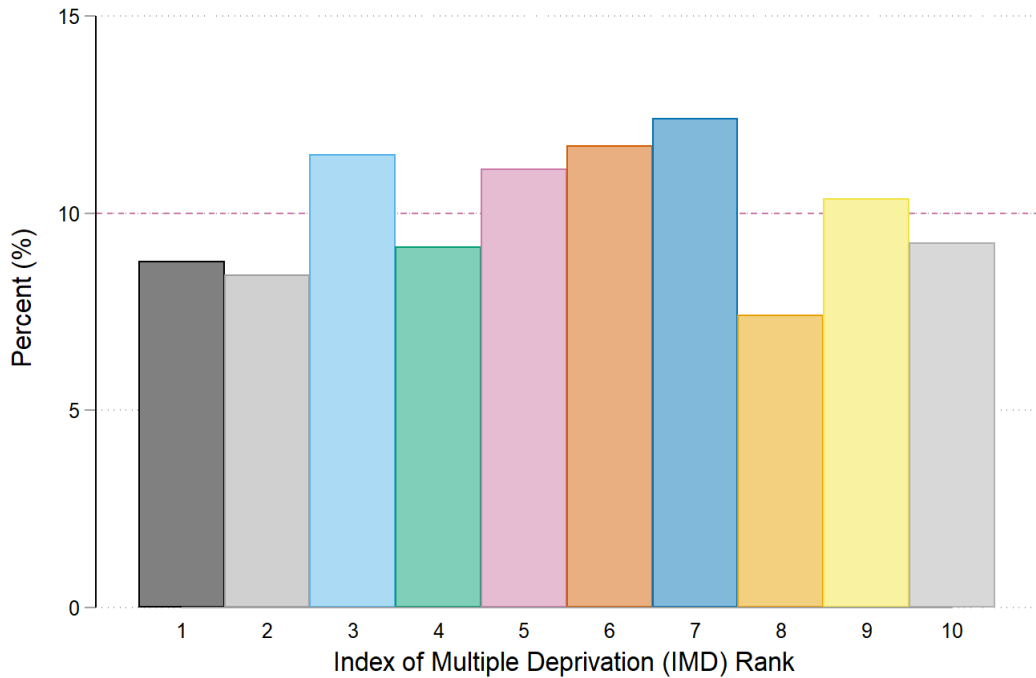
Figure 14 percentage of the GP practices (n=282) within each decile of IMD at the start of the study period (January 2015).

Data is grouped into deciles at the 2015 National English level and are ranked from 1 to 10. 1 indicates that the GP practice falls within the most deprived area and 10 indicates that the GP practice is within the least deprived 10% of areas.

5.04   Sample characteristics

There were a total of 22,448 patients with dementia included in the study (1st January 2015 – 30th April 2017), who were registered with 282 primary care practices (see Table 10).

At the start of the study period, 65.8% of the sample were female and the mean age was 82.9 years (SD 7.8). The mean CCI score was 2.8 (SD 1.8) and scores ranged from 1 to 15, with higher scores indicating worse comorbidity. There were 29.0% of patients with dementia who were living in a care home. People who were living in a care home were older (mean age 85.4 years SD 7.6) and there were more females living in a care home (75.8%) than in their own home (61.7%).

The mean age of the sample was similar at the end of the study period (April 2017) (82.2 years SD 7.7). There were less people with dementia from this sample living in a care home at the end of the study period (22.6%), likely because there were fewer people with dementia included in the study over time.

		Living situation	
Variable	Total sample	Care home	Own home
n	22,448	5,507	16,941
Practice *n*	282		
% Female	65.81	75.84	61.71
Average age *(mean, sd) (years)*	82.93 (7.77)	85.42 (7.59)	81.91 (7.61)
Comorbidity			
Mean CCI (SD)	2.76 (1.81)	2.74 (1.81)	2.77 (1.82)
CCI Range	1-15	1-12	1-15
IMD *(%)*			
Most deprived (1)	17.18	15.82	17.74
2	20.60	21.01	20.44
3	22.81	22.77	22.82
4	19.79	21.46	19.11
Least deprived (5)	19.61	18.95	19.88
Care Home *(%)*	29.01		

n = total number of individual patients / practices

Characteristics at the start of the study period, January 2015

CCI: Charlson Comorbidity Index Score: higher scores = worse comorbidity

IMD: Indices of Multiple Deprivation. Practice area-level deprivation quintiles.

(a) Comorbidity

All patients included in the study had a minimum Charlson Comorbidity Index score of one, due to the presence of a dementia diagnosis and one third of the sample had the minimum comorbidity score of one (32.7%) (See Figure 15). As expected, an increase in comorbidity score was also associated with an increase in total number of prescribed medications. Patients with a CCI score of one were prescribed a mean of 6.2 (SD 3.7) medications and patients with a CCI score of six were prescribed a mean 10.0 (SD 4.4) medications.
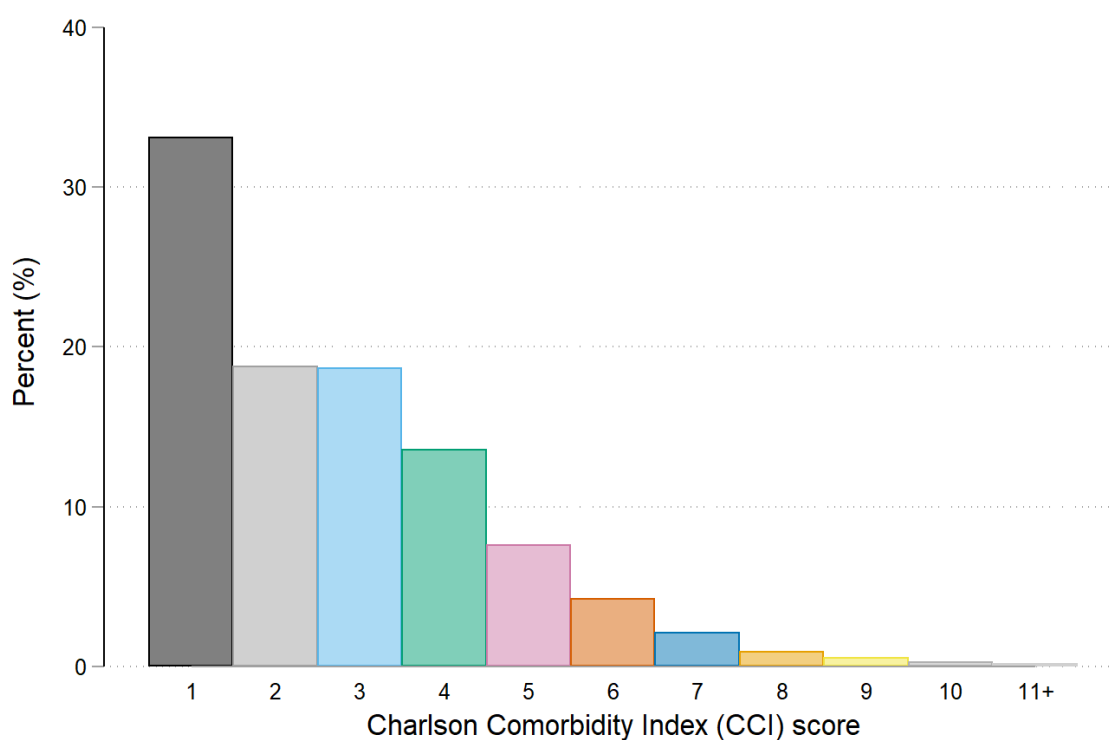
Figure 15 bar chart of the percentage of the Charlson Comorbidity Index (CCI) score across the sample of patients with dementia in January 2015 in primary care in England, greater scores indicate worse comorbidity.

5.05   Descriptive statistics: total medication use and PIMs

(a)   Total medication use of patients with dementia in primary care

The median number of medications prescribed was 7 (IQR 5-10) across the study period. The mean number of medications prescribed to a patient with dementia in England was 7.7 (SD 4.2) at the start of the study period (1st January 2015) and was 7.6 (SD 4.3) at the end of the study (30th April 2017). On average, patients with dementia who were living in a care home were taking more medications (mean=8.5 SD 4.3) than patients with dementia who were living in their own home (mean=7.3 SD 4.1). The total number of prescriptions was remarkably stable over the study period.

(b)   Prevalence of potentially inappropriate medication use

PIM were prevalent in this sample. At the start of the study 31.0% (95% CI 30.2-31.7) were prescribed long-term PPIs, 17.1% (95% CI 16.5-17.7) prescribed anticholinergics, 8.1% (95% CI 7.6-8.5), 9.4% (95% CI 9.0-9.9) prescribed antipsychotics. Across the duration of the study period, 32% were ever prescribed PPIs for more than 8 weeks (31.5% 95% CI 31.2-31.7), 17% were prescribed anticholinergic medications (16.7% 95% CI 16.5-16.9), 8% were prescribed antipsychotics (8.5% 95% CI 8.4-8.7) and 7% were prescribed tricyclic antidepressant medications (7.5% 95% CI 7.4-7.6) at any time during the study period. The prevalence of PIM use among patients with dementia remained stable across the study period. The biggest change was in antipsychotics that fell from 9.4% (95% CI 9.0-9.9) at the start of the study (January 2015), to 8.0% (95% CI 7.3-8.7) at the end of the study period (April 2018) (see Figure 16).
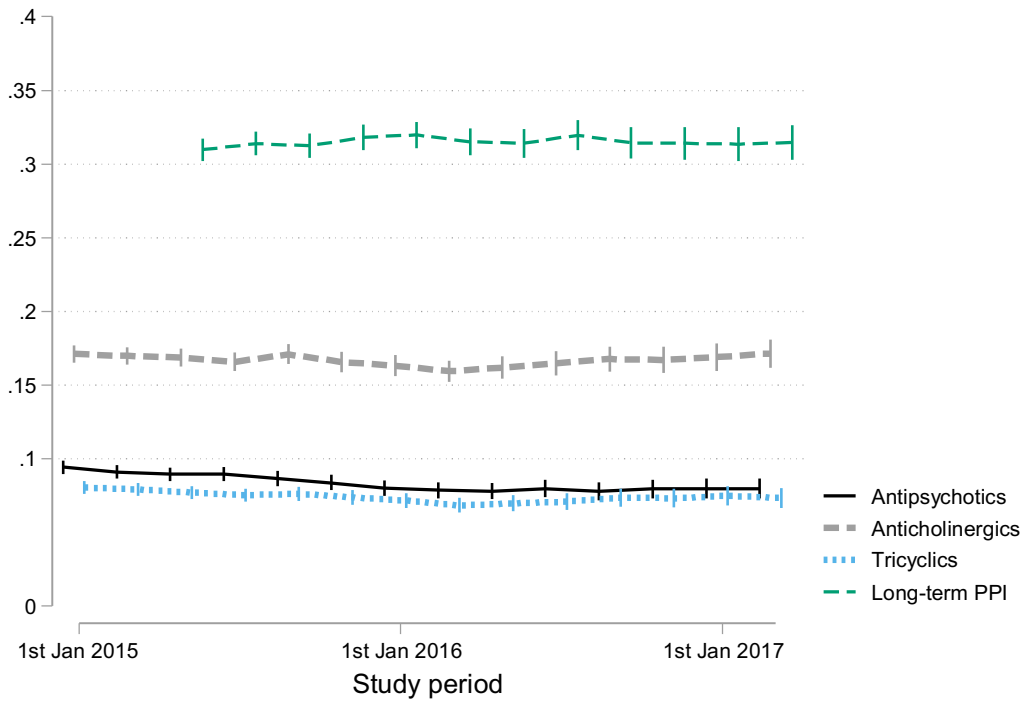
*Figure 16 prevalence and 95% CI of PIM prescription among patients with dementia in England from 1st January 2015 -
30th April 2017, split across two-month time periods (n=22,448)*

(c) Use of potentially inappropriate medication use according to living situation

Overall, prevalence of PIM prescriptions was greater among patients with dementia who were living in a care home, compared to those living in their own home (see Figure 17), although there were some similarities. As in the whole sample of patients, the prescription of long-term PPIs was most prevalent. Long-term PPI average period prevalence from 1st May 2015- 30th June 2015 was slightly greater for prescribing long-term PPIs in care homes (34.5% 95% CI 33.1-35.9) compared to patients living in their own home (30.0% 95% CI 29-30.4). At the start of the study period (1st January 2015- 28th February 2015), 19% (95% CI 18.0-20.3) of people with dementia in care homes were prescribed anticholinergics. Compared to 16.3% (95% CI 18.0-20.3) of patients living in their own home. Twice as many patients were prescribed antipsychotics who lived in a care home. In care homes, 15.0% (95% CI 14.0-16.0) of people with dementia were prescribed antipsychotics. Compared to 7.2% (95% CI 6.7-7.7) of people with dementia living in their own home. And finally, 10.1% (95% CI 9.3-11.0) of patients in a care home were prescribed tricyclic antidepressants, compared to 7% (95% CI 6.7-7.7) of patients in their own home. The average period prevalence estimates in each two month time period remained relatively stable over the study duration. In care homes, there was a small decrease in the prescription of tricyclic antidepressants from 10.1% to 8.7% (95% CI 7.4-10.4) in the last two month time period (March 1st 2017 - April 30th 2017).
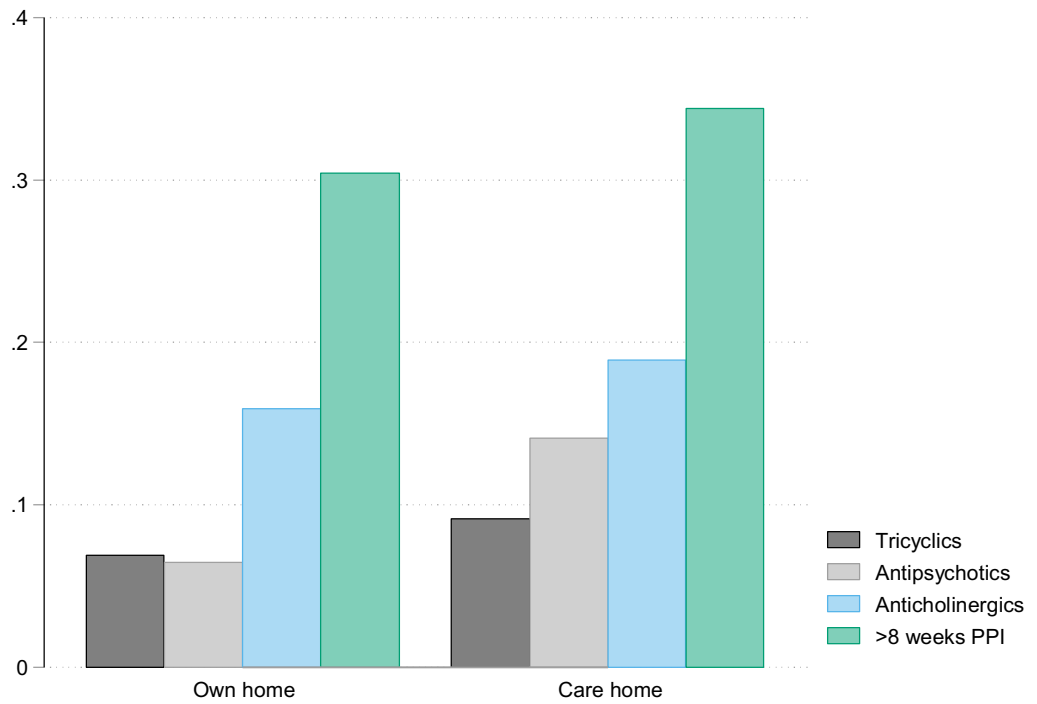
Figure 17 Prevalence of PIM prescriptions among patients with dementia in England, stratified by living situation.

Care home n= 5,507 and living in their own home n= 16,941. Average period prevalence estimates 1st May 2015 – 30th June 2015. Estimate from May time period due to long-term PPI prescriptions defined by prescription for more than 8 weeks and therefore no data is available before this point.

5.06 Dementia annual review and medication review

Less than half of all patients (40.9%) had a record of a dementia annual review. Within the first six months of entering the study, 40% of patients had had a medication review and 25% had had a dementia annual review (see Figure 18). Patient characteristics were similar across patients who did and did not have a record of a medication review. Patients were prescribed similar number of medications but only 57% had at least one medication review recorded across the study period (see Table 11). Patients who had a medication review were taking an average of 8 medications (SD 4.4), compared with an average of 7 medications (SD 7.6) among patients who did not have a review and there was relatively little difference in prevalence of PIM prescription.

Table 11 characteristics of patients with dementia in primary care in England, stratified by review.

Variable	Total sample	Medication review[1]		Dementia annual review[1]	
		No review	1 or more	No review	1 or more
n	22,448	9,649 (42.98%)	12,799 (57.02%)	13,260 (59.07%)	9,188 (40.93%)
% Female	64.65	64.64	64.94	64.63	64.95
Age at baseline *(mean, sd)*	82.9 (7.8)	82.93 (7.80)	82.87 (7.73)	82.93 (7.80)	82.94 (7.67)
Median CCI (IQR)	2 (1-4)	2 (1-4)	3 (1-4)	2 (1-4)	2 (1-4)
IMD *(%)*					
Most deprived	16.84	16.92	15.99	16.70	18.93
Least deprived	21.41	21.25	23.00	21.57	18.98
Care Home *(%)*	27.12	27.03	28.03	27.02	28.62
PIM *(% prescribed)[2]*					
Anticholinergics	16.72	16.59	18.06	16.68	17.26
Antipsychotics	8.51	8.43	9.36	8.46	9.28
Tricyclics	7.49	7.45	7.94	7.48	7.69
Long-term PPI	31.47	31.41	32.24	31.50	30.63
Mean number of medications *(sd)*	7.42 (4.11)	7.58 (4.18)	8.20 (4.36)	7.62 (4.20)	7.89 (4.27)

[1]Estimates are at any point across the study period but relate to the first record of a dementia annual review and medication review.

CCI: Charlson Comorbidity Index Score: higher scores = worse comorbidity

IMD: Indices of Multiple Deprivation. Practice area-level deprivation quintiles.

Total medications excludes topical, devices, dental, ocular and nasal products.

[2]PIM prescription ever across the study period
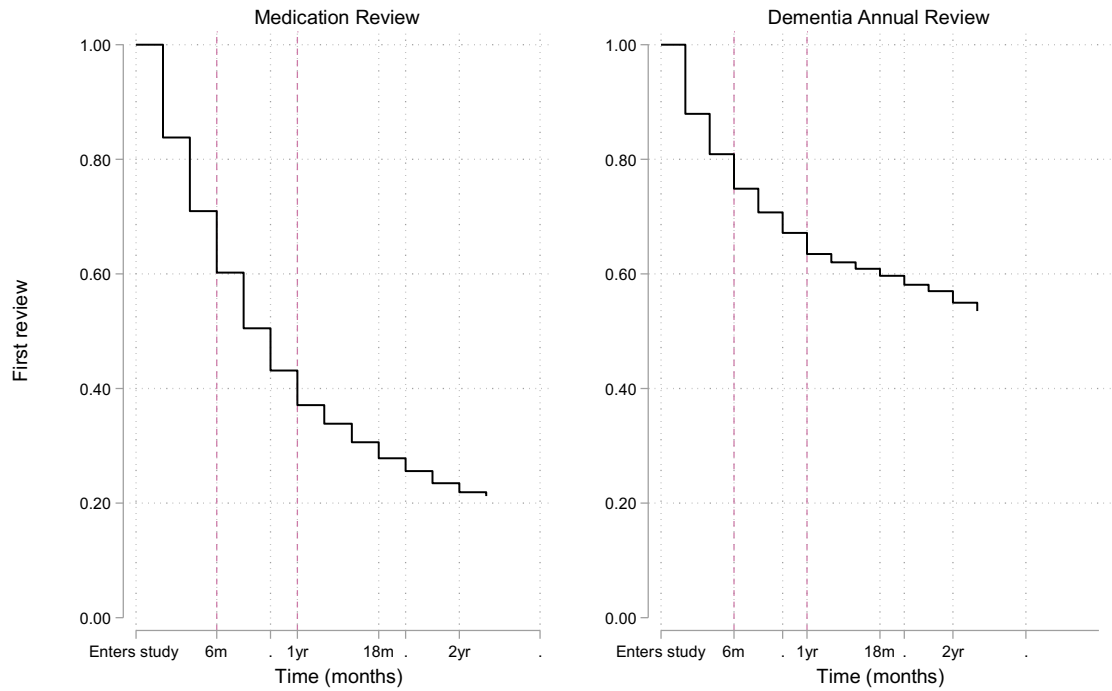
Figure 18 Kaplan-Meier survival curve of time until the first record of a review from point of entrance into the study among patients with dementia in primary care in England.

Analyses do not reflect whether patients have had a dementia review or medication review prior to entering the study. All patients were included from the point at which they entered the study, with the point of censoring identified as the first record of a review. Kaplan-Meier survival curves were estimated using Stata st commands.

(a) Estimating the change in total medication use after a review

A review was associated with a small but statistically significant increase in the number of medications prescribed in the paired t-test comparing mean number of medications before and after a review (see Table 12). The first record of a dementia review was associated with a 0.17 (95% CI 0.10-0.24) increase from a mean 7.37 (SD 4.05) medications to 7.53 (SD 4.03) mean medications. The first record of a medication review was also associated with a significant increase of 0.12 (95% CI 0.07-0.18) mean prescribed medications. Average number of medications increased from 7.54 (SD 4.04) to 7.67 (SD 4.10) after the first medication review. In comparison to patients with dementia who did not have a review, average number of medications also increased over the same time period. However, the average increase was around twice as high when there was a dementia review (0.17 95% CI 0.10-0.24) compared to no review (0.08 95% CI 0.07-0.09). Taken together, this suggests that people with dementia receive more medications over time.

When the effect of review is estimated using a linear mixed model (Chapter 4 Section 4.08), dementia annual review remained associated with a small but significant increase in average number of prescribed medications (Table 13). The unadjusted linear regression model suggested that a dementia review, across the study period, was associated with a significant increase in the mean number of prescribed medications (0.10 95% CI 0.04-0.16). This effect remained after adjusting for covariates and patient and practice effects (0.10 95% CI 0.04-0.16). In the adjusted linear model, medication review across the study period, was associated with a small decrease in the average number of prescribed medications (-0.04 95% CI -0.07-0.01). When analyses were stratified by residential status, medication review was associated with a small and significant decrease (-0.08 95% CI -0.16, -0.01) in average medication use in patients with dementia who were living in a care home.

Table 12 Paired t-test results of the difference in mean number of medications prescribed before and after the first record of a review. Comparison also provided for no record of a review in patients with dementia in comparative time periods.

Total Medications[1]	Before review (mean, SD)	After review (mean, SD)	Difference	95% CI
Dementia annual review (n=4,354)	7.37 (4.05)	7.54 (4.03)	+0.17	(0.10-0.24)
Medication review (n=7,474)	7.54 (4.04)	7.67 (4.10)	+0.12	(0.07-0.18)
No dementia annual review	7.44 (4.03)	7.52 (4.07)	+0.08	(0.07-0.09)
No medication review	7.45 (4.03)	7.53 (4.07)	+0.08	(0.06-0.09)

*p=<0.05 CI = confidence interval
[1] paired t-test estimating the change in mean number of total medications from the two month time period before the review, compared to the time period after the review.

Review is at the first record of a medication review or dementia annual review during the study period. Previous estimates of average number of prescribed medications vary as they are estimating in different time periods, here comparing the average prescriptions in the two month time period before the review to the prescribed medications in the two month time period after the review.

Comparative estimates compare total number of medications before (t-2) and after (t) the study time periods when there is not a record of a review (t-1).

Mean difference in total medications after any medication review, mean =0.09 (SD 2.25), difference without a medication review mean =0.06 (SD 2.45)
Mean difference in total medications after dementia review mean = 0.17 (SD 2.35), difference without a review, mean = 0.08 (SD 2.28)

Table 13 Mixed effects linear regression model estimating the relationship between reviews and change in total number of prescribed medications in people with a dementia diagnosis in England. Clinical Practice Research Datalink (n=17,437)

VARIABLES	Unadjusted model Change in mean number prescriptions	Adjusted mixed effects model Change in mean number prescriptions (n=17,437)	Home Residence stratification	
			Care Home (n=5,241)	Not in Care Home (n=12,849)
Age		-0.002 (-0.004 - 0.000)	-0.002 (-0.006 - 0.001)	-0.001 (-0.003 - 0.001)
Female		-0.032* (-0.062 - -0.001)	-0.095* (-0.162 - -0.027)	-0.012 (-0.046 - 0.022)
Previous Review				
Medication review	-0.038 (-0.077 - 0.001)	-0.038 (-0.077 - 0.002)	-0.081* (-0.155 - -0.007)	-0.018 (-0.065 - 0.028)
Dementia annual review	0.102* (0.043 - 0.162)	0.103* (0.044 - 0.162)	0.121* (0.007 - 0.235)	0.094* (0.025 - 0.164)
CCI		-0.004 (-0.012 - 0.004)	-0.008 (-0.024 - 0.008)	-0.003 (-0.012 - 0.006)
IMD				
3-4		-0.013 (-0.066 - 0.040)	-0.047 (-0.158 - 0.064)	0.002 (-0.052 - 0.055)
5-6		-0.016 (-0.068 - 0.037)	-0.069 (-0.178 - 0.040)	0.009 (-0.044 - 0.061)
7-8		-0.007 (-0.061 - 0.047)	-0.039 (-0.152 - 0.075)	0.007 (-0.048 - 0.061)
9-10, least deprived		0.002 (-0.050 - 0.055)	-0.048 (-0.156 - 0.061)	0.025 (-0.028 - 0.078)
Care Home		-0.003 (-0.036 - 0.029)		
Constant coefficient	0.083* (0.067 - 0.098)	0.121* (0.071 - 0.171)	0.225* (0.118 - 0.332)	0.089* (0.037 - 0.142)
Random Effects[1] Practice		0.003 (0.001-0.006)	0.011 (0.004-0.025)	-
Patients nested within practice[2]		-	-	-
		-	-	-
Residual variance	5.202 (5.156-5.248)	5.199 (5.153-5.244)	5.813 (5.718-5.901)	4.954 (4.903-5.00^)

Estimated coefficients *p<0.05

CCI: Charlson Comorbidity Index Score: higher scores = worse comorbidity

IMD: Indices of Multiple Deprivation

[1]estimated variance components of the random effects equations. Variance components are estimates of the amount of variance in the dependant variable that is attributable to the random effects. There are two random effects equations, the first is a random intercept (constant only) at the practice level and the second is the random intercept at the patient level, with patients nested within practices.

n= total number of individual patients with dementia included in analyses, smaller n than total sample as there is no available data for previous review in the first two month time period when a participant enters the study and some participants are included for one 2 month time period and there is no available data on the change in their total medication use.

Number of patients transition to care home n=653

[2] Within patient and within practice correlations were both less than 0.01. Likelihood ratio tests comparing the model without the random effect estimations did indicate a statistically significant difference between the models (X^2=8.33, df(2) p=>0.05)

Collinearity between variables mean VIF = 1.07

(b) Estimating the association of dementia annual review and medication review with PIMs

A summary of the results from McNemar tests at the first record of a review and the association of a review with starting and stopping PIM is provided in Table 14. The tables of results from the models for each PIM and McNemar tables are in Appendix Section 10.07-10.09.

(i) Anticholinergics

More patients with dementia started anticholinergic medications after the first record of medication review (started n=195, stopped n=188) and first dementia review (started n=112, stopped n=106). However, neither of the differences at the first record of a review were statistically significant (Table 14).

Across the study period, the rate of starting anticholinergics was slightly greater when patients had a medication review (n=433, 2.6%) compared to when there was no review (n=1,844, 2.1%) (Table 14). However, the rate of starting was greater without a dementia annual review (n=2,118, 2.2%), compared to when there was a review (n=159, 1.8%). The adjusted multilevel logistic regression model estimated that a medication review was associated with an increase in the odds of starting anticholinergic medication (OR 1.20 95% CI 1.06-1.36). In addition, a dementia annual review was associated with significantly less starting of anticholinergic medications (OR 0.77 95% CI 0.64-0.92), compared to when there was no record of a review.

More patients stopped anticholinergics after a medication review than a dementia annual review. The rate of stopping anticholinergics after a review across the study period was greater in patients with a medication review (n=473, 11.8%, compared to no review n=1,871 10.4%). Fewer patients stopped an anticholinergic after a dementia review (n=146 8.0%) compared to when there was no record of a review (n=2,198 10.9%). The multilevel logistic regression estimated that, in patients who were prescribed anticholinergic medications, a medication review was associated with stopping anticholinergic medications (OR 1.21 95% CI 1.06 - 1.38). A dementia annual review was associated with a significant decrease in the odds of stopping anticholinergic medication, compared to when there was no record of a review (OR 0.58 95% CI 0.48-0.71) (Table 14).

Table 14 Estimating the association of dementia annual review and medication review with PIMs results from McNemar test at the first record of a review and the adjusted mixed effects logistic regression models

	McNemar test at first record of a review					Starting			Stopping		
	Patients stopping PIM (*n*)	Patients continuing PIM (*n*)	Patients starting PIM (*n*)	Patients not taking PIM (*n*)	p-value	After any review n (%)	Unadjusted Model	Adjusted model	After any review n (%)	Unadjusted Model	Adjusted Model
Medication review											
Anticholinergics	**188**	1141	**195**	5959	0.759	433 (2.6)	1.27* (1.14 - 1.41)	1.20* (1.06 - 1.36)	473 (11.8)	1.19* (1.06 - 1.32)	1.21* (1.06 - 1.38)
Antipsychotics	**52**	320	**64**	3927	>0.001*	285 (1.6)	1.27* (1.11 - 1.45)	1.19* (1.03 - 1.39)	224 (10.8)	1.08 (0.93 - 1.27)	1.07 (0.89 - 1.29)
Tricyclics	**70**	512	**79**	6822	0.471	173 (0.9)	1.39* (1.17 - 1.64)	1.36* (1.12 - 1.67)	185 (10.6)	1.20* (1.01 - 1.42)	1.25* (1.01 - 1.54)
Long-term PPI	**85**	1324	**104**	2900	0.167	259 (1.8)	1.01 (0.89 - 1.16)	0.95 (0.81 - 1.11)	261 (2.6)	1.33* (1.16 - 1.53)	1.39* (1.18 - 1.65)
Dementia annual review											
Anticholinergics	**106**	622	**112**	3523	0.685	159 (1.8)	0.82* (0.70 - 0.97)	0.77* (0.64 - 0.92)	146 (8.0)	0.69*(0.58 - 0.82)	0.58* (0.48 - 0.71)
Antipsychotics	**80**	536	**128**	6739	0.265	98 (1.1)	0.77* (0.63 - 0.95)	0.68* (0.54 - 0.86)	73 (7.5)	0.67* (0.52 - 0.86)	0.55* (0.41 - 0.73)
Tricyclics	**44**	292	**53**	3974	0.361	64 (0.7)	0.89 (0.69 - 1.16)	0.90 (0.67 - 1.21)	58 (7.2)	0.70* (0.53 - 0.93)	0.62* (0.45 - 0.86)
Long-term PPI	**38**	662	**62**	1397	>0.05*	93 (1.3)	0.67* (0.54 - 0.83)	0.65* (0.51 - 0.83)	68 (1.0)	0.42* (0.33 - 0.54)	0.39* (0.30 - 0.52)

*p=<0.05 (OR, 95% CI)

n = number of individual patients at first record of a review

Starting and stopping without a review
Starting anticholinergics without medication review n=1,844 (2.1%), without dementia review n=2,118 (2.2%), stopping anticholinergics without medication review n=1,871 (10.4%), without dementia review n=2,198 (10.9%)
Number of patients starting without medication review n=1,211 (1.26%), without dementia review n=1,398 (1.33%), stopping antipsychotics without medication review n=914 (10.3%), stopping without dementia review 1,065 (10.7%)
Starting tricyclic without review n=664 (0.7%), starting without dementia review n=773 (0.7%), stopping without medication review n=740 (9.2%), without review n=867 (9.7%)
Patients not prescribed PPI or prescribed for less than 8 weeks after a review n=1,403 (1.83%), n=1571 (1.87%) not prescribed PPI for more than 8 weeks. Stopping long-term PPI without a medication review n=1,013 (2.1%), without a dementia review n=1,206 (2.3%)
Disconcordant pairs used to estimate McNemar Chi-squared test highlighted in bold. Change in total number of cases of each PIM from *t-1*, compared with *t+1*, when there is a record of a review at *t*. Review is at the first record of a medication review or dementia annual review during the study period.

Logistic regression models adjusted for age, gender, medication review, dementia annual review, comorbidity, living situation and patient and practice random effects.

(ii) Antipsychotics

A medication review was associated with increased prescribing of antipsychotic medications in patients with dementia in primary care (Table 14). After the first record of a medication review, significantly more patients with dementia were prescribed antipsychotic medication (n=128) than having an antipsychotic medication stopped (n=80) (p=>0.001). Proportionally, there were slightly more patients who started an antipsychotic after a medication review (n=285, 1.6%), compared to when there was no record of a review (n=1,211, 1.3%) across the study period. The adjusted multilevel logistic regression model estimated that a record of a medication review, across the study period was associated with an estimated 19% increase in the odds of starting antipsychotic medication (OR 1.19 95% CI 1.03-1.39) (Table 14). There was no evidence to suggest that medication review was associated with stopping antipsychotic medications (OR 1.07 95% CI 0.89-1.29).

A dementia annual review was associated with decreased odds of stopping as well as decreased odds of starting antipsychotic medication. At the first record of a dementia review, there was little suggestion that a review was associated with increased stopping or starting of antipsychotic medications. However, across the study period, a dementia review was associated with proportionally less starting (n=98, 1.01%) compared to no review (n=1,398, 1.3%), in patients without antipsychotic prescription. Furthermore, a dementia review was associated with proportionally less stopping (n=73, 7.5%) compared to no review (n=1,065, 10.7%), in patients prescribed antipsychotic medications. The adjusted multilevel logistic regression model estimated that a dementia annual review was associated with 32% decreased odds of starting antipsychotic medication (OR 0.68 95% CI 0.54-0.86). Dementia review was also associated with 45% decreased odds of stopping antipsychotic medication (OR 0.55 95% CI 0.41-0.73) (Table 14).

(iii) Tricyclic antidepressants

The McNemar test suggested that more patients started a tricyclic antidepressant after a review than stopped, although the difference between stopping and starting was not statistically significant (Table 14).

Overall, a medication review was associated with both starting tricyclic antidepressants in patients who were not prescribed them and stopping in patients with a tricyclic antidepressant prescription. Across the study period and after a medication review, proportionally more patients started a tricyclic antidepressant (n=173, 0.9%) compared to when there was no review (n=664, 0.7%). The adjusted multilevel logistic regression model estimated that a medication review was associated with 36% increase in the odds of starting tricyclic antidepressant medication, compared to no review (OR 1.36 95% CI1.12-1.67) (Table 14).

Proportionally more patients stopped tricyclic antidepressant medication after a medication review (n=185, 10.6%), compared to no medication review (n=740, 9.2%). The adjusted model estimated that a medication review was associated with 20% increase in the odds of stopping tricyclic antidepressant medication (OR 1.20 95% CI 1.01-1.42).

A dementia review was associated with a significant decrease in the odds of stopping tricyclic antidepressant medication (OR 0.70 95% 0.53-0.93). Proportionally, fewer patients stopped tricyclics after a dementia review (n=58, 7.2%) compared to no review (n=867, 9.7%). There was no evidence to suggest that a dementia review was associated with starting tricyclic antidepressant medications (OR 0.90 95% CI 0.67-1.21) (Table 14).

The McNemar test suggested that at the first record of a dementia annual review, more patients were prescribed a PPI for 8 weeks or more (n=62), compared to fewer patients who had a long-term PPI stopped (n=38) (p=>0.05). However, across the study period, proportionally fewer patients were prescribed a long-term PPI after a dementia review (n=91, 1.2%), compared to no review (n=1,571, 1.9%) (Table 14). Furthermore, the adjusted multilevel logistic regression model estimated that a dementia annual review was associated with significantly decreased odds of being prescribed a PPI for more than 8 weeks (OR 0.67 95% CI 0.54-0.83). However, in patients who were prescribed long-term PPI, a dementia annual review was estimated to be associated with decreased odds of stopping (OR 0.39 95% CI 0.30-0.52). A medication review was associated with significantly increased odds of stopping a long-term PPI (OR 1.39 95% CI 1.18-1.65). There was no evidence to suggest that a medication review was associated with being newly prescribed a PPI for more than 8 weeks (Table 14).

(c) Estimating the association of living situation with stopping and starting PIMs

Living in a care home was associated with greater PIM use in general. People living in care homes were more likely to start antipsychotic (OR 1.38 95% CI 1.33-1.87) and anticholinergic (OR 1.15 95% CI 1.00-1.33) medications, but were less likely to start PPI (OR 0.73 95% CI 0.60-0.90). They were also less likely to stop antipsychotics, once initiated (OR 0.68 95% CI 0.55-0.83) (Table 15).

For patients who were living in a care home, a medication review was associated with more stopping of antipsychotic medication (OR 1.45 95% CI 1.09-1.94) and tricyclic antidepressants (OR 1.62 95% CI 1.12-2.36). Whereas there was no evidence of an association of medication review among patients living in their own home with antipsychotic prescribing (OR 0.86 95% CI 0.67-1.10) or stopping tricyclic antidepressants (OR 1.10 95% CI 0.86-1.42).

Medication review in patients living in their own home was associated with significantly increased odds of starting anticholinergics, antipsychotics and tricyclic antidepressants (see Table 15). Whereas, stratified analyses did not indicate any association of a medication review among patients in a care home with starting PIMs. Conversely, a dementia annual review was associated with significantly decreased odds of starting all PIMs in patients who were living in their own homes. There was no evidence of an association of dementia annual review with starting PIMs among patients who were living in a care home (Table 15).

Table 15 estimating the association of living situation with starting and stopping PIM amongst patients with dementia in England.

	Adjusted regression model	Stratified model Care home		Stratified model Own home	
	Care Home	Medication review	Dementia annual review	Medication review	Dementia annual review
Stopping PIM					
Anticholinergics	0.99 (0.84 - 1.16)	1.64* (1.31 - 2.07)	0.66* (0.47 - 0.94)	1.04 (0.88 - 1.22)	0.55* (0.42 - 0.70)
Antipsychotics	0.68* (0.55 - 0.83)	1.45* (1.09 - 1.94)	0.70 (0.46 - 1.08)	0.86 (0.67 - 1.10)	0.45* (0.30 - 0.66)
Tricyclics	0.79 (0.61 - 1.02)	1.62* (1.12 - 2.36)	0.81 (0.46 - 1.43)	1.10 (0.86 - 1.42)	0.56* (0.38 - 0.83)
Long-term PPI	1.03 (0.83 - 1.29)	1.54* (1.12 - 2.13)	0.31* (0.18 - 0.55)	1.31* (1.07 - 1.60)	0.42* (0.31 - 0.58)
Starting PIM					
Anticholinergics	1.15* (1.00 - 1.33)	0.99 (0.80 - 1.24)	0.75 (0.54 - 1.04)	1.31* (1.13 - 1.51)	0.77* (0.62 - 0.96)
Antipsychotics	1.38* (1.33 - 1.87)	1.01 (0.78 - 1.31)	0.76 (0.52 - 1.12)	1.30* (1.08 - 1.56)	0.62* (0.47 - 0.83)
Tricyclics	0.80 (0.61 - 1.04)	1.18 (0.75 - 1.84)	1.33 (0.76 - 2.31)	1.44* (1.15 - 1.81)	0.78 (0.54 - 1.11)
Long-term PPI	0.73* (0.60 - 0.90)	0.91 (0.64 - 1.27)	0.42* (0.24 - 0.75)	0.95 (0.79 - 1.14)	0.72* (0.55 - 0.95)

$p=<0.05$ OR (95% CI)

Sample sizes mixed effects regression models:

Stopping amongst patients prescribed PIM: Anticholinergic n= 2,344, antipsychotic n=1,138 , tricyclic n=925, PPI n= 1,274

Starting amongst patients not prescribed PIM: anticholinergic n=2,277, antipsychotic n= 1,496 tricyclic n=837, PPI n=1,662

Logistic regression models adjusted for age, gender, medication review, dementia annual review, comorbidity, living situation and patient and practice random effects.

(d) Other patient and practice level factors associated with stopping and starting PIM

There were a number of patient and practice level factors associated with stopping and starting PIM. These results are summarised and the findings are presented in tables in the Appendix Section 10.08-10.09

(i) Age

Older age was associated with a decrease in the odds of being prescribed antipsychotics, anticholinergic medication and a long-term PPI. Older age was associated with decreased odds of having a long-term PPI prescription and antipsychotic medication stopped. Older age slightly increased the odds of stopping anticholinergic medication (OR 1.01 95% CI 1.00-1.02) and there was no association of age with prescribing tricyclic antidepressants.

(ii) Gender

Females were 22% less likely to be prescribed a long-term PPI and were 38% more likely to start tricyclic antidepressant medication (OR 1.38 95% CI 1.08-1.78). In patients prescribed long-term PPI, females were 19% less likely to stop than males (OR 0.81 95% CI 0.67-1.00). Furthermore, females were 32% less likely to stop tricyclics (OR 0.68 95% CI 0.52-0.87) and 18% less likely to stop anticholinergic (OR 0.82 95% CI 0.70-0.95). There was no association of gender with stopping or starting antipsychotics and no effect on starting anticholinergics.

(iii) Comorbidity

A one point increase in Charlson Comorbidity Index score was associated with a 10% increase in the odds of starting a PPI that was prescribed for 8 weeks or more (OR 1.10 95% CI 1.04-1.15) and a 7% increase in the odds of starting a tricyclic antidepressant. Greater comorbidity was also associated with increased odds of stopping long-term PPIs and antipsychotic medications (OR 1.09 95% CI 1.04-1.15). Finally, greater comorbidity was associated with reduced odds of being prescribed antipsychotic medication (OR 0.95 95% CI 0.91-1.00).

(iv) Polypharmacy

Amongst patients with dementia, being prescribed 5 or more medications (excluding PIMs) was consistently associated with statistically significant decrease in the odds of stopping PIM and significantly increased odds of starting a prescription of PIM, with the exception of tricyclic antidepressants. In addition, the odds of being newly prescribed a PIM were greatest in the patients who were already taking 10 or more medications, compared to 0-4 medications.

5.07   Summary

This chapter presented the findings of my CPRD cohort study analysis of primary care data from patients with dementia in England. These findings demonstrated that patients with dementia were prescribed on average, 8 medications. The most prevalent PIM class examined were long-term PPIs (32%), 17% of patients were prescribed anticholinergics, 8% prescribed antipsychotics and 7% prescribed tricyclic antidepressants, with little change in prevalence across the duration of the study period (1st January 2015 until 30th April 2017). PIM prevalence and average number of medications prescribed was consistently higher amongst patients with dementia who were living in a care home, compared to their own home. The prevalence of tricyclic antidepressants and antipsychotics was more than twice as high in patients with dementia living in a care home. Generally, PIMs were stopped less and started more in care homes. However, when a patient had a medication review in a care home the likelihood of stopping a PIM was much greater than among patients living in their own home who had a medication review.

A dementia annual review appeared to be associated with optimising PIMs, particularly among patients with dementia who were living in their own home. A dementia review was associated with reduced initiation of new PIM prescriptions. A dementia review was also associated with reduced likelihood of stopping PIMs. This may indicate an appropriate prescription of a PIM that has been monitored in the review and is considered appropriate for the patient.

Both a dementia annual review and medication review were associated with an overall increase in the average number of medications, compared to similar time periods where no review took place. Factors associated with PIM prescriptions included being older, female, and being prescribed 5 or more medicines. These findings are discussed in Chapter 8. The following chapter reports the methodological approach employed in my analysis of how these PIM affect survival in a cohort study (CFAS II) subsample of older adults with cognitive impairment.

VI.   Chapter 6: Methods: CFAS II subsample cohort study

6.01   Introduction

The CPRD cohort study indicated the extent of potentially inappropriate prescribing in people with dementia in primary care and suggested the potential impact of medication reviews on optimising medicines in this population. This chapter reports the methods used to address Aim 1) describing the trends in prevalence of potentially inappropriate prescribing and Aim 3) to understand the impact of PIMs and polypharmacy on health and the potential impact of frailty in this relationship. This chapter outlines the study design and setting of the Cognitive Function and Ageing Study used for these analyses. The sample included in analyses, exposures, outcomes and covariates and the methods I used to operationalise frailty criteria in CFAS II are described. The statistical approaches used to estimate prevalence and survival analyses are presented. The findings from this CFAS II subsample cohort study have been peer-reviewed and published [269].

6.02   Study design

A prospective cohort study of people with cognitive impairment in England, using data collected as part of the second Cognitive Function and Ageing Study (CFAS II) (www.cfas.ac.uk). Cross sectional estimates of the prevalence of PIM prescription estimated using the CFAS II baseline interview (collected 2008-2011). Vital status of the CFAS II participants who met the eligibility criteria at baseline interview was then obtained until the point of censoring on 31st October 2016 or until death.

6.03   Setting

The Cognitive Function and Ageing Studies is a longitudinal, multi-centre, population-based cohort study of ageing in the United Kingdom. The first MRC CFAS began in 1989 (CFAS I) in six centres across England and Wales, including Cambridgeshire, Gwynedd, Newcastle, Nottingham, Oxford and Liverpool [270]. The second study (CFAS II) conducted baseline interviews between 2008 and 2011, replicating CFAS I interviews, with new cohorts of participants recruited from three of the original centres in England (Cambridgeshire, Nottingham and Newcastle) [2]. All surviving participants of CFAS II were re-interviewed at two years follow-up. (Figure 19)
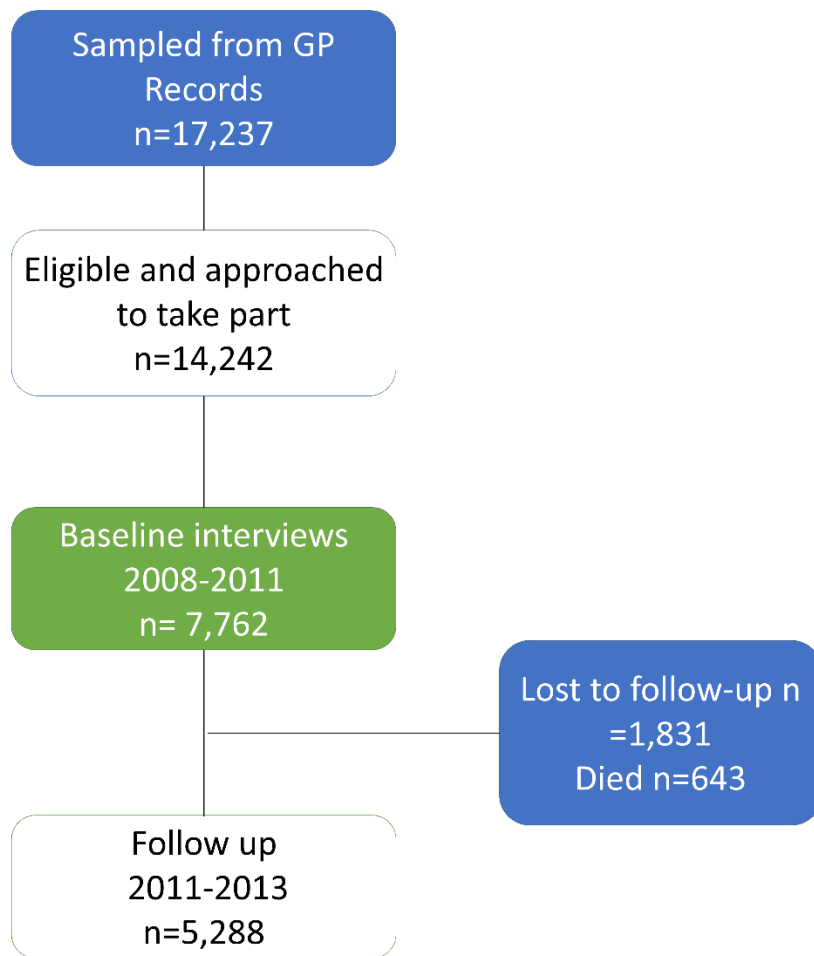
Figure 19 Participant flow diagram of the CFAS II baseline and follow-up interviews. Non-participation from people who were eligible and approached (n=14,242) to take part in CFAS II was 45% [271]

Participants were randomly sampled from primary care patient lists within the geographically defined regions in England. Using primary care registration provided a robust population sampling frame, which included individuals who were living in the community and those living in residential homes, and representative of both urban and rural populations. All participants were aged 65 years and over and the sample was stratified by age group (under 75, 75 years and over) to allow sufficient numbers in the older age groups and oversampling allowed for losses due to death, ineligibility, GP, participant or care provider refusals.

An introductory letter was sent by the GP to randomly selected eligible participants, followed by a visit for initial screening and baseline interview with a trained interviewer in the participants' usual place of residence. The interview comprised an extensive collection of demographic, health and lifestyle questions. Including current and previous health conditions, current prescribed and over-the-counter medicines, physical activity, smoking and alcohol consumption history and current habits, and markers of physical frailty, measured using gait-speed and Sit-To-Stand tests. Cognition was assessed during interviews using Mini-Mental State Examination (MMSE) score [272], Cambridge Cognitive Examination (CAMCOG) [273] and a GMS-AGECAT algorithmic approach was applied for dementia diagnosis. The algorithmic approach allowed for stability in diagnoses over time that would not be subject to change in diagnostic practices. Participants were flagged on the UK Office of National Statistics National Health Service Central Register for notification of date of death.

In circumstances when a participant was unable to answer questions, a proxy informant, where available would be interviewed to answer on the participant's behalf and the interviewer recorded whether a proxy had been required to provide the response. A proxy informant could be someone who lived with the participant, visited regularly or had been in touch with the participant for a long time. This could include the participant's formal or informal carer, family, friend or neighbour or, for care home residents, a member of staff. For a stratified sub-sample of participants with impaired cognition and random sub-sample of those without, participant proxy informants History and Aetiology Schedule (HAS) was requested, for 20% of the entire CFAS II sample [1]. Here informants were asked a series of questions that related to the participant's previous history of physical and psychiatric symptoms [274].

6.04   Population and sample

The target population for CFAS II was adults aged 65 years and over in England. The study population was drawn from patients registered with a participating GP based around the three

study centre locations, Nottinghamshire, Cambridgeshire and Newcastle. The study sample for CFAS II was randomly selected and stratified by age group. There were n=17,237 people originally sampled from GP records, 14,242 were eligible and approached to take part, of which 54.7% were interviewed. This resulted in n=7,796 CFAS II participants. For the purposes of this study, an analysis sample was drawn from the CFAS II sample based on the following inclusion and exclusion criteria.

6.05   Inclusion and exclusion criteria

Participants were included if, at baseline CFAS II interview, they were cognitively impaired and had reliable data of their medication use. In this study, reliable data of medication use was defined when the MMSE score was at least 18 points or higher. Alternatively, if the MMSE score was less than 18 points and there was a proxy available who provided the information on medication use, information on medication use was deemed reliable. Cognitive impairment was defined as a baseline MMSE score of 24 points or less. An MMSE score can range from 0-30 with higher scores indicating better cognitive function. A score of 24 points or less indicates clinically significant levels of cognitive impairment [15].

Participants were excluded if there was no recorded medication prescription information from the baseline CFAS II interview. In addition, participants with severe cognitive impairment (MMSE score of less than 18) who did not have a record of a proxy-informant reported medication use were excluded as this data was considered to lack reliability. A participant inclusion flow diagram exemplifying how the sample for this study was selected is provided (see Figure 20).

```
                        ┌──────────────┐
                        │   CFAS II    │
                        │  N= 7,762    │
                        └──────┬───────┘
                               │                    ┌────────────────────┐
                               ├───────────────────→│ Excluded: MMSE >24 │
                               │                    │     n=6,415        │
                        ┌──────┴───────────┐        └────────────────────┘
                        │ MMSE less than or│
                        │   equal to 24    │
                        │    n= 1,347      │
                        └──────┬───────────┘
                               │                    ┌────────────────────┐
                               ├───────────────────→│  Excluded: No      │
                               │                    │  medication data   │
                               │                    │     n=104          │
                        ┌──────┴───────────┐        └────────────────────┘
                        │ Current medication│
                        │  data available  │
                        │    n= 1,243      │
                        └──────┬───────────┘
                               │                    ┌────────────────────┐
                               ├───────────────────→│ Excluded: Unreliable│
                               │                    │  medication data   │
                               │                    │     n=89           │
                        ┌──────┴───────────┐        └────────────────────┘
                        │ Final sample included│
                        │    n= 1,154      │
                        └──────┬───────────┘
                               │
                        ┌──────┴───────────┐
                        │ 2 year follow up │
                        │    n=561         │
                        └──────────────────┘
```
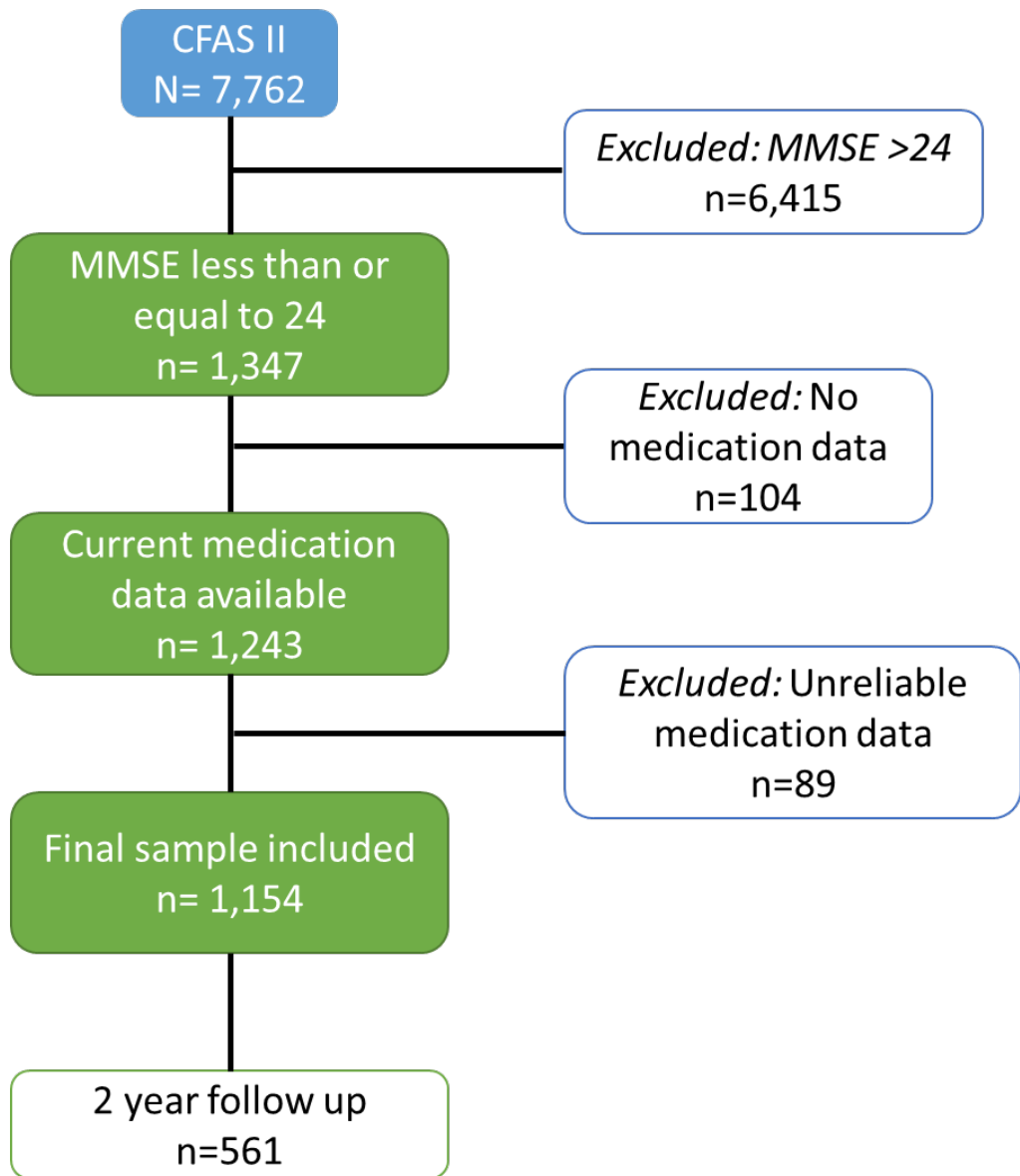
Figure 20 CFAS II analysis sample inclusion and exclusion participant flow diagram.

Reasons for there being no medication data include participants declining to provide information on the medications they are prescribed, the interview may have been terminated before getting to the medication data section or that the participant was unable to provide this data.

6.06 Exposures

The exposures of interest for this analysis were prescription of PIMs, polypharmacy and frailty. The data was ascertained from the baseline CFAS II interview (2008-2011), from a series of questions and objective tests in the interviews to both the participants and where available proxy informants.

(a) Medication use

The information on the current use of medications, including prescribed and over the counter medicines, was ascertained from the question: "Do you take any medicine, tablets or injections of any kind that either you buy yourself or that are prepared by your doctor?" The accuracy of this primarily self-reported medication use data collection was improved by the reported medicines being cross-checked with available medication packs by the CFAS II interviewer. This method is based on a process known as brown-bag medication review, where patients are encouraged to bring all of their medication packs for a clinical review [275]. In this circumstance, the brown-bag process was used to cross-check the participant reported medication use. If a participant was interviewed in a care home, staff cross-checked the reported medications with the participant medication lists. All medications were recorded as current medications by the interviewer, new medications compared to prevalent medications were not differentiated. All medications were coded using Read Codes [276].

(b) Potentially inappropriate medications

As identified in the scoping review, some key medication classes were specified to focus the analyses in this research. The identified PIMs were recognised across the scoping review as priority potentially inappropriate medications and were also highlighted by practitioners as key targets for further evidence to support deprescribing these medicines [246]. The PIMs were specifically associated with exacerbating dementia symptoms and adverse effects in people with dementia or were commonly prescribed in older populations with potential for adverse effects associated with prolonged use [243, 277]. The PIMs included in analyses in this study included medications from Section D of STOPP; Central Nervous System Criteria, including anticholinergics, antidepressants, antipsychotics and benzodiazepines [243]. Medications were defined using the

Anatomic Therapeutic Chemical (ATC) system and were identified from the CFAS data through corresponding Read Codes. The identified lists of medications were cross-checked by pharmacists to ensure key medications within each broad medication class were not missing. For analyses, medications were grouped into mutually exclusive categories due to cross-over between medication classes and medications with anticholinergic effects (Appendix Section 10.05).

(c) Anticholinergic medication

Medications with anticholinergic effects are often prescribed to treat or manage conditions or symptoms for which the medication is indicated, and the anticholinergic effect of a medication is overlooked. As identified from the scoping review, a number of anticholinergic medication scales have been developed to identify medications with anticholinergic effects, although there is no established consensus. One of the most frequently validated scales is the Anticholinergic Cognitive Burden Scale (ACB), which was used to classify anticholinergic medications in this study [254, 278]. The ACB has been predictive of a range of adverse effects, validated across a number of studies including quality of life, cognitive function, mortality, and activities of daily living, dementia and physical function [161]. The ACB classifies medications by known level of anticholinergic activity, as identified through a systematic review of medicines with anticholinergic activity and including medications where there is evidence of a relationship with detrimental effects on cognitive functioning. The identified medications were reviewed by a panel of experts from across disciplines and assessed each medication as having no anticholinergic properties, possible, or definite anticholinergic properties. According to the final ACB scale, medications were classified as having possible or definitive anticholinergic effects impacting on cognition (scores ranged from 1 to 3). Medications with definite anticholinergic properties are allocated an ACB score of 3. For the purpose of this study, medications for which there was certainty in regard to their anticholinergic effects, therefore those with an ACB score of 3, were included in this analysis (Appendix Section 10.05) [254]. Individual medications reported in CFAS II had been previously coded according to the ACB scale, and I applied these medication lists to operationalise anticholinergic medication use in my sub-sample of participants from CFAS II.

(d) Antipsychotic medication

Antipsychotic medications were defined using the ATC code N05A. Some antipsychotic medications also have anticholinergic effects and therefore medications were groups into

mutually exclusive categories of 'anticholinergic antipsychotics' and 'other antipsychotics' using the ACB scale. To create the mutually exclusive medication categories I used the ACB scale to distinguish and separate the antipsychotic medications with anticholinergic effects and antidepressants with anticholinergic effects (tricyclic antidepressants) from the remaining anticholinergic medications, then grouping the medications into the mutually exclusive medication groups used in this analysis (Appendix Section 10.05).

(e) Antidepressant medication

Antidepressant medications were defined as any medication with ATC code starting N06A and were subsequently classified from the CFAS II medication lists. Tricyclic antidepressant medications are particularly associated with a negative impact on cognition due to the high anticholinergic effects of these drugs and therefore the antidepressant medications were also grouped into two categories of 'tricyclic antidepressants', identified from the ACB scale due to the anticholinergic properties of tricyclic antidepressants, and 'other antidepressants'.

(f) Benzodiazepine medication

Benzodiazepine medications were defined using the ATC code N05CD and N05CF, which included benzodiazepine derivatives and benzodiazepine related medications, which were classified from the coded medication lists from CFAS II.

(g) Proton pump inhibitors

Proton pump inhibitors (PPI) were defined using the ATC code A02BC. According to STOPP criteria, PPIs are potentially inappropriate when they have been prescribed for 8 weeks or more, however due to the cross-sectional nature of the CFAS II interviews I was unable to ascertain the duration of use. However, PPIs are often used chronically in older adults [242] and it is possible that many of the people reporting PPIs in CFAS were reporting prevalent medications, rather than those that were new or used temporarily.

(h) Polypharmacy

The total number of medications that each CFAS II participant included in this sample was recorded during the interview, including both prescribed and over-the-counter medications. The total number of medications prescribed, excluding PIMs was categorised into three groups, zero to four medications, five to nine (polypharmacy) and ten or more (hyper-polypharmacy), as in previous studies [122, 198].

(i) Continuation of medication use

To assess the variation of the PIM exposure over time the proportion of participants who continued to be prescribed PIM was ascertained from a sub-sample of the participants who were assessed and provided medication data at the two-year follow-up interview.

6.07 Outcome variable

The outcome variable used in the analyses to address objectives of this study was survival. All CFAS II participants were flagged on the UK Office of National Statistics National Health Register for notification of date of death. This analysis included deaths up to 31 October 2016, providing up to eight years follow-up.

6.08 Confounding variables

Potentially confounding variables were coded from the CFAS II interviews and adjusted for in multivariable analyses. This included age and gender, the living situation, cognitive function, number of medications excluding PIMs and number of self-reported comorbidities. These potentially confounding variables were coded as follows:

(a) Age and sex

From the original primary care records used to sample participants, age and gender were known to the interviewer before the interview. At the start of the interview, the participants' age and date of birth were confirmed.

(b)   Living situation

The CFAS interviews took place in the participants usual place of residence and the CFAS II interviewer rated the living situation of the participant as living in an 'institution' or not. Interviewers were provided with an outline for classifying institutions. Institutions included residential homes, nursing homes and long-stay hospitals, whereas day hospitals or sheltered accommodation were not considered institutions.

(c)   Cognitive function

The baseline cognitive function was ascertained from the Mini-Mental State Examination (MMSE) score from the interview [272]. The MMSE is used widely as a test of cognition in older adults. The test is made up of a series of questions assessing attention, memory, language, visual-spatial and attention skills. Scores can range from 0 to 30 with higher scores indicating better cognition.

(d)   Comorbidities

The CFAS II participants were asked a series of questions on whether they 'had ever had or suffered from any of the following health conditions.' This was asked of the following health conditions that were reported by the participants: angina, arthritis, asthma, cancer, chronic bronchitis, depression, diabetes, epilepsy, heart attack, high blood pressure, intermittent claudication, low blood pressure, Parkinson's disease, peptic ulcers, pernicious anaemia, stroke. A cumulative count of the total number of self-reported comorbidities was created as a continuous variable for analyses.

6.09   Frailty

Frailty was classified based on the frailty 'phenotype' first described by Fried et al in 2001 [45]. Fried et al (2001) first developed and operationalised the phenotypic definition of frailty in a prospective cohort study of older adults from the Cardiovascular Health Study (CHS) in the United States. In the CHS study, standardised interviews took place at baseline (n=5,201) with annual follow-ups and examination of outcomes including hospitalisation, disability, falls and mortality. During the CHS interviews, a series of objective and self-report measures were used which were then subsequently operationalised into what became the frailty phenotype. Fried et al., proposed

that frailty was identifiable through the presence of three or more frailty components. These components were shrinking, weakness, poor endurance and energy, slowness and low physical activity. Due to variation in study designs and measurements, the phenotypic criteria cannot be operationalised exactly as in the original Cardiovascular Health Study [47] but as in other epidemiological studies of ageing [194, 195], I operationalised each component of the criteria using the data available from the CFAS II interview.

A comparison of the operationalisation of the Fried frailty phenotype as originally proposed in the Cardiovascular Health Study compared with how I operationalised the phenotype using CFAS II is provided in Table 16. The frailty phenotype was proposed as a clinical syndrome associated with a number of signs and symptoms that had been associated with frailty, including loss of strength, muscle mass, reduced resting metabolic rate, reduced walking speed, reduced activity, reduced overall energy expenditure, long-term undernutrition, and weight loss. The measures used (Table 16) were used to characterise the areas across the clinical syndrome of frailty (Figure 21).
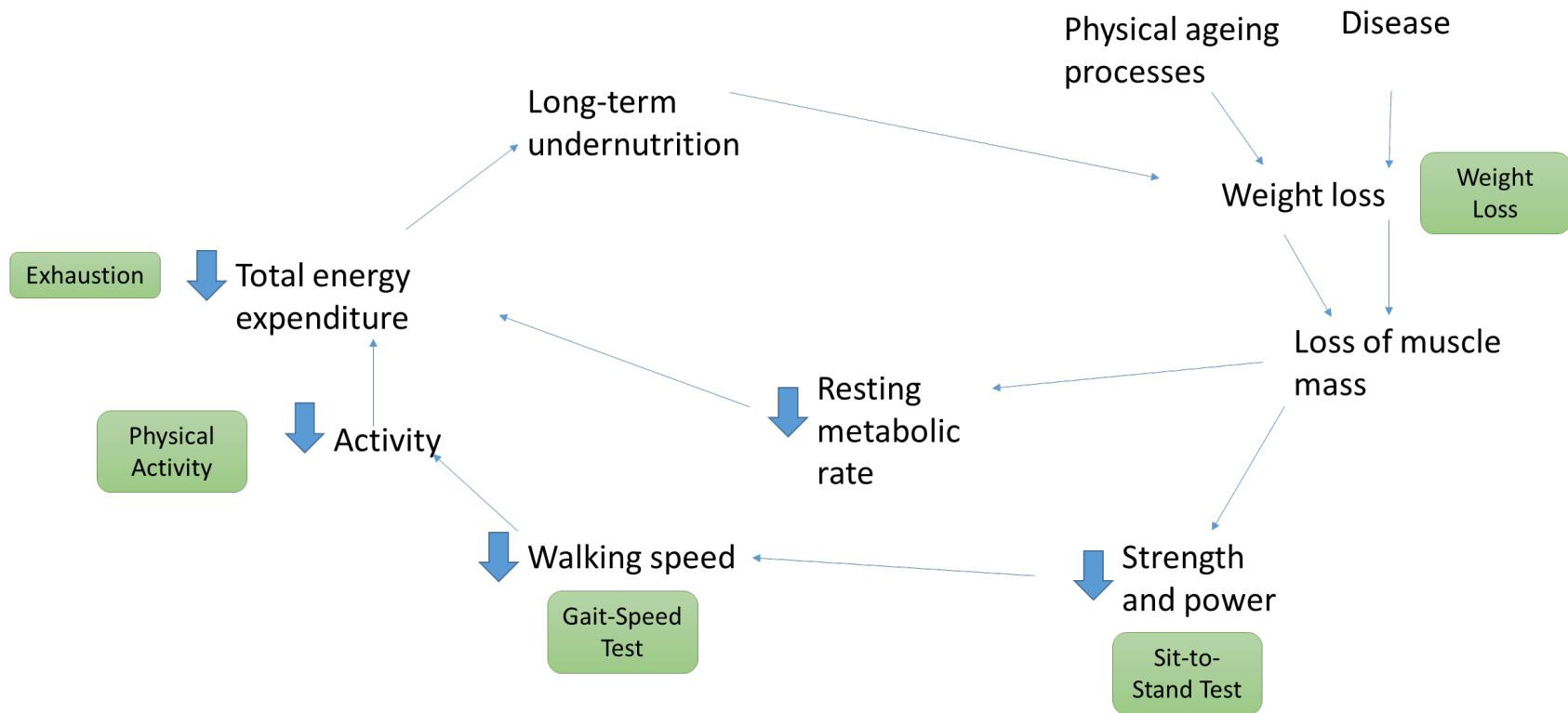
Figure 21 clinical syndrome of frailty as hypothesised by Fried et al (2001) based on clinical signs and symptoms of frailty.

Model based on cycle of frailty in Fried et al (2001), additional inclusion of operationalisation of frailty criteria from CFAS II questionnaires for this study.

Table 16 Operationalisation of Fried et al (2001) frailty phenotype in the Cardiovascular Health Study and CFAS II

Frailty phenotype	Cardiovascular Health Study Measure	CFAS II operationalisation
Shrinking: unintentional weight loss	Baseline: >10 lbs lost unintentionally in the previous year	Self-reported unintentional weight loss 4.5kg (10lbs) or more in previous six months or less
Weakness[1]	Grip strength test: lowest 20% (by gender and BMI)	Sit-To-Stand test: time taken to complete five stands
Poor endurance; Exhaustion	Self-reported exhaustion	Self-reported exhaustion
Slowness[1]	Walking time across 4.5m: Slowest 20% (by gender, height)	Average time across two gait speed test across 2.4m
Low activity[2]	Kcals per week: lowest 20% males <383 Kcals/week females <270 Kcals/week	Self-reported time spent doing physical activity

Cardiovascular Health Study Measure – originally used to propose the Fried frailty phenotype (2001)

Frailty defined as impaired on 3 or more criteria

Pre-frail defined as impaired on 1 or two criteria

CFAS II: People who did not consent or could not complete the test were considered impaired on that frailty criterion

[1]People in slowest quartile of average time across the CFAS II sample are considered impaired

[2]Operationalised through a cumulative score of time spent doing mildly, moderate and vigorous activities, participants with the lowest levels of activity (quartile) across the whole CFAS II sample were considered impaired on this criterion

(a) Slowness

The CFAS II participants were asked to complete a gait-speed test as part of the interview. This provided an objective measurement of the participants walking speed that I could use to operationalise the slowness frailty criteria. The gait speed test is a simple and objective measure of the individual walking speed that provides an indication of functional mobility, balance and endurance in older adults. Participants were allowed to use their usual walking aid if appropriate. The time taken to complete each test was recorded by the CFAS II interviewer. The average time to complete the walk was collated across all CFAS II participants, and split into quartiles with any participant within the slowest quartile coded as impaired for this frailty component. Any CFAS II participants who did not consent to take part in the gait-speed test, who were deemed unsafe to attempt the test by the interviewer or who could not complete both tests were considered to be impaired for this frailty criterion.

(b) Weakness

All CFAS II participants were asked to also take part in a Sit-To-Stand test, an objective measurement and a marker of the participant's endurance and strength, particularly of the lower-limbs [279]. Participants were asked to stand from a seated position, with their arms folded across their chest. The time taken for the individual to complete five repeated stands was recorded by the interviewer. I grouped the times from all 7,692 CFAS II participants in the test into quartiles. Participants with a time that fell within the slowest quartile across the entire CFAS II sample were coded as impaired for this criterion. Any participant who did not consent to take part in the Sit-To-Stand test, who was deemed unsafe to attempt or who could not complete the tests was considered impaired on this criterion.

(c) Exhaustion

The participant's level of exhaustion was ascertained from a self-reported answer to one question in the CFAS II interview: "Do you get worn out or exhausted towards the evening?" with possible responses of 'no', 'mildly exhausted' or 'severe exhaustion'. I operationalised this recorded data from CFAS II interviews by coding participants who reported mild or severe exhaustion that was not explained by strenuous activities as impaired on this criterion. If there was no response, the interviewer rating of observed slow movement, not readily explained by physical illness, was used

instead. The subjective interviewer rating was categorised as 'no', 'mild' or 'severe' and I coded participants recorded as 'mild' or 'severe' slow movement as impaired on this frailty criterion.

(d)   Weight loss

The participants self-reported recent weight loss as reported through one question asking whether they had lost 4.5kg (10lbs) or more in the past six months or less in CFAS II interviews. Unintentional or rapid weight loss can be common among older adults and particularly in frail older adults, and is associated with increased risk of hospitalisation, decline in day-to-day functional ability and care home admission [280]. If participants reported in the interview that they had lost 4.5kg (10lbs) or more in the past six months or less, they were coded as impaired on this frailty criterion.

(e)   Low physical activity

Physical activity levels were ascertained through a series of answers to self-reported questions on the time spent doing vigorous, moderate or mildly energetic activities. An initial question asked the participants if they took part in vigorous activity, if the participant answered 'yes' in the interview to this question they were asked a series of questions regarding the amount of time spent doing specific activities including running, swimming or cycling, for example. If the participant answered 'no' to the initial question, the interviewer proceeded to the next question, regarding moderate activity and subsequently mildly energetic activity. When asked about specific activity, participants' answers could be categorised as 'no', 'more than once a week', 'once a week', 'one to three times a month' or 'hardly ever or never'. An example of the physical activity questions asked and operationalised for this frailty criterion are provided (see Table 17).

Table 17 Example of questions about physical activity asked in the CFAS II interviews, used to identify low levels of physical activity in the sample. Not all example activities are shown, other activities were included in the questionnaire.

Vigorous activities	

Q375 Do you take part in sports or activities that are vigorous?
 	
    0.   NO
    1.   YES
 	
Specify which activity then as how often participant takes part in the activity
 	
If rated NO skip to moderate activities
	Example vigorous activities: Running or jogging, swimming, cycling, tennis…
	
	Each activity rated:
	
	    0. No
	    1. More than once a week
	    2. Once a week
	    3. One to three times a month
	    4. Hardly ever, or never

Moderately energetic activities	

Q383 Do you take part in sports or activities that are moderately energetic?
 	
    0.   NO
    1.   YES
 	
Specify which activity then as how often participant takes part in the activity
 	
If rated NO skip to mild activities
	Example moderately energetic activities: Moderate gardening, mowing lawn, cleaning the care, walking at a moderate pace…
	
	Each activity rated:
	
	    0. No
	    1. More than once a week
	    2. Once a week
	    3. One to three times a month
	    4. Hardly ever, or never

Mildly energetic activities	

Q391 Do you take part in sports or activities that are mildly energetic?
 	
    0.   NO
    1.   YES
 	
Specify which activity then as how often participant takes part in the activity
 	
If rated NO skip to next set of questions
	Example of mildly energetic activities:
	
	Light gardening, bowls, light housework, home repairs
	
	Each activity rated:
	
	    0. No
	    1. More than once a week
	    2. Once a week
	    3. One to three times a month
	    4. Hardly ever, or never

To classify participants as impaired on this frailty criterion, I created a scoring system where participants were scored based on the amount of time the participant spent doing each specific activity. For each activity, participants answering 'no', 'one to three times a month', or 'hardly ever or never', were allocated a score of 1. Participants answering, 'more than once a week', or 'once a week' were allocated a score of 0. I created a total score across each of the specific activities by summing scores to create a continuous variable, with higher scores indicating less reported physical activity. I categorised the scores into quartiles and participants in the highest quartile (indicating the lowest level of physical activity), were coded as impaired on this frailty criterion.

Participants who answered 'no' to the primary question regarding time spent doing mild, moderate or vigorous activities skipped the questions on specific activities and were considered as reporting low physical activity and I therefore classified them as impaired on this criterion.

(f)   Identifying frailty

Participants could be identified as impaired or not on each of the frailty criterion. Participants were identified as frail if they were considered impaired on three or more criteria. Participants who were considered impaired on one or two criteria were considered pre-frail and those who were free of impairment classification were identified as not frail (Table 18).

Table 18 Operationalisation of frailty criteria from CFAS II interview data

Frailty criteria	CFAS Questions	Operationalisation from CFAS II interview data	Impaired on criteria	Incomplete data
Slowness	Timed Gait Speed Test	Average time to complete two tests	Participants in the slowest quartile	No consent, unsafe to complete or unable to complete were considered impaired on criteria
Weakness	Timed Sit-To-Stand Test	Overall time take for five completed stands	Participants in the slowest quartile	No consent, unsafe to complete or unable to complete were considered impaired on criteria
Exhaustion	Do you get worn-out / exhausted towards the evening?	No, mildly exhausted or severe exhaustion as options for response. Missing data, interview report was used	Mild or severe exhaustion not explained by strenuous activity Or Mild or severe slow movement (interviewer reported)	Interview rating of observed slow movement used instead
Physical activity	Vigorous, moderate or mildly energetic activities	Scored based on time spent doing each activity, higher scores indicates less activity	Participants in the highest quartile (least active quartile)	No to first question on overall activity time classified as impaired
Weight loss	Weight loss	Loss of 4.5kg (10lbs) or more in the past six months or less	Impaired if reported they had lost 4.5kg or more in the past six months	

6.10   Statistical analysis

The statistical analyses used to address the objectives of this study outlined in Chapter 3 are described below, starting by describing the descriptive analyses, followed by a description of the statistical methods used to address objectives,1b, 3a-3c.

(a)   Descriptive statistics

Participant characteristics and proportion of PIM use was reported, stratified by frailty. Additionally, descriptive statistics of the proportion of patients diagnosed with dementia, within each categorical MMSE score (<=18, 19-21, 22-24), resident in a care home, death before 31/10/2016 and total number of participants classified as positive on each frailty component. Means and standard deviations were used to describe age (years), number of comorbidities and number of other medications reported. Descriptive statistics were also stratified by frailty group (not frail, pre-frail, and frail).

(b)   Prevalence of PIM use and polypharmacy

Addressing objective 1b, the prevalence of PIM use in the sample was estimated using inverse probability weighting to provide an estimation of the proportion of the population with cognitive impairment prescribed PIMs and polypharmacy. Inverse probability weights were used in the CFAS studies to reduce the likelihood of biased estimates, giving each participant a weight inversely proportional to the probability of non-response during recruitment. This helps to balance the impact of estimates associated with people who were more or less likely to take part in CFAS and reduces bias in the estimates that correspond to the population [281]. Weights were applied to the CFAS cohort to adjust for non-response based on the following factors: birth cohort, gender, care setting and deprivation status of postcode [1]. Prevalence estimates from CFAS I and II have been widely used to estimate dementia prevalence in the UK and this method was applied to the CFAS to estimate the proportion of people with a dementia diagnosis in the UK [28]. The weights estimated for the CFAS II sample were applied to estimates of PIM and polypharmacy proportions in this study sample to estimate the proportion of the population with cognitive impairment with polypharmacy and PIM.

To estimate the association between polypharmacy, PIM use and survival (objective 3a), the moderating role of frailty on this relationship (objective 3b) and the predictive validity of the frailty phenotype (objective 3c), Cox proportional hazards regression models were estimated [282].

(c)   Cox proportional hazards regression

Multiple Cox proportional hazards regression models were estimated to address the objective of aim three of this research. A Cox proportional hazards model is a regression model used in the analysis of time-to-event data, for example time to death or disease incidence. In this study, the Cox model is used to estimate the hazard ratio amongst people with cognitive impairment who are PIM users compared to non-users. Multiple predictor variables can be included in a Cox model. The association of each predictor variable with time until mortality can be estimated. A key assumption of the Cox proportional hazards regression model is that the hazards between the groups are proportional, meaning that the hazard ratio does not change over time. The Cox model equation is provided and explained below (see Figure 22).

$$h(t) = h_0(t)\exp(b_1X_1 + b_2X_2 + \cdots + b_pX_p)$$

Expected hazard at time t

Baseline hazard at time t.

Predictors (exposure variables and potentially confounding variables).
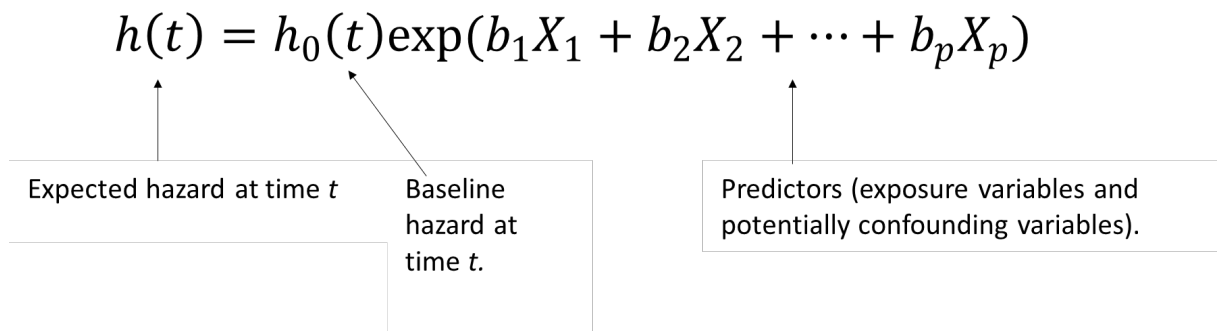
Figure 22 Cox proportional hazards regression model equation.

Where t is survival time, h(t) is the expected hazard at time t, $b_1, b_2 \ldots b_p$ are the coefficients of the covariates (predictors) $X_1, X_2 \ldots X_p$. The predicted hazard is a product of baseline hazard and exponential function of the linear combination of the predictors. The predictors have a multiplicative or proportional effect on the hazard at each time point, which is the probability of the occurrence of an event at that time, in this case the event being death. $h_0(t)$ is the baseline hazard function, that is the hazard at each time when all predictors are equal to 0. The effects of predictors (exposures and confounding variables) are measured by the exponential coefficients (exp(b)) which are hazard ratios (HR); a HR of 1 (corresponding to b=0) indicates no effect on mortality, greater than 1 is an increased risk of mortality and less than 1 is a decreased risk of mortality associated with that predictor, all other predictors adjusted for.

(i) Cox proportional hazards regression model with interaction terms

$$h(t) = h_0(t)\exp\left(b_1x_1 + b_2x_2 + \cdots + b_pX_p + b_qx_{frailty}x_{antipsychotic}\right)$$

Example of a Cox proportional hazards regression model equation with interaction terms used to test frailty and PIM interactions. Where $x_{frailty}$ is the dichotomous variable of frailty, with three levels of not frail, pre-frail and frail and $x_{antipsychotic}$ as a binary variable for antipsychotic medication use (exemplar of the other PIMs also analyzed). Therefore there were six levels, represented by five coefficients in the model for each PIM; not frail by PIM, pre-frail by no PIM, pre-frail by PIM, frail by no-PIM and frail by PIM. The final group is the baseline (no PIM and not frail).

(d) Association between PIMs, polypharmacy and survival

For time-to-event analyses, participants were considered 'at risk' of death from the time of CFAS II interview, until their death or censoring on 31st October 2016. Time since interview was the time scale for all analysis.

To address objective 3b, to estimate the association between polypharmacy and PIMs at baseline and subsequent survival, separate univariate analyses were first estimated. For univariate analyses, Kaplan-Meier survival curves were used to visualise the proportion surviving over time, corrected for censoring, log-rank tests to assess the null hypothesis of no difference (*p=<0.05)* and unadjusted Cox regression models estimating unadjusted hazard ratios (95% CI). Multivariate analyses estimated Cox regression models adjusted for potentially confounding covariates, estimating hazard ratios and 95% confidence intervals.

(e) Univariate analyses for polypharmacy and survival

Kaplan-Meier survival curves were used to estimate survival probabilities from baseline until censoring or death for users of zero to four medications, five to nine (polypharmacy) and ten or more (hyperpolypharmacy) medications that excluded PIMs. Log-rank tests were used to assess the null hypothesis of no difference in survival between users of polypharmacy and hyperpolypharmacy compared to zero to four medications. Unadjusted Cox regression model estimated univariate hazard ratios (with 95% confidence intervals) for participants with polypharmacy and hyper-polypharmacy compared to participants who reported zero to four medications.

(f) Univariate analyses for PIM and survival

Kaplan-Meier survival curves were used to estimate survival probabilities from baseline until censoring or death in reported users compared to non-users of each PIM. Log-rank tests were used to assess null hypothesis of no difference in survival between users and non-users of each PIM (*p=<0.05)*. Cox regression models estimated univariate hazard ratios (95% confidence intervals) for each PIM.

(g) Multivariate analyses for polypharmacy, PIM and estimated survival

Cox proportional hazards regression models were used to estimate the independent effect of polypharmacy and PIMs on survival, controlling for potentially confounding variables. Hazard ratios (95% CI) were estimated for polypharmacy and each PIM class. The models were adjusted for age, sex, baseline cognitive impairment, living situation and comorbidities. Subsequent models were also adjusted for frailty.

(h) Frailty as a moderator

To address objective 3c of this research, to estimate the moderating role of frailty on the relationship between polypharmacy, PIM use and survival, three approaches were applied. First, the multivariate analyses described above were adjusted for frailty. Second, analyses were stratified by frailty to estimate differences in survival between patients with different frailty status. And finally, interaction terms were used to estimate the effect of frailty on the association between each PIM and polypharmacy on subsequent survival. Likelihood ratio tests were used to assess the statistical significance of the PIM and polypharmacy and frailty interactions ($p=<0.05$) compared to the adjusted model without frailty and PIM or polypharmacy interaction term.

(i) Testing the proportional hazards assumption

The key assumption of the Cox proportional hazards regression model is that the hazards are proportional, meaning that the hazard between groups are proportional to each other and therefore their ratio does not change over time. The proportional hazards assumption was tested using Schoenfeld residuals, testing the independence between residuals and time. Kaplan-Meier survival curves were also used as a visual assessment of the proportionality of the hazards and the assumption was subsequently tested with scaled Schoenfeld residuals [283].

(j) The association of frailty phenotype with mortality

To assess the predictive validity of the phenotype criteria and addressing objective 3c of this research, I also estimated the independent association of the five frailty phenotype criteria with mortality, rather than considering a single 'frailty' variable, as in the main analysis. Firstly, each of the frailty criteria (weakness, slowness, low physical activity, weight loss and exhaustion) were

included in an unadjusted Cox regression model as separate variables and second, a multivariate model was estimated adjusting for age, sex, living situation and comorbidities. The independent hazard ratios (95% confidence intervals) for each of the frailty criteria were estimated.

(k) Sensitivity analyses

(i) Behavioural and psychological symptoms of dementia

A subset of the CFAS II sample also had proxy informants who completed the HAS questionnaire. This questionnaire was used to gauge further information relating to the history and aetiology of disease or related behaviours. The informants were asked about previous and recent behaviours and about the participants' education, memory, cognitive abilities, aphasia, apraxia, personality, behaviour, delirium, depression, and judgment. They were asked about noticeable changes and when these changes in these behaviours were recognised.

Antipsychotic medication is often prescribed to manage behavioural and psychological symptoms of dementia. Although the CFAS II interview data does not collect information about medication indications, the HAS informant questionnaire answers were used as a proxy indicator of antipsychotic indication for behavioural and psychological symptoms of dementia. Behavioural and psychological symptoms of dementia were operationalised from a series of questions around apathy, sleep problems, irritation, suspicion, hallucinations and wandering. Sensitivity analyses estimated an adjusted Cox regression model in the sub sample who had HAS informant questionnaires, adjusted for BPSD symptoms.

(ii) Measure of cognitive impairment

Sensitivity analyses were used to assess the robustness of the results using an alternative measure of cognitive impairment used in the CFAS II interview. An alternative measure of cognitive function, the Cambridge Cognition Examination (CAMCOG) was also completed as part of the CFAS interviews. The CAMCOG includes questions relating to orientation, memory, language, attention, calculation, perception, praxis and abstract thinking. The maximum score on the CAMCOG is 107 and higher scores indicate better cognitive function. The CAMCOG is a widely used and validated measure of cognitive function [284]. However, there is evidence to suggest that the CAMCOG is less sensitive in identifying people with milder levels of cognitive impairment [285] and has shown mixed effectiveness in accurately predicting people who would later go on to

develop dementia [286, 287]. A sensitivity analysis was used to compare the estimation of cognitive impairment within the sample to the MMSE estimation.

Scores from the CAMCOG [273] were used as an indicator of baseline cognitive impairment and a Cox regression model was estimated to compare the estimates using CAMCOG to the estimates from the model using MMSE as a baseline marker of cognitive impairment. Models were adjusted for age, sex, and total medication use excluding PIMs, living situation, comorbidities and frailty.

(iii) Adjusting for comorbidities

A sensitivity analysis was used to estimate the model adjusting for individual comorbidities and compared to the main model adjusting for number of comorbid health conditions. Each individual comorbid health condition (angina, arthritis, asthma, cancer, chronic bronchitis, depression, diabetes, epilepsy, heart attack, high blood pressure, intermittent claudication, low blood pressure, Parkinson's disease, peptic ulcers, pernicious anaemia, stroke) was adjusted for in separate binary variables in the full multivariate Cox regression model.

(iv) Frailty criteria

A sensitivity analysis was undertaken using the lowest quintile, as in the original study by Fried et al, (2001). The variables operationalising the slowness, weakness and low physical activity criterion were estimated with the lowest quintile (compared to quartile) being operationalised as impaired on these criteria. A second frailty variable was then generated to account for the changes in the slowness, weakness and physical activity criteria. As before, individuals were classified as not frail, pre-frail or frail. Individuals were classified as frail if they were impaired on three or more individual frailty criteria, pre-frail if they were impaired on one or two frailty criteria.

The univariate and multivariate association of frailty with mortality according to this criteria was estimated. The model adjusting for frailty operationalised using the lowest quintile was compared to the main model adjusting for frailty using lowest quartile, estimated in multivariate Cox regression models.

(l)   Sample size considerations

The original aim of this CFAS II study had been to estimate the risk of mortality associated with PIM use in people with dementia, however given the small sample of people with dementia (n= 154, 13%), people with severe cognitive impairment were also included in analyses. The sample would have likely been underpowered to detect effects had the sample been limited to people with dementia. This was an important part of the decision to include people with cognitive impairment in the sample, rather than restricting the sample to people with dementia.

When exploring the data set of the people in the CFAS II subsample who were prescribed PIMs, there was 1 (0.6%) person with dementia prescribed antipsychotics, 7 (4.6%) people prescribed tricyclic antidepressants, 7 (4.6%) prescribed other anticholinergic medications, 21 (13.7%) people with dementia prescribed antidepressants and 48 (31.2%) people with dementia prescribed PPIs. It was therefore expected that within the sample of people with dementia, there would have been too few instances of PIM prescriptions to be able to detect an effect.

Based on estimates from a previous large cohort study of people with dementia who were prescribed antipsychotic medications (n 10,615) [288]. An estimated hazard ratio of 1.30 of mortality associated with antipsychotics with 80% power and 5% significance level test, and an estimated 0.77 probability of the event (death), the estimated required sample size of people with dementia prescribed antipsychotics would be 593 with 457 events (deaths). Given the limited number of people with dementia (n=154) available in the CFAS II sample, the sample was expanded to include people with cognitive impairment (MMSE less than or equal to 24 points) (n=1,154).

It is notable that the sample size analyses for the CFAS II and CPRD studies presented in this thesis were considered using different approaches, given the differences in the databases that were used.

(m) Data quality and missing data

One of the inevitable and often unavoidable challenges of conducting surveys in epidemiological studies, using questionnaires and interviews is the quality of the data and missing data. Given this, considerable time was needed to clean the raw data so that it was suitable for analyses. This was a particular challenge for the operationalisation of the frailty criteria from the available data. A

participant is always able to make the choice to miss a question or series of questions, the interviewer may also decide to miss a question or series of questions if they deem it inappropriate or if it may harm the participant. In addition, whenever answers and information is manually inputted into a database there is a possibility of human error when inputting the data and a lack of consistency in how missing data is coded.

Decisions about coding of variables from the CFAS dataset were made alongside in-depth discussions with researchers and interviewers with experience of working with the CFAS data. Given the understanding of the process of the interviews, multiple imputation was not applied to the missing data as the data were not deemed to be missing at random but were missing due to considered processes, involving the participant and the interviewer in choosing whether to complete particular questions or tests. Examples of this process of understanding the CFAS interview procedures are explained.

(i)   Medication use

To cross-check the reliability of reporting of medication use, the interviewers would ask to see medication prescriptions or boxes. Participants were excluded if they did not have data that was considered reliable for the primary exposures of medication use. Reliable medication data was considered when the participant had a MMSE score of more than 18 points. Furthermore, those with severe impairment were required to have their medication data reported by a proxy.

(ii)   Frailty

When investigating the missing data in the objective frailty criteria tests (gait speed and Sit-To-Stand test), whether or not the participant agreed to do the test, on the grounds of safety, was used to understand firstly, who had not consented to the test and secondly who had given consent but did not complete the test.

Firstly, there were 237 (20.6%) participants who did not consent to the gait speed test. On average, those who did not consent were older (mean age non-consent= 81 years, consent = 78 years), had greater cognitive impairment (mean MMSE score non-consent=20.8, consent=22.2), were more likely to live in a care or residential home (non-consent=11%, consent =2%) the distribution of males and females within those who did vs those who did not consent (non-consent =63% female, consent =62% female) and the average number of comorbidities (non-consent = 2.7, consent =2.3) was similar. Overall, 244 (21.1%) participants had a missing time score, of which the majority (n=237) did not consent and the remaining 7 consented but did not

complete the test. For the gait speed test, it was clear that those who had missing data on the specific question of time taken to complete the test had missing data because they had not consented to the test or the interviewer had deemed it unsafe to allow them to do the test. Alternatively, as amongst the remaining 7 participants, they did not complete the test.

In the interviews, the Sit-To-Stand test was conducted after the gait speed test. The Sit-To-Stand test required participants to fold their arms across their chest and from a chair, stand five times consecutively. A larger proportion of the sample did not consent to the chair rise test, which is likely due to fatigue or safety concerns leading on from the gait speed test. Overall, there were 482 (42%) participants who did not consent to the chair rise test. Overall, there were missing data for the chair rise test from 603 (52%) participants. The majority of these participants did not consent to the test (n=482) and the remaining did not complete the test. The test stipulated that the chair rise had to be repeated 5 times for the time to be recorded. Therefore, it was understood that the remaining missing data came from people who attempted but could not complete the test.

The inability to complete these tests was characterised by people who were older, more likely to live in a care home and were more cognitively impaired. There were 229 participants who did not consent to either test. The average age of these participants was 81 years, 63% were female, mean baseline MMSE score was 20.8, with an average of 2.7 comorbid health conditions and 11% lived in a care or residential home. The inability to complete the test was therefore deemed consistent with the positive indication of frailty within these criterion, and the missing data from the Sit-To-Stand and gait speed test was therefore classified as identifying people who were impaired on these frailty criterion.

Participants, with missing MMSE scores were excluded from the subsample. Missing MMSE scores were an indication of severe cognitive impairment and an inability to complete large portions of the interview. There is a possibility that this may have introduced selection bias into these results, however based on understanding of the interview process, it is assumed that MMSE scores were missing only if it was deemed inappropriate by the interviewer to complete the test and were therefore indicative of severe cognitive impairment.

Due to the inclusion and exclusion criteria that were applied, there is little data missing for the majority of the covariates and none for the exposures (medication use) and the outcome (mortality).

6.11 Summary

The CFAS II is a population representative cohort of older adults and a subsample with cognitive impairment was sampled and used in analyses described in this chapter. The Fried et al (2001) frailty phenotype was operationalised using the data available from CFAS II interviews to estimate the role of frailty on the relationship between polypharmacy, PIM use and mortality and to assess the predictive validity of the frailty phenotype criteria. Chapter 7 will present the results of the analyses described.

VII. Chapter 7: Results: CFAS II subsample analysis

7.01   Introduction

This chapter reports the findings from the CFAS II subsample analysis, reporting prevalence estimates of polypharmacy and PIM use and estimating the impact of potentially inappropriate prescribing on survival amongst older adults with cognitive impairment. The association of frailty on this relationship and the predictive validity of frailty criteria are presented.

7.02   Description of the sample

There were 7,762 participants in CFAS II, of these 1,154 met the inclusion criteria. Of these , 62.1% were female and the mean age of the sample was 79 years (SD =7.4) (see Table 19). There were 789 (68.4%) people who had a MMSE score of 22-24 points, 283 (24.5%) had a MMSE of 19-21 points and 82 (7.1%) had a MMSE of 18 points or less. There were 154 (13%) people who had a diagnosis of demenita as diagnosed by the GMS-AGECAT algorithm. There were 47 (4.1%) people who were living in a care or residental home at the time of the CFAS II interview. The small proportion of people who were living in a care home may be accounted for by the exclusion of people without a MMSE score or a proxy informant to answer questions.

Table 19 Unweighted sample characteristics of older adults with cognitive impairment sampled from CFAS II (n=1,154), stratified by frailty

Characteristic	Total sample n=1,154	Not frail n = 204	Pre-frail n = 530	Frail n = 420
Gender (% female)	717 (62.1)	96 (47.1)	314 (59.3)	307 (73.1)
Mean age (years, SD)	78.8 (7.4)	75.7 (6.5)	78.8 (7.4)	80.4 (7.3)
PIMs (count, %)				
Antipsychotics	21 (1.8)	4 (2.0)	7 (1.3)	10 (2.4)
Anticholinergics	78 (6.8)	6 (2.9)	36 (6.8)	36 (8.6)
Tricyclic Antidepressants	76 (6.6)	5 (2.5)	30 (5.6)	41 (9.8)
Other Antidepressants	119 (10.3)	14 (6.9)	35 (6.6)	70 (16.7)
Benzodiazepines	46 (4.0)	4 (2.0)	14 (2.6)	28 (6.7)
Proton Pump Inhibitors	331 (28.7)	34 (16.7)	149 (28.1)	148 (35.2)
Polypharmacy				
0-4	551 (47.8)	143 (70.1)	260 (49.1)	148 (35.2)
5-9	493 (42.7)	56 (27.5)	229 (43.2)	208 (49.5)
10+	110 (9.5)	5 (2.5)	41 (7.7)	64 (15.2)
Cognitive impairment				
Dementia (count, %)	154 (13.3)	16 (7.8)	79 (14.9)	59 (14.1)
MMSE score (count, %)				
22-24	789 (68.4)	164 (80.4)	362 (68.3)	263 (62.6)
21-19	283 (24.5)	37 (18.1)	127 (24.0)	119 (28.3)
<=18	82 (7.1)	3 (1.5)	41 (7.7)	38 (9.1)
Number of Comorbidities (mean, SD)	2.4 (1.6)	1.6 (1.2)	2.3 (1.5)	2.9 (1.7)
Care home resident (count, %)	47 (4.1)	2 (1.0)	22 (4.2)	23 (5.5)

MMSE: Mini-Mental State Examination score (0-30 higher scores indicate better cognition).

7.03 Prevalence of PIM and polypharmacy use in people with cognitive impairment

Around 40% of older, cognitively impaired adults were prescribed at least one PIM. The weighted proportional estimate of any PIM use in the population of older adults with cognitive impairment was 41.1% (95% CI 38.2 - 44.0) (see Table 20). In the sample, this equated to 40.6% with a prescription of at least one PIM (n=469). The most prevalent PIM was PPIs with an estimated 28.6% (95% CI 26.0 – 31.3, n=331) of older cognitively impaired adults prescribed PPIs. Antidepressant medication (excluding tricyclic antidepressants) was the second most prevalent PIM (10.3% 95% CI 8.6-12.2, n=119). Tricyclic antidepressants were prescribed in an estimated 6.8% (95% CI 5.4-8.4, n=76) of cognitively impaired older adults, as were anticholinergic medications (excluding tricyclics) (6.8% 95% CI 5.4-8.3, n=78). An estimated 4.2% (95% CI 3.1-5.6, n=46) were prescribed benzodiazepines and 2.1% (95% CI 1.3-3.2, n=21) were prescribed antipsychotic medications.

Polypharmacy (5-9 medications) was prevalent in an estimated 43.3% (95% CI 40.4-46.3 n=493) of older adults with cognitive impairment and 9.8% (95% CI 8.1-11.7) were prescribed hyper-polypharmacy (10 or more medications), excluding PIMs.

(a) Weighted prevalence stratified by frailty

Frailty was associated with greater PIM use and polypharmacy in older adults with cognitive impairment. The weighted prevalence estimates for tricyclic antidepressants, other antidepressant medications, benzodiazepines and other anticholinergic medicines were at least twice as high in frail participants compared to participants who were not frail. Prevalence estimates of antipsychotic medication use were similar across frailty (see Table 20).

Table 20 Weighted polypharmacy and PIM prevalence amongst older adults with cognitive impairment, estimated from CFAS II sample (n=1,154) stratified by frailty.

PIM	Prevalence estimate (95% CI)	Frailty		
		Not frail	Pre-frail	Frail
Antipsychotics	2.1 (2.3-3.2)	2.2 (1.0-5.8)	1.6 (1.0-3.5)	2.6 (1.4-4.9)
Anticholinergics	6.7 (5.4-8.3)	2.7 (1.2-5.9)	6.9 (5.0-9.5)	8.2 (5.9-11.2)
Tricyclic Antidepressants	6.8 (5.4-8.5)	2.9 (1.2-6.9)	5.7 (3.9-8.3)	9.6 (7.1-12.9)
Other Antidepressants	10.2 (8.6-12.2)	7.0 (4.1-11.6)	6.7 (4.8-9.3)	15.9 (12.6-19.7)
Benzodiazepines	4.2 (3.1-5.6)	2.0 (1.0-5.5)	2.8 (1.6-4.6)	6.8 (4.7-9.8)
PPI	28.6 (26.0-31.3)	16.7 (12.1-22.6)	28.3 (24.5-32.4)	33.9 (29.5-38.7)
Polypharmacy				
0-4	46.9 (44.0-49.9)	69.2 (62.4-75.4)	48.1 (43.7-52.5)	36.2 (31.6-41.1)
5-9	43.3 (40.4-46.3)	27.5 (21.7-34.2)	44.0 (39.7-48.4)	49.0 (44.1-53.9)
10+	9.8 (8.1-11.7)	3.3 (1.3-7.7)	7.9 (5.8-10.7)	14.8 (11.6-18.6)

Weighted prevalence (95% CI)

Prevalence estimates weighted using CFAS inverse probability weighting sampling weights

(b) PIM use in care home residents

Around 4% of the sample lived in a care or nursing home (n=47, 4.1%). PIM use was greater in care home residents for all PIMs, with the exception of other anticholinergic medications, with 4.2% of care home residents reporting use of other anticholinergics compared with 6.9% of people living in their own home (see Figure 23). The use of antipsychotic medications was ten times greater in people living in a care home, compared to those living in their own home. Reported use of benzodiazepines and antidepressant medications (not tricyclic antidepressants) was nearly twice as high in people living in a care home compared to those living in their own home.
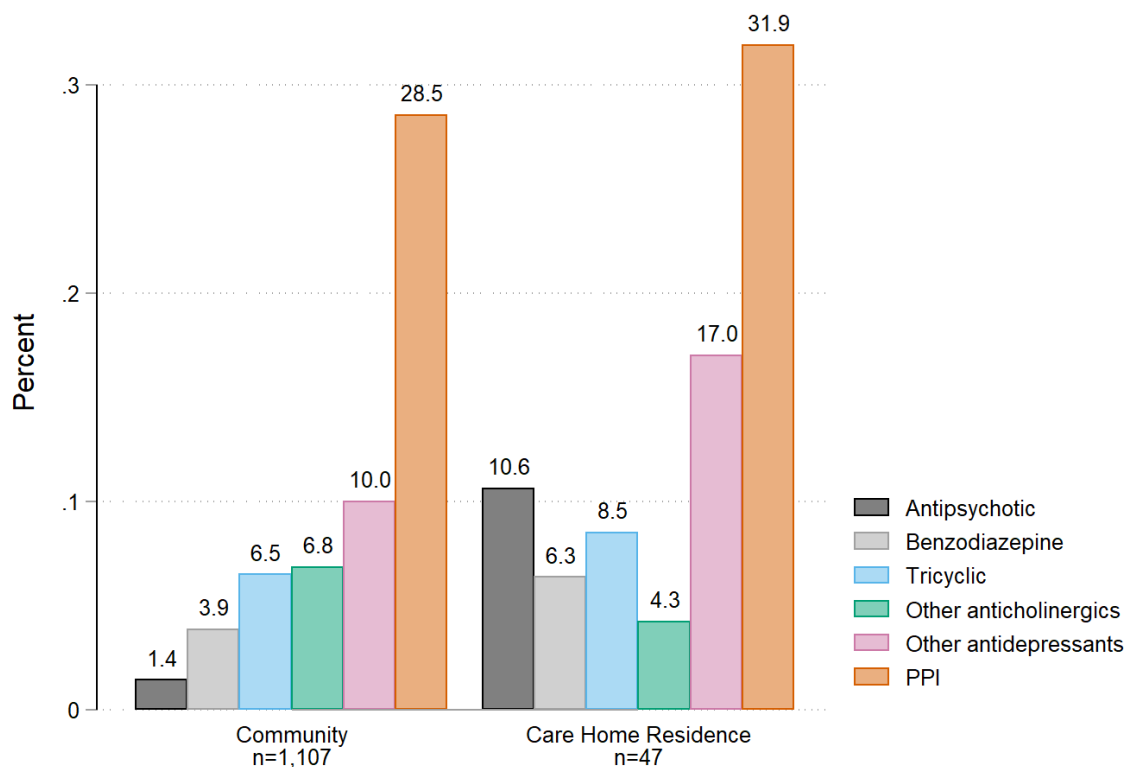
Figure 23 Percentage of PIM use in people with cognitive impairment (MMSE<=24) from CFAS II, stratified by living situation

(c)   Characteristics of PIM users and polypharmacy compared to non-users

There were a few differences between participants who reported taking 0-4 medications compared to those with polypharmacy or hyperpolypharmacy (see Table 21). Participants with 0-4 medications reported fewer comorbidities (1.7 SD 1.3) compared to people with polypharmacy (2.9 SD 1.5) and hyperpolypharmacy (3.8 SD 1.7). Fewer participants with 0-4 medications were living in a care home (n=15 2.7%) compared with people with polypharmacy (n=24 4.9%) and hyperpolypharmacy (n=8 7.3%).

Of the participants reporting antipsychotic medication use, 23.8% (n=5) were care home residents, 4.8% (n=1) were diagnosed with dementia according to the CFAS algorithm and the mean MMSE score of antipsychotic users was 21 (SD 3.9). Among participants reporting taking other anticholinergics, 9.0% (n=7) were diagnosed with dementia according to CFAS algorithm and 2.6% (n=2) were living in a care home. The mean number of comorbidities was similar in users compared to non-users of PIMs. The exception was for tricyclic antidepressant users who had 3.1 (SD 1.5) comorbidities compared to non-users who had 2.4 (SD 1.6) and benzodiazepine users who had 3.5 (SD 1.9) comorbidities compared to 2.4 (SD 1.6) among non-users.

Table 21 Characteristics of participants reporting 0-4 medications, polypharmacy and hyperpolypharmacy from CFAS II subsample analysis (n=1,154)

Characteristic	Medication use		
	0-4 (n=551)	Polypharmacy (5-9) (n=493)	Hyperpolypharmacy (10+) (n=110)
Gender (%, female)	334 (60.6)	321 (65.1)	62 (56.4)
Age (years)	78.3 (7.6)	79.6 (7.1)	78.9 (7.4)
Dementia (count, %)	76 (13.8)	65 (13.2)	13 (11.8)
MMSE score (count, %)			
22-24	393 (71.3)	321 (65.1)	75 (68.2)
21-19	125 (22.7)	131 (26.6)	27 (24.6)
<=18	33 (6.0)	41 (8.3)	8 (7.3)
Number of Comorbidities (mean, SD)	1.7 (1.3)	2.9 (1.5)	3.8 (1.7)
Care home resident (count, %)	15 (2.7)	24 (4.9)	8 (7.3)

7.04   Survival among the sample

By the end of the follow-up period (October 2016), 489 (42.4%) of the people with cognitive impairment included in this sample had died (see Table 22). Of those who reported PIM use, the largest proportion of people who had died were those who reported antipsychotic medication use. Overall, 52.3% (n=11) of those using antipsychotics, 47.4% (n=37) of those using other anticholinergic medications died. In addition, 43.4% (n=33) of tricyclic antidepressant users, 46.5% (n=21) of benzodiazepine, 46.2% (n=55) of other antidepressant and 44.0% (n=145) of those using PPIs had died. Among those experiencing polypharmacy and hyper-polypharmacy, 45.2% (n=233) and 55.4% (n=60) had died, compared to 33.0% (n=182) of people who reported taking 0-4 medications.

Table 22 Table of sample characteristics of survival across each exposure and covariate

Characteristic	Total sample n=1,154	Death by 31/10/16 n=489
Gender (% female)	717 (62.1)	222 (44.4)
Mean baseline age (years, SD)	78.8 (7.4)	-
PIMs (count, %)		
Antipsychotics	21 (1.8)	11 (52.3)
Anticholinergics	78 (6.8)	37(47.4)
Tricyclic Antidepressants	76 (6.6)	33 (43.4)
Other Antidepressants	119 (10.3)	55 (46.2)
Benzodiazepines	46 (4.0)	21 (46.5)
Proton Pump Inhibitors	331 (28.7)	145 (44.0)
Number of medications		
0-4	551 (47.8)	182 (33.0)
5-9	493 (42.7)	223 (45.2)
10+	110 (9.5)	60 (55.4)
Cognitive impairment		
Dementia (count, %)	154 (13.3)	112 (72.7)
MMSE score (count, %)		
22-24	789 (68.4)	282 (35.7)
21-19	283 (24.5)	150 (53.0)
<=18	82 (7.1)	57 (69.5)
Number of Comorbidities (mean, SD)	2.4 (1.6)	
Care home resident (count, %)	47 (4.1)	33 (70.2)
Frailty (count, %)		
Not frail	204 (17.7)	45 (22.1)
Pre-frail	530 (45.9)	226 (42.6)
Frail	420 (36.4)	281 (51.9)

MMSE: Mini-Mental State Examination score (0-30 higher scores indicate better cognition).

7.05 Estimating the association between polypharmacy and survival

(a) Univariate analyses

Kaplan-Meier survival curves suggested a difference in survival associated with polypharmacy and hyper-polypharmacy (see Figure 24). Log-rank tests estimated a statistically significant difference in survival across the categories for polypharmacy, excluding PIMs ($\chi^2 = 23.15\ df = 2, p =< 0.01$). Unadjusted Cox regression model estimates also suggested that polypharmacy and hyper-polypharmacy were both significantly associated with mortality, hazard ratio of 1.39 (95% CI 1.14-1.70) and 1.95 (95% CI 1.45-2.61) respectively, compared to people who reported using 0-4 medications (Table 23). The proportional hazards assumption was tested using Schoenfeld residuals and the assumption was not violated ($\chi^2 = 1.63\ p = 0.443$).

(b) Multivariate analyses

Adjusting for potentially confounding variables accounted for around half of the univariate effect of polypharmacy on mortality, reducing the hazard ratio to 1.21 (95% CI 0.97-1.50). Hyper-polypharmacy remained significantly associated with increased risk of mortality (HR 1.60 95% CI 1.16-2.22). The proportional hazards assumption was not violated in the multivariate model, as confirmed in tests of proportional hazards for the hazard associated with polypharmacy ($\chi^2 = 1.36\ p = 0.243$) and hyper-polypharmacy ($\chi^2 = 0.01\ p = 0.968$) and in the global test of the model ($\chi^2 = 13.88\ p = 0.383$).
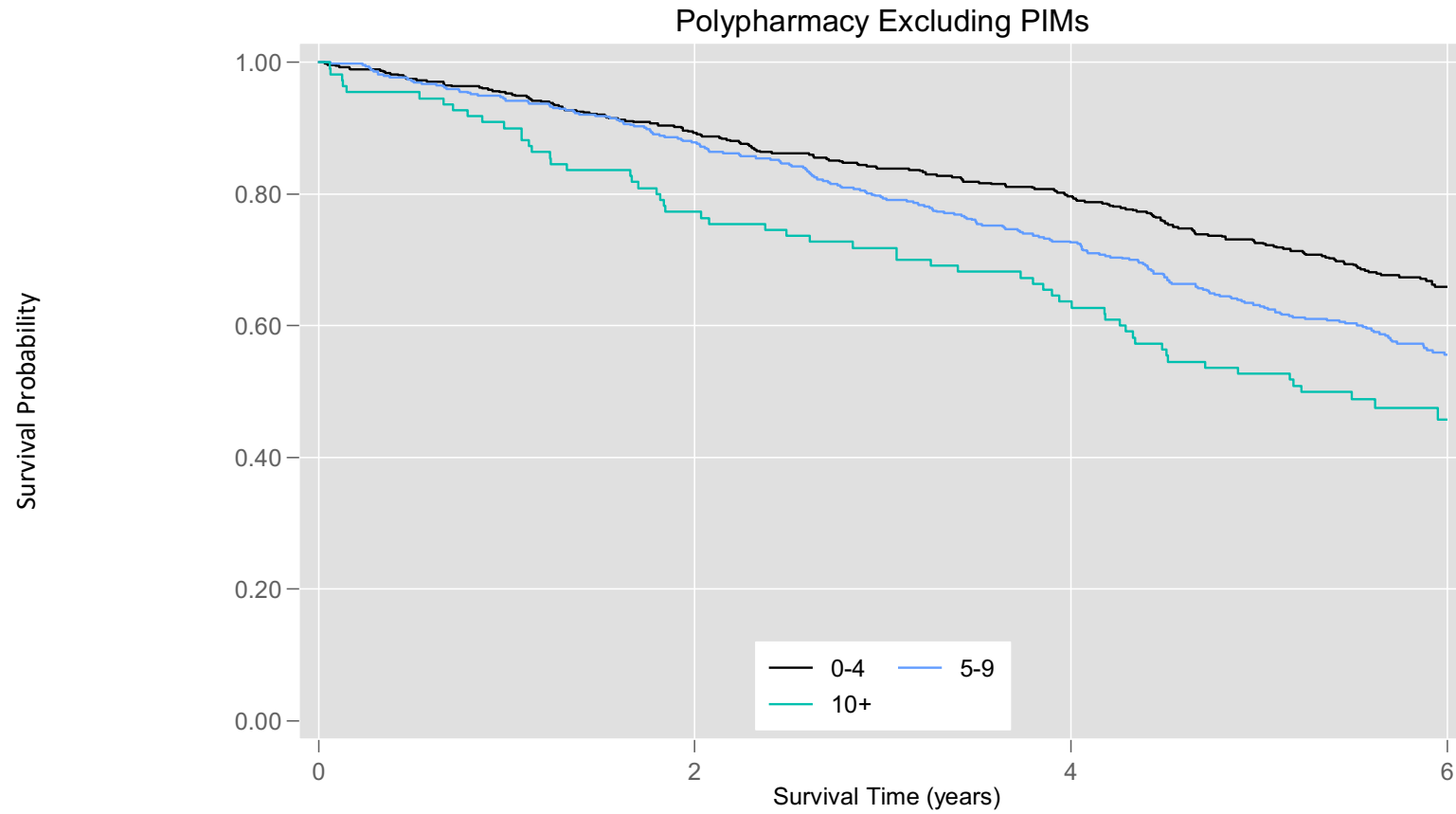
Figure 24 Unadjusted Kaplan-Meier survival curves estimating time until mortality in people with cognitive impairment taking 0-4, 5-9 and 10 or more medications. CFAS II (n=1,154). Hazards were assumed to be proportional ($\chi^2 = 1.63$ $p = 0.443$).

7.06   Estimating the association between PIMs and survival

(a)   Univariate analyses

Kaplan-Meier survival curves suggested there was a substantial difference in survival of users of antipsychotics compared to non-users, and a small difference in survival amongst users of PPIs compared to non-users. However there appeared to be relatively little difference in survival amongst the remaining PIM users compared to non-users (Figure 25). A statistically significant difference was estimated in users of antipsychotic medications, compared to non-users ($\chi^2 = 8.21\ df = 1, p = < 0.01$). Unadjusted Cox regression models estimated that antipsychotic medication use was associated with 2.19 increased hazard of mortality (HR 2.19 95% CI 1.26-3.81) and PPIs were associated with 16% increased risk of mortality, however this was not statistically significant (HR 1.16 95% CI 0.95-1.42). In addition, whilst the hazard associated with the remaining PIM were all above 1, none of the remaining PIMs were associated with a statistically significant difference in mortality in users compared to non-users.

On inspection of the Kaplan-Meier survival curves (Figure 25), the hazard associated with antipsychotic medication and tricyclics use appeared to lack proportionality, however the univariate estimate was tested and results suggested no significant difference in the proportionality of the hazards associated with antipsychotics ($\chi^2 = 1.16\ p = 0.282$) or tricyclics ($\chi^2 = 0.30\ p = 0.585$) .
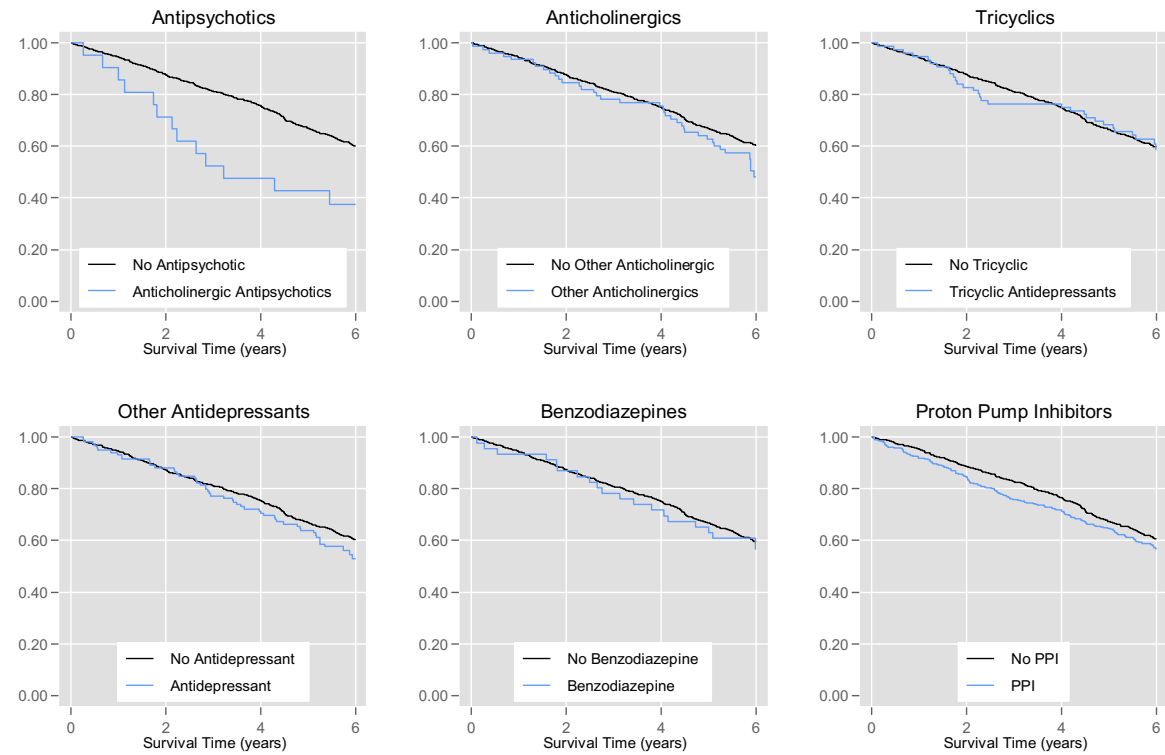
Figure 25 Kaplan-Meier survival curves comparing survival time in users compared to non-users of PIMs. CFAS II (n=1,154).

Schoenfeld residuals were used to test the proportionality assumption in the univariate models. Tricyclics $\chi^2 = 0.30$ $p = 0.585$, other anticholinergics $\chi^2 = 1.28$ $p = 0.257$, other antidepressants $\chi^2 = 0.47$ $p = 0.495$, benzodiazepine $\chi^2 = 0.08$ $p = 0.772$, PPI $\chi^2 = 3.48$ $p = 0.062$, antipsychotic $\chi^2 = 1.16$ $p = 0.282$.

(b)   Multivariate analyses

Estimates from the Cox regression models, adjusted for age, sex, baseline cognitive impairment, living situation and comorbidities saw an increase in the hazard associated with antipsychotic medication use to 3.24 (95% CI 1.83-5.73) (see Table 23). With the exception of antipsychotic medications, PIM were not associated with increased risk of mortality in this sample of cognitively impaired older adults.

The other covariates included in the model were also significantly associated with mortality in this sample (see Table 23). In this sample of cognitively impaired adults, being male, older and having worse cognitive impairment and more comorbid health conditions was independently associated with an increased risk of mortality, after adjusting for potential confounders.

Table 23 Unadjusted and adjusted potentially inappropriate medication use hazard ratios for survival, univariate and multivariate models. Cognitive Function and Ageing Study (CFAS) II n=1,154.

Variables	Univariate	Multivariate	Frailty model[a]
PIM			
Antipsychotics (n=21)	2.19* (1.26 – 3.81)	3.24* (1.83 - 5.73)	3.28* (1.85 - 5.80)
Tricyclic Antidepressants (n=76)	1.01 (0.70 - 1.47)	1.11 (0.76 - 1.63)	1.06 (0.72 - 1.55)
Anticholinergics (n=78)	1.29 (0.92 - 1.80)	1.18 (0.83 - 1.67)	1.17 (0.83 - 1.66)
Other Antidepressants (n=119)	1.21 (0.91 - 1.61)	0.94 (0.70 - 1.28)	0.90 (0.66 - 1.22)
Benzodiazepines (n=46)	1.08 (0.67 - 1.72)	0.75 (0.47 - 1.21)	0.72 (0.45 - 1.16)
Proton Pump Inhibitor (331)	1.16 (0.95 - 1.42)	1.08 (0.88 - 1.33)	1.05 (0.86 - 1.30)
Polypharmacy			
0-4 (n=551)	1	1	1
5-9 (n=493)	1.39* (1.14 - 1.70)	1.21 (0.97 - 1.50)	1.17 (0.95 - 1.45)
10+ (n=110)	1.95* (1.45 - 2.61)	1.72* (1.24 - 2.38)	1.60* (1.16 - 2.22)
Covariates			
Age at interview (per year)	1.10* (1.09 - 1.12)	1.10* (1.09 - 1.12)	1.10* (1.08 - 1.12)
Gender (female)	0.76* (0.63 - 0.91)	0.62* (0.51 - 0.75)	0.57* (0.46 - 0.69)
MMSE score (per point)	0.88* (0.85 - 0.90)	0.91* (0.88 - 0.94)	0.91* (0.89 - 0.94)
Care Home Residence	2.36* (1.63 - 3.42)	1.23 (0.83 - 1.84)	1.20 (0.81 - 1.80)
Comorbidities	1.06* (1.00 - 1.13)	1.08* (1.01 - 1.15)	1.05 (0.98 - 1.13)
Frailty			
Pre-frail	2.22* (1.59 - 3.09)		1.56* (1.11 - 2.20)
Frail	2.92* (2.09 - 4.07)		1.90* (1.32 - 2.72)

MMSE: Mini-Mental State Examination score (0-30 with higher scores indicating better cognition).
[a]Multivariate model adjusted for frailty*p<0.05 HR(95% CI)
Proportional hazards assumption assessed using Schoenfeld residuals, overall both models did not violate proportional hazards assumption and hazards were estimated as not violating assumption for significant exposures (antipsychotics and hyperpolypharmacy). Multivariate model ($\chi^2 = 13.88$ $p = 0.383$), antipsychotics test ($\chi^2 = 0.05$ $p = 0.819$), hyperpolypharmacy ($\chi^2 = 0.01$ $p = 0.968$). Frailty model ($\chi^2 = 16.91$ $p = 0.324$), antipsychotics (($\chi^2 = 0.09$ $p = 0.760$), hyper-polypharmacy ($\chi^2 = 0.01$ $p = 0.977$).

7.07 Estimating the association of potentially inappropriate prescribing, survival and frailty

People who were frail were exposed to a greater number of medications and PIMs. In this sample, a greater proportion of people who were frail were taking polypharmacy (n=208 49.0% 95% CI 44.1-53.9) and hyperpolypharmacy (n=64 14.8% 95% CI 11.6-18.6) compared to people who were pre-frail and not frail (see Table 20). In addition they were more exposed to all PIMs. There were only marginally more people who were frail (n=23, 5.5%) who were living in a care home compared to those who were pre-frail (n=22, 4.2%), however there was a greater proportion of people who were pre-frail and frail living in a care home, compared to not frail people (n=2, 1%).

(a) Proportion of PIM and polypharmacy by frailty status

At baseline 36.4% of the sample were classified as frail (n=420), while 45.9% were pre-frail (n=530) (Table 19). Use of multiple medications was associated with increasing levels of frailty. People who were not frail were taking a mean of 3.2 (SD 2.7) medications, people who were in the pre-frailty state were taking a mean of 4.8 (SD 3.3) medications and frail adults were taking 6.0 (SD 3.3) medications. The proportion of people with cognitive impairment who reported PIM use was greatest amongst those who were identified as frail (see Figure 26). PPI use was twice as common in people who were identified as frail (35.2%) compared to not frail (16.7%). The use of antidepressants (not including tricyclic antidepressants) was twice as great among people who were considered frail (16.7%) compared to pre-frail (6.6%) or not frail (6.7%). Similarly, the reported use of benzodiazepines, tricyclic antidepressants and other anticholinergics was twice as high in people who were pre-frail and frail compared with people who were not frail.

(b) Association of frailty with mortality

At the point of censoring, around half of those who were frail at baseline (51.9% n=218), 42.6% (n=226) pre-frail and 22.1% (n=45) of non-frail participants had died. In the univariate analyses, mortality was greater in those classified as pre-frail (HR 2.22 95% CI 1.59-3.09) and frail (HR 2.92 95% CI 2.09-4.07) (see Table 23) compared to those not considered frail. The proportional hazards assumption was not violated ($\chi^2 = 3.45\ p = 0.179$). After adjusting for PIM use, polypharmacy and other covariates, people who were considered pre-frail and frail remained independently

associated with a significantly increased risk of mortality compared to non-frail people (HR 1.56 95% CI 1.11 – 1.20 and HR 1.90 95% CI 1.32-2.72 respectively).
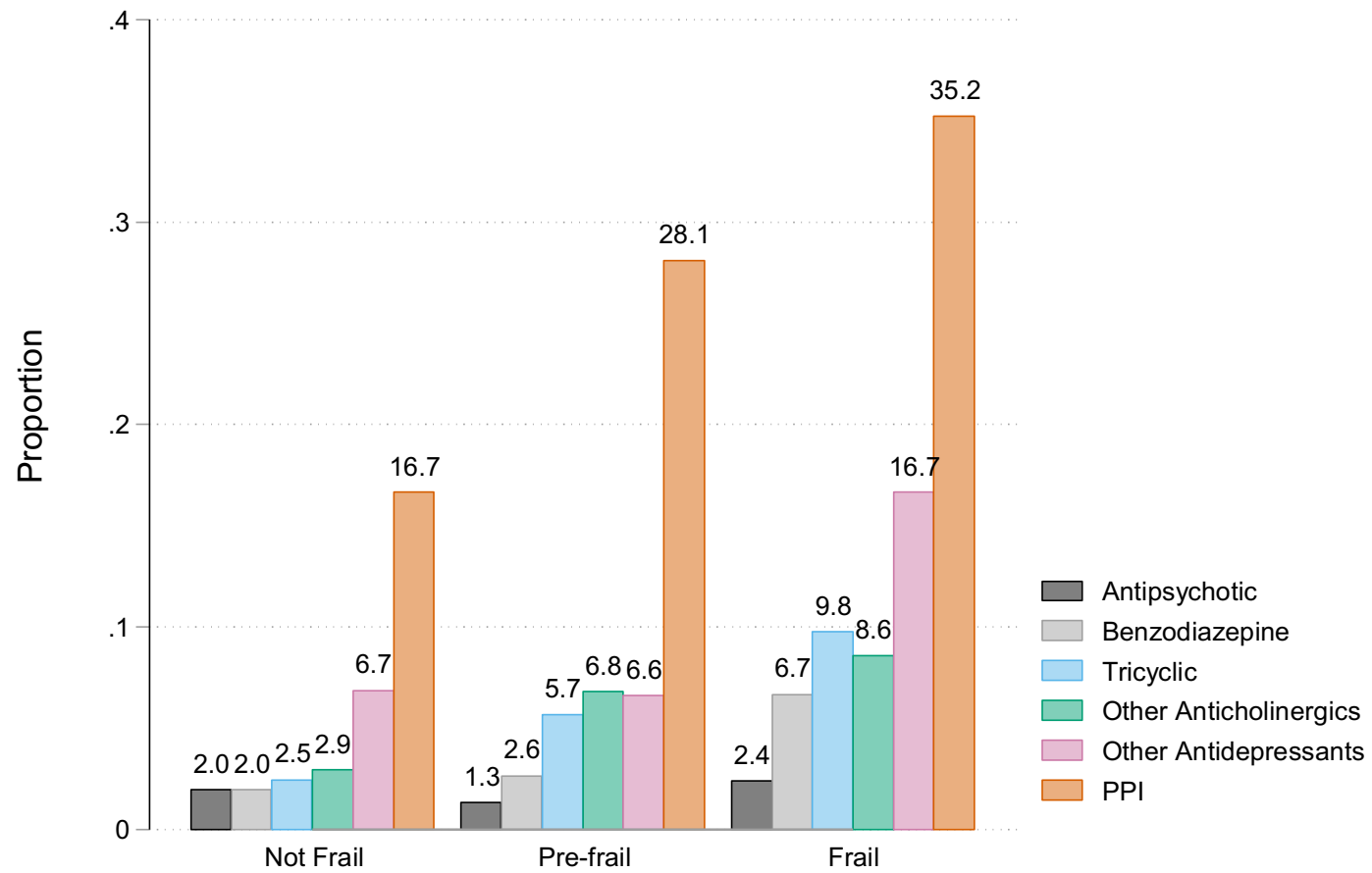
Figure 26 proportion of reported PIM use in people with cognitive impairment, stratified by frailty

(c) Frailty as a moderator of the effect of PIM and polypharmacy

Cox regression models were estimated adjusting for PIM, polypharmacy, age, sex, baseline cognitive impairment, and comorbidities and were stratified by frailty status (see Table 24 and Figure 27). Stratified analyses suggested that polypharmacy (5-9 medications) was associated with an increased risk of mortality across frailty status however the risk was greatest among people who were considered not frail (HR 2.34 95% CI 1.16-4.70). Similarly, the risk associated with 10 or more medications was greatest among people who were not frail. However, this was not statistically significant (HR 4.22 95% CI 0.90-19.90). For people who were identified as frail, use of 10 or more medications was associated with an 80% increased risk of mortality compared with frail older adults with cognitive impairment taking 0-4 medications (HR 1.80 95% CI 1.15-2.82). Terms representing the interaction of frailty with polypharmacy were added into the model and there was no significant interaction of frailty with polypharmacy.
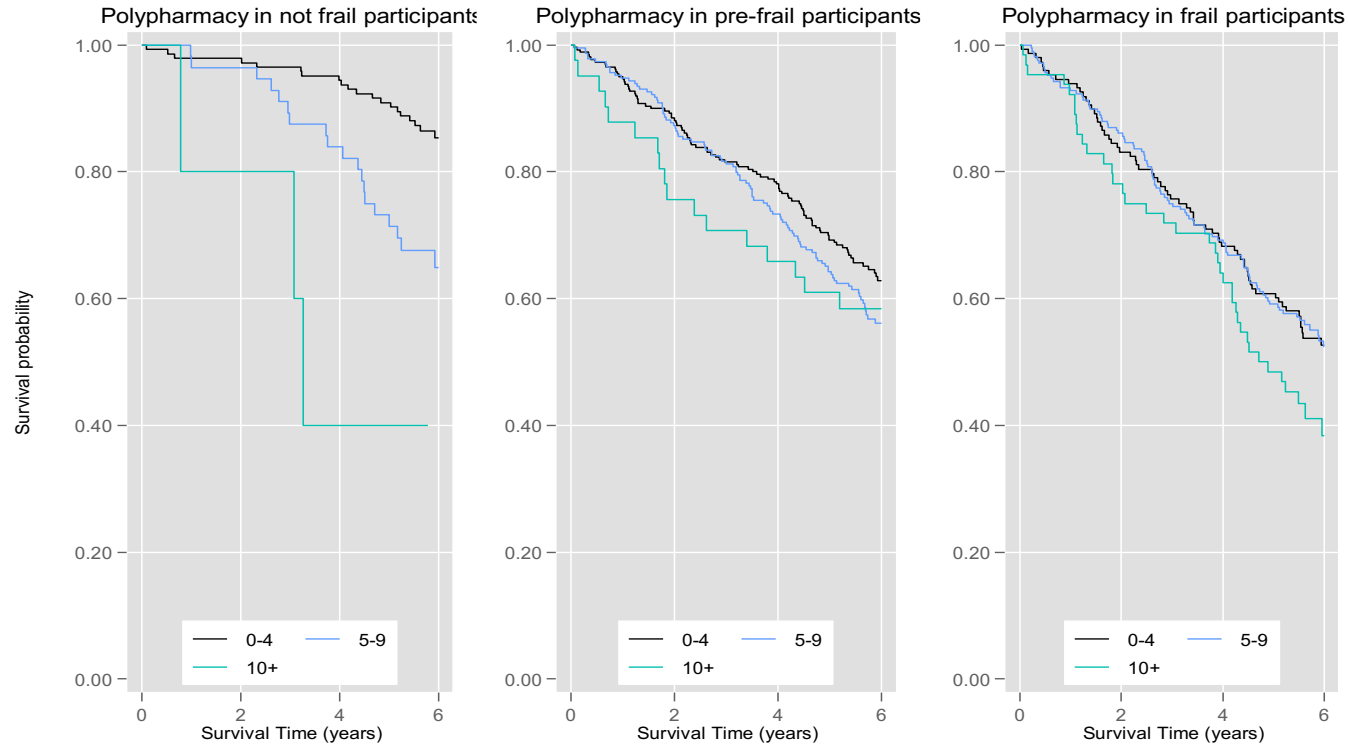
Figure 27 Unadjusted Kaplan-Meir survival curve of polypharmacy, stratified by frailty status.

Hazard ratio associated with polypharmacy and hyper-polypharmacy compared to survival in people taking 0-4 medications; Adjusted hazard ratios, not frail participants: 5-9 medications HR 2.34 95% CI 1.16-4.70 n=56, 10+ medications HR 4.22 95% CI 0.90-19.90 n=5; pre-frail 5-9 medications HR 1.07 95% CI 0.78-1.45 n=229, 10+ medications HR 1.31 95% CI 0.75-2.29 n=41; frail 5-9 medications HR 1.17 95% 0.84-1.64 n=208, 10+ medications HR 1.80 95% CI 1.15-2.82 n=64.

The hazard ratio associated with each PIM was consistent across all levels of frailty in adjusted models. In antipsychotic users compared to non-users, the hazard in non-frail participants was 3.60 (95% CI 0.40-31.99), 2.89 (95%CI 1.26-6.66) in pre-frail participants and 3.34 (95% CI 1.37-8.12) in frail participants (see Figure 28 and Table 24). However, the number of deaths in across the frailty groups was very small, particularly among people who were not frail, making it difficult to draw strong conclusions.
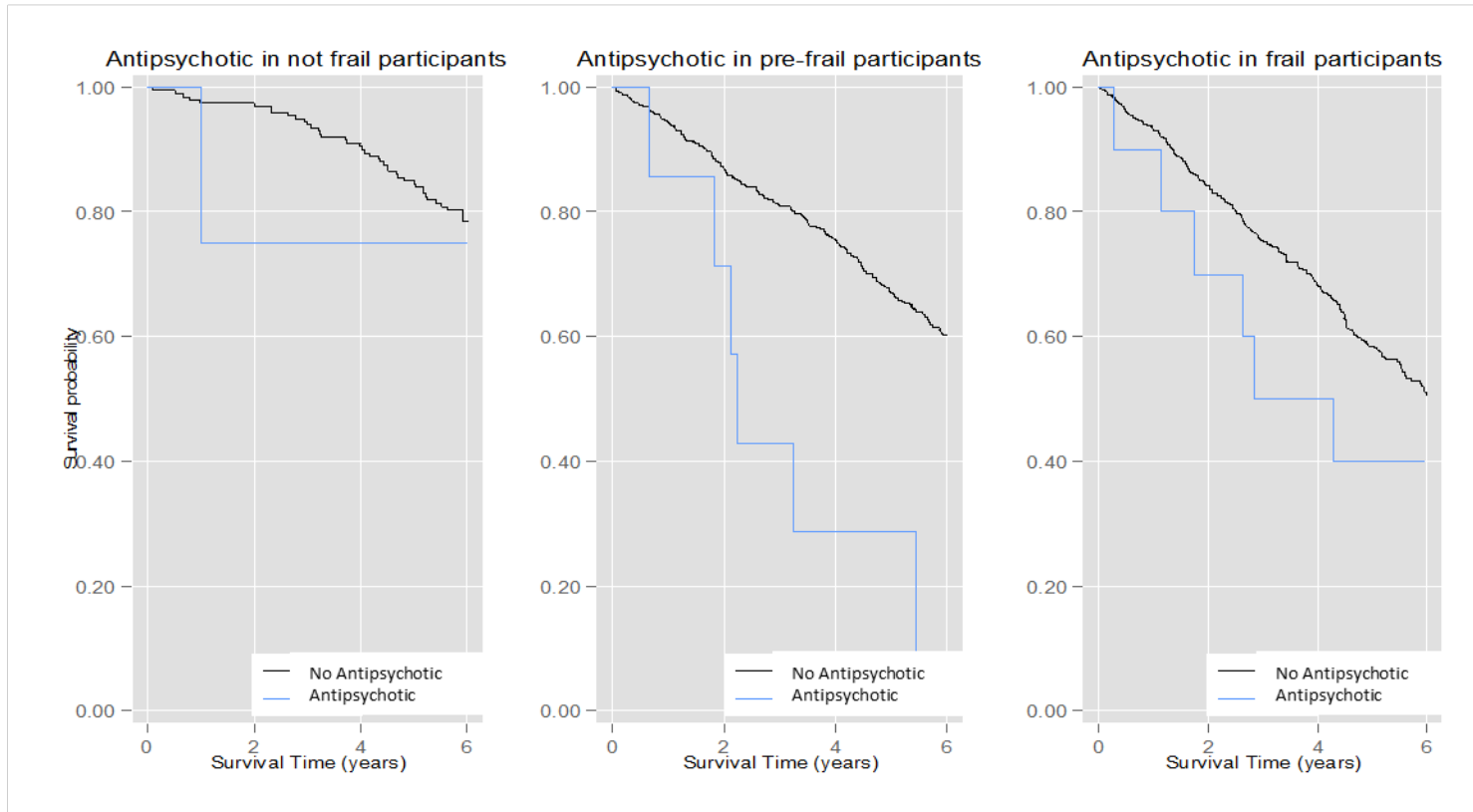
Figure 28 Unadjusted Kaplan-Meier survival curve of antipsychotic medication users compared to non-users, stratified by frailty.

Antipsychotic use in not frail n= 4, pre-frail n=7 and frail n=10. Adjusted HR non-frail participants 3.60 (95% CI 0.40-31.99), 2.89 (95%CI 1.26-6.66) in pre-frail participants and 3.34 (95% CI 1.37-8.12) in frail participants.

(d) Frailty and exposure interaction

Terms representing the interaction between frailty statuses with each of the medication exposures were entered into the model (see Table 24). Likelihood ratio test of the interaction for frailty and benzodiazepine use was statistically significant, however there were very few deaths in the not frail group (n=1) (x^2 6.05 *p*=0.049). There were no other statistically significant interactions for the PIM exposures and polypharmacy. Frailty did not moderate the effect of the remaining PIM exposure or polypharmacy on the risk of mortality in cognitively impaired older adults.

Table 24 Hazard ratios estimated by Cox regression models for association between potentially inappropriate medication use and mortality, stratified by frailty. Cognitive Function and Ageing Studies II (CFAS II)

Variables	Cox regression analysis stratified by frailty classification[a]			P-value for interaction
	Not frail	Pre-frail	Frail	
	n=204	n=530	n=420	
PIM				
Antipsychotic	3.60 (0.40 - 31.99)	2.89* (1.26 - 6.66)	3.34* (1.37 - 8.12)	0.995
Tricyclic Antidepressant	0	1.84 (0.98 - 3.44)	0.90 (0.55 - 1.48)	0.060
Anticholinergics	1.29 (0.16 - 10.61)	1.05 (0.61 - 1.79)	1.23 (0.76 - 2.01)	0.854
Other Antidepressants	0.86 (0.23 - 3.20)	1.12 (0.67 - 1.89)	0.74 (0.49 - 1.12)	0.230
Benzodiazepines	0.92 (0.11 - 7.78)	1.40 (0.66 - 2.97)	0.43* (0.21 - 0.86)	0.049*
Proton Pump Inhibitor	1.05 (0.43 - 2.59)	1.04 (0.76 - 1.42)	1.09 (0.80 - 1.49)	0.808
Polypharmacy				
0-4	1	1	1	0.102
5-9	2.34* (1.16 - 4.70)	1.07 (0.78 - 1.45)	1.17 (0.84 - 1.64)	
10+	4.22 (0.90 - 19.90)	1.31 (0.75 - 2.29)	1.80* (1.15 - 2.82)	
Covariates				
Age at interview	1.13* (1.07 - 1.19)	1.11* (1.09 - 1.13)	1.08* (1.06 - 1.11)	
Gender (female)	0.71 (0.35 - 1.43)	0.67* (0.50 - 0.89)	0.43* (0.31 - 0.58)	
MMSE score (per point)	0.87* (0.77 - 0.98)	0.92* (0.88 - 0.96)	0.91* (0.87 - 0.96)	
Care Home Residence	0	0.92 (0.50 - 1.71)	1.68 (0.98 - 2.88)	
Comorbidities	1.16 (0.90 - 1.50)	1.03 (0.93 - 1.14)	1.02 (0.92 - 1.12)	

MMSE: Mini-Mental State Examination score (0-30 with higher scores indicating better cognition).
[a]Classified as positive on individual frailty components if score, rating or time within the upper quartile. Classified as frail if positive on 3-5 individual frailty components and pre-frail if 1-2 components.

[b]Likelihood ratio test comparing exposure*frailty interaction models with multivariate frailty model with pre-frail group as baseline.

*p<0.05 HR (95% CI)

Proportional hazards test: not frail ($\chi^2 = 5.12\ p = 0.972$), pre-frail ($\chi^2 = 23.72\ p = 0.034$), and frail ($\chi^2 = 11.3\ p = 0.586$). Test suggests hazards were not proportional over time in the model with pre-frail participants, proportionality was assumed however hazard may be varied across the time period.

7.08 Proportional hazards assumption

The proportional hazards assumption, assessed using Schoenfeld residuals was not violated in the model estimating the effect of PIM and polypharmacy exposure on mortality, adjusting for potentially confounding variables and frailty ($\chi^2 = 16.91 \; df = 15, p = 0.324$). The proportional hazards assumption was tested across analyses for each covariate the results are included in the relevant tables in-line with the analyses that were conducted.

7.09 Predictive validity of frailty phenotype criteria

The proportion of the sample who were impaired on each frailty criteria is described in Table 25. Close to 70% (n=802) of the sample were impaired on the weakness criteria (Sit-To-Stand test), 60% (n=702) were impaired on the slowness criteria from the gait-speed test, 29% (n=334) were impaired on the self-reported exhaustion criteria and 27% (n=313) were impaired on the physical activity criteria.

Table 25 proportion of the sample impaired on each frailty criteria, stratified by frailty

Frailty criteria		Frailty phenotype		
(count, %)		Not frail	Pre-frail	Frail
		n = 204	n = 530	n = 420
Low physical activity	313 (27.1)	-	58 (10.9)	255 (60.7)
Weight Loss	122 (10.6)	-	29 (5.5)	93 (22.1)
Weakness[a]	802 (69.5)	-	388 (73.2)	414 (98.6)
Slowness[b]	702 (60.8)	-	313 (59.1)	389 (92.6)
Exhaustion	334 (28.9)	-	74 (14.0)	260 (61.9)

MMSE: Mini-Mental State Examination score (0-30 higher scores indicate better cognition).

[a]Missing n=603: categorised as impaired, missing due to inability to complete the test

[b]Missing n=244: categorised as impaired, missing due to inability to complete the test

Three of the five frailty criteria were univariately associated with an increased risk of mortality. Low physical activity, weakness and slowness were each independently associated with mortality risk in unadjusted Cox regression estimates. The greatest unadjusted risk was associated with weakness (HR 2.23 95% CI 1.77-2.83), followed by slowness (HR 1.99 95% CI 1.62-2.45) and low physical activity (HR 1.41 95% CI 1.15-1.71). The independent effect is illustrated in the Kaplan-Meier survival curves in Figure 29. Both exhaustion and weight loss were associated with an increased hazard but this was not statistically significant (see Table 26). After adjustment for PIM use, polypharmacy and the other potentially confounding variables, slowness was the only frailty criteria with an independent and significant association with mortality. Being impaired on the slowness frailty criteria was associated with a 42% increased risk of mortality (HR 1.42 95% CI 1.12-1.81). Including the individual frailty components rather than the composite frailty categories did not affect the overall estimates associated with PIMs or polypharmacy previously estimated.
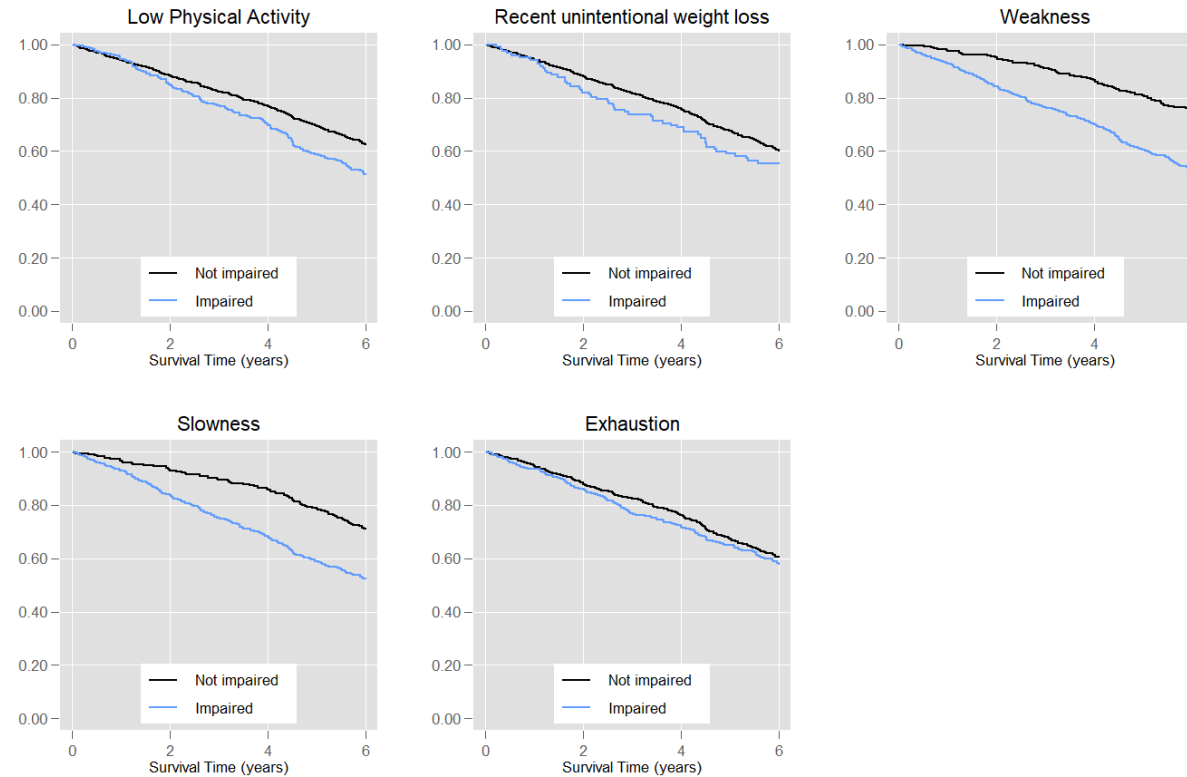
Figure 29 Unadjusted Kaplan-Meier survival curves estimating survival associated with individual frailty component, unadjusted estimates.

Cognitive Function and Ageing Study II (CFAS II) n=1,154. 0 = unimpaired on frailty criteria, 1 = impaired on frailty criteria. Adjusted hazard ratios for each criteria: physical activity HR 1.22 95% CI 0.98 - 1.51, weight loss HR 1.19 95% CI 0.89 - 1.60, weakness HR 1.13 95% CI 0.86 - 1.49, slowness HR 1.42 95% CI 1.12 - 1.81, exhaustion HR 0.98 95% CI 0.79 - 1.22. Proportional hazards assumption test: Low physical activity ($\chi^2 = 0.62$ p $= 0.430$), weight loss ($\chi^2 = 1.27$ p $= 0.261$), weakness ($\chi^2 = 3.09$ p $= 0.079$), slowness ($\chi^2 = 6.02$ p $= 0.01$), exhaustion ($\chi^2 = 1.45$ p $= 0.229$). The test suggests that the hazard for the slowness frailty component was not proportional, visual inspection of Kaplan-Meier curves appears to show a small variation in the hazards over time, therefore hazard is assumed to be proportional for the purpose of this analysis.

Table 26 Risk of mortality associated with the use of PIM and individual frailty components in univariate and multivariate models. Cognitive Function and Ageing Studies (CFAS II) n=1,154.

VARIABLES	Univariate HR (95% CI)	Multivariate[a] HR (95% CI)
Antipsychotic	2.19* (1.26 – 3.81)	3.30* (1.86 - 5.86)
Tricyclic antidepressant	1.01 (0.70 - 1.47)	1.04 (0.71 - 1.53)
Anticholinergic	1.29 (0.92 - 1.80)	1.17 (0.83 - 1.66)
Other Antidepressants	1.21 (0.91 - 1.61)	0.88 (0.65 - 1.20)
Benzodiazepines	1.08 (0.67 - 1.72)	0.73 (0.46 - 1.18)
PPI	1.16 (0.95 - 1.42)	1.05 (0.85 - 1.29)
Polypharmacy		
0-4	1	1
5-9	1.39* (1.14 - 1.70)	1.17 (0.95 - 1.46)
10+	1.95* (1.45 - 2.61)	1.65* (1.19 - 2.29)
Frailty components		
Low Physical Activity	1.41* (1.15–1.71)	1.22 (0.98 - 1.51)
Weight loss	1.25 (0.94–1.66)	1.19 (0.89 - 1.60)
Weakness	2.23* (1.77–2.83)	1.13 (0.86 - 1.49)
Slowness	1.99* (1.62-2.45)	1.42* (1.12 - 1.81)
Exhaustion	1.10 (0.90–1.35)	0.98 (0.79 - 1.22)

[a]Adjusted for age, sex, MMSE, care home residence and comorbidities (heart attack, diabetes mellitus, bronchitis, stroke, arthritis, asthma, angina pectoris, hypertension, epilepsy, thyroid problems, Parkinson's disease, pernicious anaemia, and depression).

*p<0.05

7.10   Continuation of medication use

There were 561 (48.6%) people included in this sample who had two year follow-up data that could be used to understand the continuation of medications they reported taking at baseline. The majority of people who reported taking PIMs at baseline, also reported taking the same medications two years later. PPIs were the PIM with the largest proportion of people who reported taking the medication at baseline and at two year follow-up with 85% (n=136/160) reporting long-term use. At least 60% of the people who reported taking any of the PIMs at baseline also reported the same PIMs at follow-up. There were 29 people (69%, n=29/42) who reported other anticholinergic medications at both baseline and follow-up. There were 5 people who were taking antipsychotics at follow-up in the sample and three of these were prevalent users who also reported antipsychotic use at baseline interview. In addition, around 76% of people reported tricyclic antidepressants and other antidepressant medications at both baseline and follow-up (n=31/40 tricyclics, n= 43/56 other antidepressants).

7.11 Sensitivity analyses

(a) Adjusting for behavioural and psychological symptoms of dementia

There was little difference in mortality estimates associated with polypharmacy and hyperpolypharmacy in the sub-sample analysis of participants who had responses to HAS informant questionnaires (n=214) (Table 27). Polypharmacy and hyper-polypharmacy were both associated with similar hazard estimates as in the overall sample, however the effects were not statistically significant. Hyper-polypharmacy was associated with a hazard ratio of 1.60 (95% CI 1.16 - 2.22) in the overall sample and a hazard of 1.50 (95% CI 0.72 - 3.12) in the sub-sample. In this sub-sample, antipsychotic medications remained associated with a significant increase in mortality (adjusted HR 4.10 95% CI 1.42 - 11.89). This subsample analysis included adjustments for behavioural and psychological symptoms of dementia including irritability, hallucinations, wandering and sleep problems.

In this analysis, other anticholinergic medications were also associated with increased risk of mortality (HR 1.99 95% CI 1.07 - 3.73). This may be attributable to the adjustment for behavioural and psychological symptoms of dementia, consequences of medication use or to differences in the sample and sub-sample. A larger proportion of the sub-sample were male than the whole sample (52% female sub-sample 62% female in the sample) a larger proportion had a dementia diagnosis at baseline (47.7% dementia) and a larger proportion of the sub-sample had died by the end of the follow-up period (57.5% died compared with 42% in the sample).

Table 27 Cox regression models estimating survival associated with exposures and covariates in sub-sample with information on BPSD, BPSD symptoms are adjusted for individually in the model and collectively to compare estimates as the symptoms are adjusted for in the model.

Variables	Adjusted frailty model (n=1,154)	Adjusted BPSD symptoms (n=214)	Sleep Problems (n=214)	Irritability (n=214)	Hallucinations (n=214)	Wondering (n=214)
PIMs						
Antipsychotic	3.28*(1.85 - 5.80)	4.10*(1.42 - 11.89)	4.16*(1.49 - 11.61)	4.46*(1.60 - 12.46)	4.00*(1.41 - 11.29)	4.60*(1.66 - 12.75)
Tricyclic antidepressant	1.06(0.72 - 1.55)	0.78(0.28 - 2.15)	0.76(0.28 - 2.07)	0.71(0.26 - 1.91)	0.73(0.27 - 1.97)	0.75(0.28 - 2.02)
Anticholinergic	1.17(0.83 - 1.66)	1.99*(1.07 - 3.73)	1.96*(1.06 - 3.64)	1.96*(1.05 - 3.66)	1.97*(1.06 - 3.66)	1.95*(1.05 - 3.64)
Other Antidepressants	0.90(0.66 - 1.22)	0.90(0.50 - 1.61)	0.86(0.48 - 1.54)	0.87(0.49 - 1.57)	0.89(0.50 - 1.58)	0.87(0.49 - 1.55)
Benzodiazepines	0.72(0.45 - 1.16)	0.66(0.22 - 2.01)	0.66(0.22 - 2.00)	0.59(0.20 - 1.73)	0.61(0.21 - 1.78)	0.59(0.20 - 1.70)
PPI	1.05(0.86 - 1.30)	1.09(0.70 - 1.69)	1.08(0.70 - 1.67)	1.06(0.68 - 1.66)	1.07(0.69 - 1.66)	1.07(0.69 - 1.66)
Polypharmacy						
5-9	1.17(0.95 - 1.45)	1.04(0.66 - 1.64)	1.02(0.65 - 1.60)	1.02(0.65 - 1.61)	1.02(0.65 - 1.59)	1.03(0.66 - 1.62)
10+	1.60*(1.16 - 2.22)	1.50(0.72 - 3.12)	1.55(0.76 - 3.15)	1.49(0.73 - 3.03)	1.46(0.72 - 2.97)	1.53(0.75 - 3.12)
Frailty						
Pre-frail	1.56*(1.11 - 2.20)	1.54(0.78 - 3.05)	1.59(0.81 - 3.15)	1.56(0.79 - 3.08)	1.54(0.78 - 3.05)	1.55(0.78 - 3.06)
Frail	1.90*(1.32 - 2.72)	1.89(0.91 - 3.93)	1.88(0.91 - 3.88)	1.94(0.94 - 4.01)	1.91(0.93 - 3.92)	1.91(0.93 - 3.94)
BPSD						
Sleep problems		0.76(0.34 - 1.73)	0.73(0.32 - 1.63)			
Irritability – mild		1.08(0.67 - 1.74)		1.09(0.68 - 1.75)		
Irritability – severe		0.90(0.37 - 2.17)		0.93(0.39 - 2.21)		
Hallucinations		1.79(0.59 - 5.42)			1.87(0.63 - 5.50)	
Wondering – mild		1.17(0.48 - 2.84)				1.19(0.49 - 2.88)
Wondering – severe		1.89(0.52 - 6.85)				1.84(0.52 - 6.53)

HR (95% CI) *p<0.05 Likelihood ratio test (chi, p=<0.05) Individual symptoms added into model and model estimated including all symptoms. Models were adjusted for age, gender, care home residence baseline cognitive impairment, number of self-reported comorbidities and frailty

(b)   Adjusting for alternative measures of cognitive impairment

Including the CAMCOG as the marker of baseline cognitive impairment instead of MMSE provided similar hazard estimates associated with PIM use (see Table 28). The mean CAMCOG score in the sample was 75.7 (SD 10.8), scores ranged from 19 to 98. There were 123 participants in the sample who did not have a CAMCOG score and thus were missing in the CAMCOG model. In models including the MMSE or CAMCOG, the hazard associated with antipsychotic use was similar, but slightly higher in the CAMCOG model. The risk associated with antipsychotics in the MMSE model was 3.28 (95% CI 1.85-5.80) compared with 3.43 (95% CI 1.89-6.22) in the CAMCOG model. The association of polypharmacy varied in the different models. Polypharmacy was not associated with significant increased risk of mortality in the MMSE model, but was associated with a 26% increased risk in the CAMCOG model (95% CI 1.00-1.59). However, this just reached the statistical significance threshold and is interpreted with caution. Hyper-polypharmacy was associated with an increased risk of mortality in both models. Across the remaining covariates included in the model, the estimates were comparatively similar. Overall, a model including MMSE or CAMCOG as the baseline measure of cognitive impairment provides remarkably similar estimates.

(c)   Adjusting for comorbities

Including each comorbidity separately in the full multivariate Cox regression model made little difference to the model estimates compared to the number of comorbid health conditions (Table 29).

Table 28 Cox regression model estimates using alternative measures of baseline cognitive impairment. Cognitive Function and Ageing Study (CFAS II) (n=1,154).

Variables	Adjusted Cox regression models Cognitive impairment measure	
	MMSE (n=1,154)	CAMCOG (n=1,031)
Antipsychotic	3.28* (1.85 - 5.80)	3.43* (1.89 - 6.22)
Tricyclic antidepressant	1.06 (0.72 - 1.55)	1.03 (0.68 - 1.56)
Anticholinergic	1.17 (0.83 - 1.66)	1.17 (0.80 - 1.71)
Other Antidepressants	0.90 (0.66 - 1.22)	0.86 (0.61 - 1.20)
Benzodiazepines	0.72 (0.45 - 1.16)	0.70 (0.41 - 1.18)
PPI	1.05 (0.86 - 1.30)	1.10 (0.88 - 1.37)
Polypharmacy		
5-9	1.17 (0.95 - 1.45)	1.26* (1.00 - 1.59)
10+	1.60* (1.16 - 2.22)	1.46* (1.01 - 2.10)
Covariates		
Age at interview	1.10* (1.08 - 1.12)	1.10* (1.08 - 1.11)
Gender (female)	0.57* (0.46 - 0.69)	0.52* (0.41 - 0.64)
Care Home Residence	1.20 (0.81 - 1.80)	1.29 (0.83 - 1.99)
Comorbidity	1.05 (0.98 - 1.13)	1.06 (0.98 - 1.14)
Frailty		
Pre-frail	1.56* (1.11 - 2.20)	1.69* (1.16 - 2.45)
Frail	1.90* (1.32 - 2.72)	2.03* (1.37 - 3.01)
Cognitive impairment measure		
MMSE at w1	0.91* (0.89 - 0.94)	
CAMCOG		0.98* (0.97 - 0.98)

MMSE: Mini-Mental State Examination score (0-30 with higher scores indicating better cognition).
CAMCOG: Cambridge Cognition Examination (higher scores indicative of better cognition)

*$p<0.05$ HR (95% CI)

Table 29 Adjusted hazard ratios for survival comparing models with alternative comorbidity variables. Cognitive Function and Ageing Study (CFAS II n=1,154)

Variables	Multivariate Number of comorbidities	Multivariate Individual comorbidities
PIM		
Antipsychotics	3.28* (1.85 - 5.80)	3.58* (1.99 - 6.45)
Tricyclic Antidepressants	1.06 (0.72 - 1.55)	1.16 (0.78 - 1.71)
Anticholinergics	1.17 (0.83 - 1.66)	1.16 (0.82 - 1.64)
Other Antidepressants	0.90 (0.66 - 1.22)	0.89 (0.65 - 1.22)
Benzodiazepines	0.72 (0.45 - 1.16)	0.74 (0.46 - 1.20)
Proton Pump Inhibitor	1.05 (0.86 - 1.30)	1.08 (0.87 - 1.34)
Polypharmacy		
0-4		
5-9	1.17 (0.95 - 1.45)	1.16 (0.93 - 1.45)
10+	1.60* (1.16 - 2.22)	1.59* (1.13 - 2.22)
Covariates		
Age at interview (per year)	1.10* (1.08 - 1.12)	1.11* (1.09 - 1.12)
Gender (female)	0.57* (0.46 - 0.69)	0.62* (0.50 - 0.77)
MMSE score (per point)	0.91* (0.89 - 0.94)	0.92* (0.89 - 0.95)
Care Home Residence	1.20 (0.81 - 1.80)	1.11 (0.74 - 1.68)
Frailty		
frailty = 1, pre-frail	1.56* (1.11 - 2.20)	1.56* (1.10 - 2.21)
frailty = 2, frail	1.90* (1.32 - 2.72)	1.82* (1.26 - 2.62)
Comorbidities		
Number of comorbid health conditions	1.05 (0.98 - 1.13)	
Comorbidities		
Heart attack		1.30 (0.97 - 1.74)
Fits or epilepsy		1.24 (0.70 - 2.21)
Chronic bronchitis		1.18 (0.89 - 1.57)
Asthma		1.09 (0.81 - 1.46)
Parkinson's disease		1.98* (1.01 - 3.87)
Peptic ulcers		1.36 (0.98 - 1.87)
Vitamin B12 deficiency		1.47 (0.95 - 2.27)
Arthritis		0.99 (0.80 - 1.21)
Stroke		1.30* (1.01 - 1.67)
Angina		0.85 (0.64 - 1.12)
High blood pressure		0.80* (0.65 - 0.97)
Cancer		1.17 (0.90 - 1.52)
Diabetes		1.43* (1.10 - 1.85)
Cardiovascular disease		0.68 (0.30 - 1.57)
Depression		0.76 (0.55 - 1.03)

MMSE: Mini-Mental State Examination score (0-30 with higher scores indicating better cognition).
*p<0.05 HR(95% CI)

(d) Frailty Criteria

Adjusting for frailty criteria, operationalised using the lowest quintile, rather than lowest quartile, made no difference to the association of PIMs and polypharmacy with mortality (Table 30). As in the main analyses, being pre-frail and frail remained associated with mortality in univariate and multivariate adjusted models. Fewer people were classified as frail when frailty was operationalised using the lowest quintile (n=373 32.3%), compared to quartile (n=420 36.4%). Marginally more people were classified as pre-frail when frailty was operationalised using the lowest quintile (n=533 46.2%), compared to quartile (n=530 45.9%). More people were classified as not frail when frailty was operationalised using the lowest quintile (n=248 21.5%), compared to quartile (n=204 17.7%).

Table 30 Sensitivity analysis adjusting for frailty operationalised using lowest quintile as in Fried et al., 2001 study.

VARIABLES	Main analysis multivariate model	Sensitivity analysis multivariate model
PIM		
Antipsychotic	3.28*(1.85 - 5.80)	3.29* (1.86 - 5.82)
Tricyclic antidepressant	1.06 (0.72 - 1.55)	1.04 (0.71 - 1.53)
Anticholinergic	1.17 (0.83 - 1.66)	1.20 (0.85 - 1.70)
Other Antidepressants	0.90 (0.66 - 1.22)	0.87 (0.64 - 1.19)
Benzodiazepines	0.72 (0.45 - 1.16)	0.72 (0.45 - 1.16)
PPI	1.05 (0.86 - 1.30)	1.07 (0.87 - 1.31)
Polypharmacy		
5-9	1.17 (0.95 - 1.45)	1.17 (0.94 - 1.45)
10+	1.60* (1.16 - 2.22)	1.59* (1.14 - 2.20)
Covariates		
Age (per year)	1.10* (1.08 - 1.12)	1.10* (1.08 - 1.12)
Gender (female)	0.57* (0.46 - 0.69)	0.58* (0.47 - 0.70)
MMSE score (per point)	0.91* (0.89 - 0.94)	0.91* (0.88 - 0.94)
Care Home Residence	1.20 (0.81 - 1.80)	1.19 (0.80 - 1.77)
Comorbidities	1.05 (0.98 - 1.13)	1.05 (0.99 - 1.13)
Frailty (quartile)		
Not frail (n=204)		
Pre-frail (n=530)	1.56* (1.11 - 2.20)	
Frail (n=420)	1.90* (1.32 - 2.72)	
Frailty (quintile)		
Not frail (n=248)		
Pre-frail (n=533)		1.45* (1.07 - 1.98)
Frail (n=373)		1.83*(1.32 - 2.55)

MMSE: Mini-Mental State Examination score (0-30 with higher scores indicating better cognition).
*p<0.05 HR(95% CI)
n=1,154

7.12 Summary

In the CFAS II subsample analysed, around 28% reported use of PPIs, 10% reported antidepressant medications (excluding tricyclics) around 7% were reported tricyclic antidepressants, 7% reported anticholinergic medications (excluding tricyclics and antipsychotics). Around 4% of the sample reported benzodiazepine use and around 2% reported antipsychotic medications. Reported PIM use was consistently greater among people living in a care or residential home compared to people living in their own home.

Polypharmacy and hyperpolypharmacy were associated with increased risk of mortality. In general, there was no evidence of an association of PIMs with subsequent survival. With the exception of antipsychotic medications, which were associated with increased risk of mortality in unadjusted and adjusted model estimates and across different levels of frailty status.

Frailty was associated with increased medication use and PIM use. The prevalence of antidepressants (excluding tricyclics) in people who were frail was twice as high as in people who were pre-frail. There were twice as many frail people reporting PPIs than people who were not frail. Baseline frailty was independently associated with an increased risk of mortality in both unadjusted and adjusted model estimates. Although there was little evidence of a moderating role of frailty between the majority of PIMs and subsequent mortality. In addition, polypharmacy was associated with the greatest risk of mortality in people who were not frail and hyper-polypharmacy was associated with the greatest risk of mortality in people who were frail, however when tested, there was no evidence of a moderating role.

VIII. Chapter 8: Discussion

8.01 Introduction

The overall aim of this research was to understand the impact of potentially inappropriate prescribing in people with dementia and the effectiveness of existing approaches to improving care in this population. The three key aims of the research were (1) to describe the prevalence of PIMs and polypharmacy among people with dementia, (2) to estimate factors predicting the use of PIMs and polypharmacy, particularly the effect of dementia annual review and medication review, and (3) to understand the impact of PIMs and polypharmacy on the health of older cognitively impaired adults and the impact of frailty on this relationship.

The process of prescribing medicines is multifactorial and involves complex and careful decision making for the prescriber, patient and carer. Polypharmacy and PIMs are prevalent amongst people with dementia and cognitive impairment and there is potential for adverse effects. Optimising medicines in this population is a clinical priority.

In this chapter, first I outline the key findings of my research and then I discuss the findings and methods used to address the aims and objectives of this research and present ways in which these findings may be applied to help optimise medicines among people with dementia.

8.02 Central findings

It was the central aim of my research to understand potentially inappropriate prescribing in people with dementia. My findings from the scoping review of reviews highlighted the breadth of research into polypharmacy and PIMs in older adults but the lack of research into the impact of polypharmacy and PIMs among people with dementia. The optimisation of medications was recognised as a priority across numerous studies included in the review, specifically amongst vulnerable older adults and those with cognitive impairment, who may be at increased risk of adverse effects associated with polypharmacy and PIMs. The scoping review was used to inform the development of the aims and objectives of my CFAS II and CPRD analyses.

(a) Prevalence of polypharmacy and PIM

Prevalence estimates from CFAS II and CPRD were consistent for tricyclic antidepressants and PPIs, with PPIs consistently estimated as the most prevalent PIM (see Table 31). Antipsychotics

were more prevalent in CPRD cohort of people diagnosed with dementia, compared to the less cognitively impaired CFAS II sample. Findings from CPRD estimated that people with diagnosed dementia were prescribed 7.7 medications on average, and 5.5 mean medications in the less cognitively impaired CFAS II subsample.

Prescribing varied across severity of frailty and across care settings. Findings from CFAS II estimated that PIM prevalence was greater in frail, cognitively impaired older adults compared to people who were less frail or not frail. In the CFAS II and CPRD cohort, the prevalence of PIM was consistently higher among patients with dementia who were living in a care home, compared to their own home.

Table 31 Comparative reported and prescribed PIM and mean number of prescribed medications in CFAS II subsample and CPRD cohort

PIM	CFAS II subsample n= 1,154	CPRD Cohort n=22,448
Antipsychotics	2.1 (1.3-3.2)	8.5 (8.4-8.7)
Anticholinergics	6.8 (5.4-8.3)	16.7 (16.5-16.9)
Tricyclic antidepressants	6.8 (5.4-8.4)	7.5 (7.4-7.6)
PPIs	28.6 (26.0-31.3)	31.5 (31.2-31.7)
Mean number of prescribed medications	5.5 (3.6)	7.7 (4.2)

Mean (95% CI); Mean (SD)
Benzodiazepines (CFAS II) 4.2 (3.1-5.6)
CFAS II analysis of anticholinergics excluding tricyclic antidepressants
CFAS II subsample; cognitively impaired participants
CPRD; patients with dementia diagnosis

(b) Factors associated with polypharmacy and PIMs

(i) Medication review and dementia annual review

The scoping review of reviews indicated that further research was required to evaluate the effect of interventions to minimise PIM use, particularly outside of clinical trial settings to evaluate the effect of interventions in practice [131, 133, 169, 172, 176, 182, 289]. My CPRD cohort analysis suggested that when a medication review takes place in primary care, most of the PIMs analysed were more likely to be stopped in patients with dementia who were prescribed them. With the exception of antipsychotics, where there was no difference associated with a medication review or not. Comparatively, a medication review was also associated with increased prescribing of anticholinergics, antipsychotics and tricyclic antidepressants in patients who were not currently prescribed these PIM. My analysis also suggested that a record of a dementia annual review was associated with less stopping and also less starting of all PIM that were analysed.

In the CPRD cohort PIM prescriptions were higher in care homes and living in a care home was associated with greater likelihood of starting a PIM. However, when a medication review took place for a patient who was living in a care home, the review was associated with more stopping of PIM.

(ii) Patient factors associated with polypharmacy and PIM

My scoping review also suggested that further research was needed to verify risk factors for PIM use [160, 290]. The findings from the CPRD cohort suggested that there were a number of patient characteristics associated with both starting and stopping PIMs. Although, given that there were multiple hypotheses tested, there remains a possibility that there are some false positive results.

Being older was associated with less new prescriptions of antipsychotics, anticholinergics and long-term PPIs. However, in patients with dementia who were already prescribed antipsychotics and long-term PPI, being older was also associated with less stopping of these PIMs. Female patients with dementia were less likely to stop long-term PPIs, tricyclic antidepressants and antipsychotic medications than male patients with dementia. Multimorbidity was also associated with increased new prescribing of long-term PPI and tricyclic antidepressants. In addition, multimorbidity was associated with more stopping of long-term PPI and antipsychotic

medications. Being prescribed 5 or more medications was consistently associated with reduced stopping and greater likelihood of starting PIM in patients with a dementia diagnosis.

(c) Understanding the impact of PIM on health

The CFAS II analysis suggested that the use of 5 or more medications was associated with an increased risk of mortality in cognitively impaired older adults. Polypharmacy and hyperpolypharmacy remained associated with mortality risk after adjustment for covariates. Hyperpolypharmacy was associated with the greatest risk of mortality in cognitively impaired older adults. With the exception of antipsychotic medications, PIMs were not associated with mortality. Antipsychotic medications were associated with increased risk of mortality in adjusted models and for all levels of frailty.

(i) Frailty

Frailty was independently associated with mortality in older cognitively impaired adults from the CFAS II cohort, although frailty did not moderate the association between polypharmacy or PIMs and mortality. The results did suggest that frailty attenuates the risk of mortality associated with benzodiazepine use, however given the small number of deaths that occurred across levels of frailty, it is difficult to draw conclusions from this finding. In stratified analyses, frailer people with hyperpolypharmacy were at the greatest risk of mortality, however relative risk of mortality associated with polypharmacy was greatest among people who were not frail.

My findings from the CFAS II cohort partially supported the validity of the frailty phenotype in predicting risk of adverse outcomes among people with cognitive impairment. Slowness, was the only phenotype criterion to independently predict mortality and there was no evidence that the remaining criterion were predictive of adverse outcomes.

(d) The key findings of my research

- People with dementia and cognitive impairment are exposed to polypharmacy and PIMs.

- Polypharmacy and PIM use among people with dementia is greater in care homes.

- Polypharmacy and PIM prescriptions are more prevalent in people who are frail.

- In general, PIMs are not associated with increased risk of mortality in people with cognitive impairment, with the exception of antipsychotic medications.

- Polypharmacy was associated with increased risk of mortality in cognitively impaired older adults and particular attention should be given to reducing the overall number of medications prescribed to reduce potential for harm.

- Medication reviews used in primary care and in care homes are effective tools for identifying and reducing exposure to PIMs.

- Around half of all patients with dementia in primary care receive a dementia annual review.

- Dementia annual review was associated with less starting and less stopping of PIM.

- Frailty was independently predictive of mortality but is not predictive of vulnerability to another risk factor, such as potentially inappropriate prescribing. Hence, frailty as operationalised by the Fried criteria does not provide a way to identify those more susceptible to polypharmacy.

8.03 Discussion of key findings

Prevalence of PIMs and polypharmacy in people with dementia

My findings showed that the use of PIMs was prevalent in people with cognitive impairment and people with dementia, with around 40% (95% CI 37.8-43.5) of people with cognitive impairment reported at least one PIM. These findings are comparable to some previous research and present a picture of a population at risk of high levels of exposure to PIMs. A previous study of PIM prescriptions amongst people with dementia in the UK estimated 29% of people with dementia were prescribed at least one PIM [291]. A systematic review of PIM in people with cognitive impairment and dementia found that prevalence was estimated between 20% and 56% [142]. Although, it remains unclear whether cognitive impairment is consistently associated with greater risk of PIM use as previous studies have also estimated a lower likelihood of PIM in people with cognitive impairment [142].

Similarly to the findings from my research, different care settings are associated with differences in PIM prevalence. My findings showed a greater prevalence of PIM in care homes and although I did not estimate prevalence in hospital settings, previous studies have found that PIM prevalence is often, but not consistently, higher among people with cognitive impairment (39% to 88%) compared to people without (20% to 63%) [292]. Estimates from the RightTimePlaceCare (RTPC) study across 8 European countries also estimated a high prevalence of PIM according to the European Union(7)-PIM list, with 60% of participants with dementia prescribed at least one PIM [193]. However, the RTPC study is representative of a cohort distinct from the CFAS II as the CFAS subsample was predominantly people with cognitive impairment living in the community. The higher prevalence of PIM in the RTPC study likely represents more severe cognitive and physical impairment, as this sample was characterised by people recently admitted to long-term care or at risk of admission within 6 months.

The high prevalence of PIM amongst the CFAS II subsample could reflect changes in prescribing around the time of a dementia diagnosis. My CFAS II analysis was conducted in a sample characterised by significant cognitive impairment, a common symptom of prodromal stages of dementia. Previous studies have found that the diagnostic process for dementia is associated with an increase in total medication use and PIMs and this increase varied by dementia sub-type. Previous studies found that total medication use increased by 10% in the first year following incident Alzheimer's disease diagnoses and by 15% for people with Lewy body dementia. Use of

anticholinergic medications increased by 39% in the first year following diagnosis, among people with Lewy body dementia [293]. However, in a recent study comparing PIM prescription around dementia diagnosis with matched controls, total medication use and exposure to PIMs increased within the year leading to and the year after diagnosis. However, PIM use also increased in matched controls across the same period, meaning that people both with and without dementia were increasingly exposed to PIMs overtime [294]. In summary, while PIM prevalence appeared to be high amongst the CFAS sample, this is comparable to previous estimates and may reflect prescribing across the dementia diagnosis process. However, previous studies also suggest that it may reflect a pattern of high exposure to PIMs across the older population rather than a trend specific to cognitive impairment and dementia diagnosis.

(a) Proton Pump Inhibitors

My findings consistently found PPIs as the most prevalent PIM across the two cohorts. In my analyses, 28% (95% CI 26.0-31.2) were prescribed PPIs in CFAS II and 32% (95% CI 30.0-31.7) of people with dementia in CPRD. It is unsurprising that PPIs were the most prevalent PIM across the two cohorts. PPIs are one of the most commonly prescribed medications to older adults and are often cited amongst the most commonly prescribed PIMs [189, 193, 291]. In one observational study, 23% of people with dementia in the Northern Ireland primary care prescribing study were prescribing potentially inappropriate PPIs [189]. Similar estimates have been found across Europe with 19% prevalence of PPI in the RightTimePlaceCare study [193]. The lower prevalence estimates can likely be explained by differences in estimating inappropriate PPI use because therapeutic dose was not accounted for in the analyses employed in this research. Previous studies have also found that that 26% of people prescribed PPI are continually prescribed for over 1 year, despite limited evidence of long-term efficacy and safety [242]. Given that PPIs are generally considered safe and effective, it is possible that heuristics play a key role in individual cognitive decision making processes around when to continuing to prescribe. Heuristics make decision making processes easier and are often associated with intuition and previous experience and with appropriate decision making. However, this can also lead to biases and affect the individuals subjective interpretation of evidence that is contrary to the status quo [295]. The evidence for adverse effects associated with PPIs is largely limited to observational studies and the risk to benefit considerations may weigh predominantly in favour of the perceived benefits.

However, there is a considerable economic argument for reducing unnecessary prescriptions, of which PPIs may be considered if they continue to be prescribed beyond the point of clinical benefit. The prescription of PPIs is costing the NHS over £100 million annually and PPIs may be unnecessarily adding to medication burden and increasing polypharmacy in many patients [244]. Deprescribing guidelines have recently been developed based on evidence that PPI are suitable targets for deprescribing, through processes of reducing dose, prescribing to be used as needed or stopping the prescription all together [296]. This is not to say that PPIs should always be deprescribed. PPIs should be prescribed as required, for as long as needed. Previous studies have estimated around 60% of older adults prescribed PPIs should be considered for deprescribing, with 20% prescribed PPIs without a clear indication [297]. PPIs should be reviewed and the process of deprescribing considered, with the individual priorities and decision-making incorporated. PPIs may be a suitable target for deprescribing in people with dementia to reduce overall medication burden and overall prevalence of PIMs in this population.

(b) Anticholinergics

Despite the known evidence for adverse effects, particularly amongst people with cognitive impairment, my findings estimated that one fifth of people with dementia in England are prescribed anticholinergic medications (17% 95% CI 16.5-17.7) [225]. These prevalence estimates are also comparable to previous estimates of anticholinergic drug use amongst people with dementia in different populations. A US sample of community dwelling people with dementia from the Medical Expenditure Panel Surveys (MEPS) estimated 23% of people with dementia were prescribed level 2 or 3 anticholinergic drugs according to the anticholinergic drug scale (ADS) [298]. Whilst estimates are not directly comparable due to differences in populations and anticholinergic drug scale used, previous studies comparing estimates between ACB and ADS scales have found little difference in the results depending on the scale use [223]. Similarly, cross-sectional estimates from US Medical Expenditure Panel Survey participants (2009-2010) estimated 27% prevalence of anticholinergic medication use amongst people with dementia [299]. In addition, estimates of anticholinergic use amongst people with dementia living in care homes was comparatively lower (19% 95% CI 18.0-20.3) in this cohort compared to other studies. Previous studies have estimated that 31% of people with dementia living in a nursing home were prescribed anticholinergic medications [300]. Differences in estimates may be reflective of variation in prescribing practices in the UK and US. The slightly lower prevalence estimates in my

study could also represent a greater awareness of adverse cognitive effects in people with dementia and recent initiatives to reduce exposure of anticholinergic medicines in people with dementia [231]. However, there is established evidence of adverse cognitive effects associated with anticholinergics and anticholinergics are consistently included in PIM criteria [225, 277]. Reducing exposure to anticholinergics should be a priority. Recent evidence from a clinical trial in residential homes in New Zealand indicates that deprescribing of anticholinergics is acceptable to patients and associated with improved outcomes on frailty, falls and adverse drug reaction outcomes that were evident at 6 months post-intervention [301].

(c) Polypharmacy and PIMs in care homes

Across both cohorts, polypharmacy and PIMs were more prevalent amongst people who were living in a care home. In CPRD, people with dementia living in a care home were taking 8.5 medications, compared to 7.3 in the community. Previous studies have estimated that advanced dementia in care homes is associated with hyperpolypharmacy. One study estimated that people with advanced dementia were receiving 14 different medications on average [302]. The presence of advanced dementia may be associated with greater medication use as symptoms become more complex, which may explain my finding that prevalence is greater in care homes, which are more likely to include people at later stages of the disease. However more conservative estimates have been observed in other studies. In the Services and Health for Elderly in Long Term Care (SHELTER) study from 1,449 residents across 57 nursing homes in eight countries, the mean number of prescribed drugs was 6 for residents with severe cognitive impairment [303]. Variation between the findings from the SHELTER study and the results in this thesis are likely accounted for by different ways in which total number of prescribed medicines are measured, including self-report or patient records and the decision to include or exclude over the counter medicines. In the CFAS II cohort, it is possible that medications recorded as part of the CFAS interview were more reliably reported in care homes as reported medications were either provided by care home staff or were cross-checked with medication records. It is interesting that prescribing practices vary across different care settings and ought to be considered when understanding prescribing in a people with dementia because they are cared for across a range of settings. However, it is somewhat unsurprising that medication use was found to be greater in care homes as people living in care homes are often more frail, multimorbid and living at more severe stages of the disease.

8.04 Adverse effects of PIM and polypharmacy

(a) Antipsychotics

The findings from my CFAS II analysis suggest that antipsychotic medications should continue to be prescribed with caution in people with cognitive impairment and dementia. The results showed that antipsychotics were the only PIM associated with mortality. This finding is consistent with a large body of literature into the adverse effects of antipsychotics in people with dementia [304]. My findings are important because they add to this body of literature by demonstrating the potential for adverse effects in people with cognitive impairment too.

In response to the building evidence of serious adverse effects, the practice of prescribing antipsychotics to people with dementia has changed over recent years and there has been a cultural shift in attitudes towards antipsychotic prescribing in this population in primary care. A previous study by Martinez et al, (2013) of people with dementia in UK primary care (1995-2011) estimated that antipsychotic prescribing had decreased from 12.5% in 1995 to 7.4% in 2011 [204], similar to my finding of 8% (95% CI 7.3-8.7) prevalence in people with dementia in primary care in April 2017. However, estimates in the Martinez et al (2013) study were at the first recording of a dementia medications which are more commonly prescribed at the point of diagnosis for managing symptoms in mild-moderate stages of the disease and are not indicated in severe dementia. Therefore this may underestimate the prevalence of antipsychotics at later stages of the disease.

Moreover, contrary to the observed decrease in primary care, my findings consistently estimated greater exposure to antipsychotics in care homes. A study estimating prevalence of antipsychotic use in care homes before and after the launch of the National Dementia Strategy in 2009 found no significant difference in antipsychotic prescribing in care homes across a 4 year period [305]. People who are living in care homes may be more physically and cognitively impaired and behavioural and psychological symptoms of dementia can be more severe. Antipsychotics may be prescribed to manage behaviours in this context however, the potential for serious adverse effects should still be considered and discussed with the patient and family when possible. Recommendations to regularly review antipsychotics were incorporated into the National Dementia Strategy in 2009 [306] and despite national initiatives to reduce exposure to antipsychotics in people with dementia, their use is still prevalent in care homes. The findings

from this thesis indicate that risk of adverse effects of antipsychotics should also be carefully considered in people with severe cognitive impairment, regardless of dementia diagnosis and particularly amongst people living in care homes who may be at greater risk of exposure to inappropriate antipsychotic use.

(b) Benzodiazepines

In the findings from my CFAS II analysis, it was surprising to observe that benzodiazepines were not associated with mortality in this sample, which was contrary to what I had expected to find, given the existing evidence base. A number of previous studies have reported higher risk of mortality in people who are prescribed benzodiazepines. In one large retrospective cohort study of over 34,000 people with a first prescription of an anxiolytic and hypnotic medication, use was associated with mortality. There was evidence of a dose response relationship and the risk was greatest in the first year after initial prescription [307]. Moreover, a systematic review and meta-analyses of 25 observational studies estimated a 43% higher risk of mortality in users of anxiolytic and hypnotic drugs. However, the evidence is not always consistent and there have been contradictory findings observed in other studies [308]. The quality of previous studies has often been limited by the failure to appropriately adjust for important confounders such as depression [309].

A plausible explanation for the difference in my findings compared to some of the previous literature is that the users of benzodiazepines in my CFAS II sample are likely to be representative of prevalent benzodiazepine users, rather than newly initiated users of the drug. In CFAS II, medication data was collected at baseline interview and my findings suggest that use was long-term, with 60% of people who reported taking PIM at baseline also reporting PIMs at the two-year follow-up. Including prevalent users of drugs may introduce survivor bias, particularly in studies when the risk varies with time, such as the risk of falls in benzodiazepine users is greatest around the initiation of the drug. Therefore the sample of prevalent drug users have already 'survived' the higher risk period associated with the initiation of a new benzodiazepine prescription [310]. Similarly, the CFAS II sample of prevalent users may include fewer people who experience adverse effects associated with the drug as it is more likely that there is early attrition amongst people who stop taking the drug early on if they are experiencing adverse effects [311].

Compared to prevalent user study designs, new-user study designs are more comparable to the intervention element of a RCT, as the cohort is sampled based on the initiation of a prescription of a drug (i.e. the intervention) [312]. The participants in previous studies were incident benzodiazepine users (new-users) and enter the study at the point when the prescription is given [307]. New-user designs are argued by some to alleviate some of the biases that are inherit in prevalent user study designs [313]. Moreover, in some cases it has even been argued that prevalent users should be excluded from pharmacoepidemiologic studies because of the inherent bias associated with prevalent user-designs [310]. However, studies of prevalent users answer different questions to studies of incident users. Careful consideration of prevalent or new-user study design and adjustment of covariates is required when interpreting pharmacoepidemiologic studies. My findings therefore may be representative of prevalent users of benzodiazepines in the CFAS II sample, who are introducing survivor bias into the estimates, are able to tolerate the drug and are less susceptible to adverse effects of benzodiazepines. Therefore, the different study designs are asking different research questions of different populations. In new users of benzodiazepines, risk may be greater but in prevalent users, their use may not be associated with such harm.

(c) Mortality associated with polypharmacy

The results from my CFAS II analyses indicated an increased risk of mortality associated with polypharmacy in older, cognitively impaired adults. These findings are comparable to previous studies, including a meta-analysis of pooled estimates from a number of studies analysing polypharmacy and mortality. This review also found an increased risk associated with the number of medications prescribed and a dose response relationship across categorical polypharmacy thresholds [314]. Residual confounding associated with poor adjustment for indications and comorbidities is recognised as a possibility across studies of medication use. However, my analyses adjusted for all available comorbidities, frailty and use of other medications to reduce the implications of residual confounding on the results. My findings are similar to those found in reviews of studies that have accounted for the quality of adjustment for comorbidities and polypharmacy remained associated with mortality, hospitalisation, adverse drug events and falls [315]. Recent studies have sought to further delineate the association between polypharmacy and mortality by using propensity score matching. This study found that when propensity score matching was used, hazard ratios attenuated some of the association (HR 1.26 95% CI 0.70-2.28)

compared with adjusting for a comorbidity index (HR 2.01 95% CI 1.15-3.51) [316]. My findings suggest that careful consideration should be afforded to the number of medicines prescribed and whilst these findings add to the literature in this area, future studies may benefit from further understanding the role of propensity score matching in adjusting for confounding by indication to further understand the association between polypharmacy and mortality.

My results suggested that the adverse effect associated with polypharmacy was observed regardless of exclusion of PIMs. Previous studies have also found that polypharmacy but not PIM criteria was predictive of functional status decline [150]. Polypharmacy may be a more suitable marker of the quality of prescribing and prediction of some adverse effects than PIM criteria. Moreover, PIM criteria do not account for the potential serious adverse effects of polypharmacy and hyper-polypharmacy in older adults [107, 277]. Consideration of the evidence of harm associated with polypharmacy ought to be accounted for in PIM criteria, like clinical practice guidelines that recommend regular medication review, in older adults with polypharmacy [108].

8.05   Moderating role of frailty

In this novel investigation of frailty and PIM use in people with cognitive impairment, frailty was a marker of mortality, as expected, but was not found to identify susceptibility to adverse effects associated with another risk factor (polypharmacy or PIM). The level of excess risk associated with antipsychotics, for example was similar regardless of frailty. The results from stratified analyses did suggest that whilst hyperpolypharmacy was associated with the greatest risk of mortality in people who were frail, polypharmacy was associated with greatest risk in people who were not frail. However, there was no significant evidence of a moderating role of frailty in my analysis. The role of frailty in understanding susceptibility to another risk factor is not clear and frailty may not be a useful marker for identifying people at greatest risk of harm associated with polypharmacy or PIM. Previous studies in older adults have also found that polypharmacy and use of sedative and anticholinergic medications was associated with the greatest risk of death in people who were not frail. Additionally, in previous studies there was no association between medication use and transitions across levels of frailty and death [317]. In a study of delirium in hospital admissions, mortality risk associated with delirium was particularly high amongst fitter individuals [196]. A recent pathology analysis of participants from the Rush Memory and Ageing Project suggested that frailty (measured using the Frailty Index) moderated the relationship between Alzheimer's

disease pathology and dementia (diagnosis of Alzheimer's disease or not) [318]. Although there was some evidence of a moderating role of frailty, this was associated with the presence of dementia diagnosis or not, however whether the relationship with frailty was incrementally associated with the severity of cognitive impairment in people with dementia was not assessed. The potential moderating role of frailty and the utility of frailty as a predictor of vulnerability to the adverse effects of another risk factor is not well established and requires further investigation, because the identification of vulnerability is such a key claim of the benefit of frailty measures.

My findings showed some evidence that the least frail group of people with polypharmacy were at increased risk of mortality (compared to people who were not frail and without polypharmacy). This finding may understood by considering the sample, who are cognitively impaired and may therefore be inherently living with a underlying level of frailty that is not accounted for in the Fried frailty classification [47]. Therefore the sample may be living with an underlying level of vulnerability to the adverse effects of polypharmacy, regardless of frailty. Interestingly, similar findings have been seen in previous studies involving samples with an inherit and underlying level of vulnerability to adverse outcomes, such as older, multimorbid adults. Previous studies in older adults have found that people who are frail with hyperpolypharmacy were six times more likely to die during follow-up, compared to people who were not frail and without polypharmacy [198]. However in this study of community dwelling older adults in France (n=2,350), the study findings were also comparable to my results as the risk of mortality amongst non-frail people with hyperpolypharmacy was greater than the risk in people who were more frail. However, in a study of hospitalised older adults, where an underlying level of vulnerability may be expected, there was no evidence of an effect in people who were the least frail. Moreover, it was estimated that the least frail group with hyperpolypharmacy were least likely to experience adverse outcomes [319]. In addition, in a Spanish cohort (Frailty and Dependence in Albacete study), participants were grouped according to frailty and polypharmacy status and estimated that people who were frail with polypharmacy had five times greater odds of mortality or disability, compared to people without frailty and without polypharmacy [122]. However, around one third of this cohort were hospitalised during follow-up and may therefore be representative of a cohort with high baseline vulnerability to adverse effects. As my findings suggest, the relationship between frailty, polypharmacy and mortality is complex and there is no evidence of a linear relationship. In addition, it is difficult to make comparisons across studies due to lack of consistency in approach to operationalising frailty, including failing to objectively measure slowness and strength. [198]. Furthermore, whether the population includes people with dementia clearly impacts on findings,

as dementia may overshadow prescribing decisions and outcomes in many cases [320]. Therefore, these findings suggest that whilst frailty is a useful way to identify sub-groups of the older population who are particularly vulnerable to adverse effects, frailty is not necessarily a viable tool for identifying people who are at risk of adverse effects associated with potentially inappropriate prescribing.

(a) Predictive validity of frailty phenotype

Applying the frailty phenotype criteria among people with dementia may not be the optimal way to identify those at risk, particularly when the evidence suggests that individual criteria are not consistently associated with adverse outcomes. The findings from my study showed that slowness, as measured by the gait speed test, was the only frailty criterion independently associated with the outcome of mortality. These findings are consistent with previous studies assessing the prognostic value of frailty criteria which also found that individual frailty criteria were not consistently associated with adverse effects. Another study also found that in adjusted models, slowness was the strongest predictor of disability and falls [54]. Slow gait could be considered a reflection of a range of physiological processes, comorbidity, and effect of medications, loss of strength and endurance, exhaustion and low mood. However, this study also found that low physical activity and weight loss were associated with disability, nursing home stay and mortality [54]. My unadjusted analyses of the CFAS II sample were comparable and low physical activity was associated with mortality but there was no evidence of the association of weight loss with mortality in my findings. The difference may be explained by the operationalising of the weight loss criteria, which in CFAS II was a self-reported unintentional weight loss 4.5kg (10lbs) or more in previous six months or less. In the original operationalisation of the Fried frailty criteria [47], weight loss was estimated over one year rather than six months. This could mean that the number of people who were impaired on the weight loss criteria may be underestimated in the CFAS II sample analysis.

As part of the GP contracts and recommendations from NICE [78], it is a requirement that frailty is assessed in older people. Understanding frailty is considered a clinical priority but in practice a frailty assessment will vary considerably between practices and practitioners and there is limited standardisation of frailty assessment in practice [321]. Resource and time constraints will invariably impact upon the comprehensiveness of frailty assessments used in practice [322]. My findings support previous studies that suggest that the gait speed test is a simple and valid initial

indicator of frailty and vulnerability to adverse effects [323]. However, detailed assessment as part of a comprehensive geriatric assessment may be important in identifying factors that are contributing to frailty and where interventions may be possible [324].

8.06 Interventions to optimise prescribing in people with dementia

(a) Effectiveness of medication review and dementia annual review on PIMs

My findings show that a record of a medication review was associated with reducing the prescription of PIMs in people with dementia in primary care in England. Medication review was also associated with increased newly prescribed PIMs. This finding somewhat corroborates with a number of reviews of intervention studies that were included in the scoping review of the literature, which found that medication review was commonly used and was effective in reducing PIMs across a range of clinical trial intervention studies [134, 173, 325]. To my knowledge, this is the first study of the impact of medication review outside of a clinical trial and reflecting real-world clinical practice. In practice, medication reviews were associated with stopping PIMs in patients who were already prescribed them. However, medication reviews were also associated with initiating new PIM prescriptions. Guidelines from NICE recommend medication reviews to patients with polypharmacy and my findings indicate some effectiveness of these reviews [78]. My findings also indicate that further awareness of PIMs in people with dementia is needed among some prescribers to improve prescribing quality.

The purpose of a comprehensive medication review is to critically consider the safety, efficacy and acceptability of medicines with the aim of optimising medications [78]. The individual's preferences, beliefs, values and goals should also be accounted for in prescribing decisions. A dementia annual review should take place in primary care but there are no stipulations as to who would conduct the review in practice [111][112]. The current QOF dementia annual review does not stipulate a medication review is required, however the review clearly represents an opportunity for a comprehensive assessment of the patient, which should include a review of medications to manage symptoms of dementia and comorbidities, if necessary. Guidelines from NICE suggest that medications should be reviewed regularly in people who are prescribed multiple medications or prescribed medications for long-term conditions [108, 109]. Given the potential for adverse effects associated with PIMs and polypharmacy in people with dementia, optimising medicines should continue to be a public health priority in this population. Medication

management can be challenging and complex for people with dementia [326]. Previous qualitative studies highlight the integral role carers play in medicines management, which can provide a number of challenges including a sense of responsibility for adherence [38] The incorporation of a medication review into a dementia annual review could improve standardisation of practice in the regular review of medicines in this population, which may reduce overall treatment burden if medications that are no longer indicated are deprescribed and reduce the potential for adverse effects.

My findings showed that a medication review was associated with deprescribing of anticholinergics, tricyclics and long-term PPIs amongst people with dementia in primary care in England. These findings indicate that PIMs are being identified and stopped, although medication review was also associated with newly prescribed PIMs, which indicates a review may also recommend an appropriately required medication. While medication reviews may be effective in reducing PIM use and does not increase adverse withdrawal events [173], the impact of reviews on subsequent health outcomes, such as adverse drug events [129], hospitalisation [169], quality of life, physical functioning [173] or medication costs [129], is not well established. My findings also indicate that it may not be PIMs per se that are the issue but that polypharmacy may be associated with more harm, which may explain why there is limited evidence for the subsequent benefits of deprescribing PIMs.

The results from my analyses suggested that whilst care home residence was associated with greater medicines use in both cohorts, the results from the CPRD cohort suggested that living in a care home was associated with improved management of potentially inappropriate medicines. This was evident when there was a medication review for a patient living in a care home. Antipsychotics were more than twice as prevalent in people with dementia in a care home (14%) compared to those living in the community (6%). However, the results showed that when a medication review was recorded in a care home, the likelihood of an antipsychotic (and all PIMs) being stopped was significantly increased (association of medication review with stopping antipsychotic in care home OR 1.45 95% CI 1.09-1.94) compared to patients in their own home (OR 0.86 95% CI 0.67-1.10) (see Table 14). This finding may be an example of how the populations and prescribing in care homes, compared to people in primary care, varies and should be accounted for in studies. As care home residents have access to regular care, the opportunities for effectively monitoring medications may be greater than for those with dementia living alone in the community. Previous studies have recognised that incorporating a specialist practitioner, such as a geriatrician or pharmacist into nursing home staff is associated with medicines

optimisation in care homes [303]. However, the resource costs associated with this would be extensive and the practical application of this may be limited in reality. Further training opportunities and access to deprescribing resources for nurses and care providers to recognise potential medication-related adverse effects which are flagged for review with the residents GP may be a more feasible alternative for future research to investigate [327, 328].

(b) Incentivising the quality of health care

My findings suggested that a dementia annual review may be associated with changes in the prescription of PIMs, which could be indicative of the reviews being associated with optimisation of medicines in people with dementia. However, my findings also found that less than half of all patients had a record of a review across the study period. It is difficult to ascertain the true quality of the QOF reviews conducted in primary care and there is evidence to suggest the quality is below the expected standard set by QOF [113] [263]. Moreover, previous studies also suggest that the quality of care lacks standardisation across people with dementia and there are inequalities in care provision compared to people without dementia [263]. A dementia review is intended to be a holistic process and there may be gains for a person with dementia and their carer that are not medication related. However, because the quality and content of the reviews is not accounted for in QOF scorings, there is no guarantee that the areas expected within the review are taking place. The quality of holistic indicators like the dementia annual review ought to be accounted for in QOF scorings. Moreover, given the key opportunity an annual review presents, future studies should evaluate the effectiveness of the inclusion of a medication review in the optimisation of medicines for people with dementia.

The QOF has been a contentious issue since its inception in 2004 with mixed evidence for its effectiveness and impact on increasing workloads. While standardisation of care provision across primary care practices levelled and there was an initial modest improvement in care, reaching quality markers for many long-term conditions hit a ceiling effect soon after [329, 330]. In addition, there is evidence that the quality of care for non-incentivised conditions was negatively affected and the system is often viewed as a 'tick-box' exercise, increasing workloads and reducing opportunities for patient-centred, individualised care [331]. In 2017 QOF in England underwent a considerable review [332] and QOF in English primary care practices is evolving in response to the findings and feedback from practitioners. From 2019, QOF will now also include Quality Improvement modules that will change each year and for 2019/2020 this will include two

modules on prescribing safety and end of life care. The findings from my research are timely as medicines optimisation is prioritised across practice, the overprescribing of medicines is reviewed in the NHS, and role of clinical pharmacists in primary care is expanded.

8.07   Understanding potentially inappropriate prescribing in people with dementia

My findings indicate a number of associated factors that help in understanding how and why potentially inappropriate medications are prescribed to people with dementia, despite the known adverse effects. Over the course of the research I've have completed, the findings from my studies, alongside the existing literature, collectively present a vast and complex set of factors that are associated with prescribing. Specifically, my findings have identified that age, gender, cognitive impairment, frailty, comorbidities, and polypharmacy, living in a care home, prescribing in primary care, medication reviews and dementia annual reviews are all factors associated with prescribing in people with dementia. In order to interpret and discuss the complex and multifactorial processes associated with prescribing in people with dementia, I applied an established model of health service use, The Andersen Behavioural Model, to my findings [333, 334].

Under the Andersen Behavioural Model of health service use [333, 334], there are predisposing, enabling and need factors that are associated with access to and use of services (Figure 30 Model 1). My findings apply this model to understand potentially inappropriate prescribing in people with dementia. The results have shown that there are additional factors particular to the experience of people with dementia that are important in this process (Figure 30 Model 2). The model shows factors that have been identified from my findings, and other relevant factors from the existing literature. My results have shown that age, frailty, cognitive impairment, comorbidities and living situation are influential factors that may predispose individual exposure to polypharmacy or PIMs. If this model is applied to these findings, with the outcome identified as a dementia annual review or prescribing as the provided health care service, it is clear from my research that there are many factors that influence provision of services to patients. Moreover, there are factors that are unique to prescribing to people with dementia. These are additional factors that need to be considered when understanding the process of prescribing in this population. Other factors include frailty and care home residence, as my findings showed that people who were frail, and people with dementia who were living in care homes were prescribed more PIM and were taking more medications on average. Previous literature has

also identified other factors that are influential in the process of prescribing in people with dementia, including medication adherence. Cognitive impairment has previously been associated with up to 60% non-adherence to medication regimes [91]. Non-adherence will make managing the potential for side effects of medications more complicated for prescribers, if they are uncertain about the level of adherence to the prescribed medication regime. Prescribers need to understand their patients holistically, with all available information from the patient or from their carer and consider these factors when prescribing, deprescribing or managing polypharmacy.

My findings also demonstrated the potential for medication review to reduce PIMs. The model is useful in understanding the range of factors that may also be at play when a medication review is requested and completed in primary care. As the model suggests (Figure 30, Model 2), there are also a number of factors associated with the prescriber that influence the evaluated need around prescribing decisions. Previous studies have identified that individual factors such as prescriber experience and confidence are influential in the individual prescribing decisions for general practitioners prescribing to complex, multimorbid patients, for example [335]. In addition, my findings indicated that top-down regulatory practices such as recommendations for medication review from NICE guidelines [108] and the QOF dementia annual review [111][112] may influence the prescribers evaluated needs around prescribing decisions. By incorporating medication review into QOF incentivised dementia annual review, reviews of medications in a population vulnerable to serious adverse effects of PIMs could reduce the exposure to potential for harm. Moreover, improve standardisation of prescribing practice and reviews across primary care practices, if appropriately accounted for in QOF scoring systems.

Furthermore, previous qualitative studies involving people with dementia and their carers have highlighted that the role of managing medicines often shifts from the individual, as carers of people with dementia will often take responsibility for managing medications. Medication management can add challenges to the caring role and increase emotional load, particularly as the disease progresses alongside more complex medication regimes [38]. Carers are integral enabling factors in managing medicines. Their role should also be considered in dementia annual reviews. To ensure carers are well-supported, and the views, beliefs and goals of care for the individual with dementia and their carer are accounted for (Figure 30 Model 2).

8.08   Deprescribing

The process of withdrawal and dose reduction of medicines is known as deprescribing and involves the consideration of the risk and benefits of individual medicines and the cumulative risk associated with the use of multiple medicines [336]. Optimising medicines can be additionally challenging among people with dementia because of changes in decision making, communication, cognitive capacity and increased carer involvement across disease progression [38, 337]. A lack of guidelines and training in deprescribing as an integral element of the prescribing process can also impede prescribers. Recent development of evidence-based deprescribing guidelines should progressively enhance the opportunities and support for deprescribing. Using deprescribing patient handouts and pharmacist and GP education materials has supported 30% deprescribing of chronic benzodiazepines through patient education (compared with 5% in the control group) and 43% deprescribing (12% in control group) in practitioner education in studies from the Canadian Deprescribing Network [338, 339]. Future developments are also expected within the UK as the English Deprescribing Network launches in 2019 [340]. The process of prescribing occurs across drug initiation, monitoring, adjustments and reviews and should also include evidence-based support for deprescribing medicines. For older adults and people with dementia this is a priority given their increased susceptibility to adverse effects and the change in the benefits to harm ratio across physiological and cognitive decline. A medication review and dementia annual review may be enhanced with the support of guidelines to deprescribe in primary care and previous research suggests that patients can also be educated about the options for deprescribing. Further research is needed to understand the impact of deprescribing guidelines and education on people with dementia and their carers.

Model 1: Andersen Behavioural Model

Model 2: Andersen Behavioural Model applied to findings from scoping review, CFAS II subsample analyses and CPRD analyses. The factors that have been evidenced through my research are distinctly identified from those which exist within the wider literature.
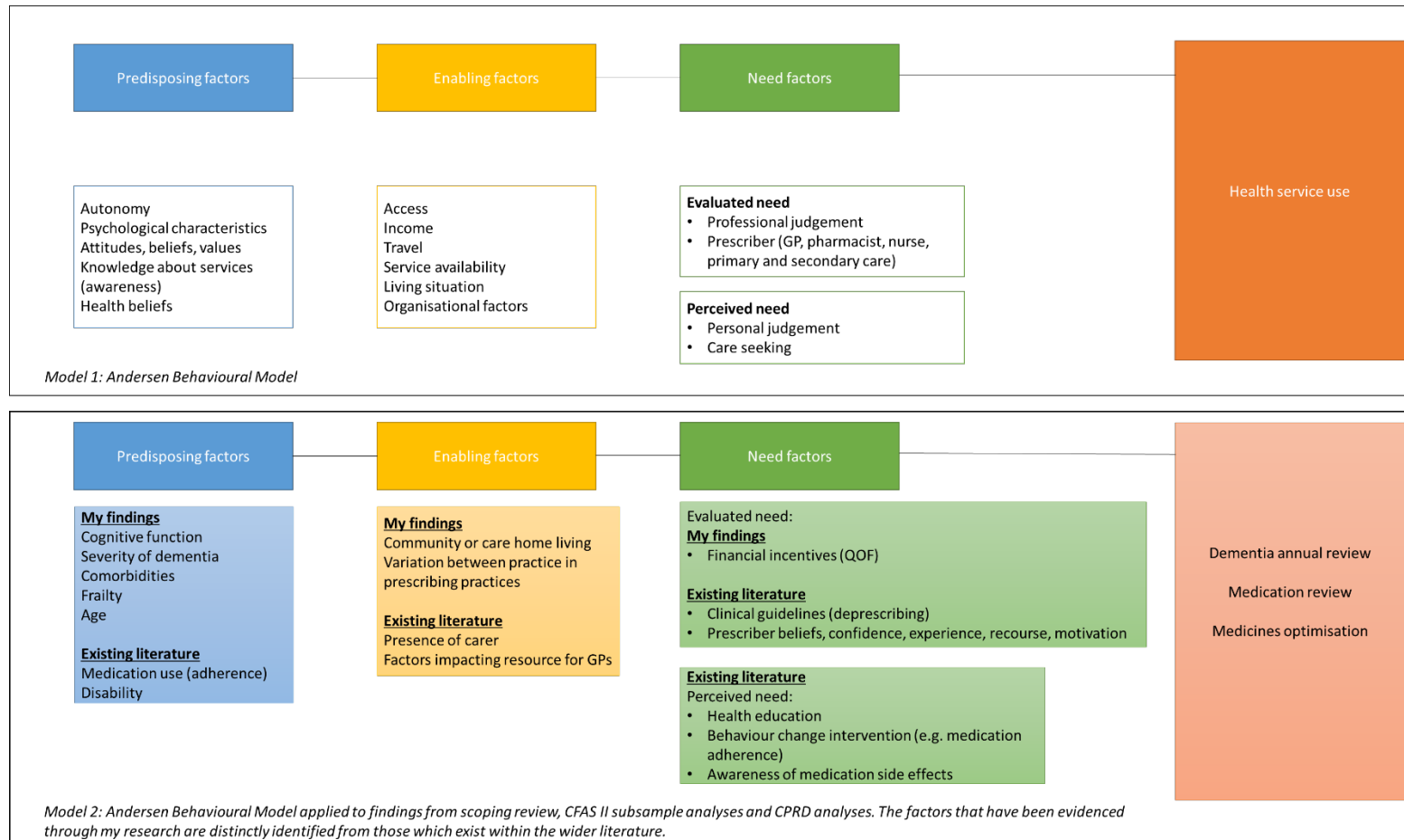
Figure 30 Model 1: Andersen Behavioural Model (Andersen & Newman 1973, Andersen, 1995) of health service use. Model 2: Andersen model applied to findings from scoping review, CFAS II and CPRD cohorts, understanding the use of potentially inappropriate medication in people with dementia.

8.09   Potentially 'inappropriate' medicines

Whilst the medications included in the analyses for these studies and those which are also included in prescribing criteria such as Beers and STOPP are considered potentially inappropriate, it is also important to recognise that these medications are often prescribed appropriately, with careful consideration of both benefits and harms. The results suggested that a medication review was associated with an increase in the odds of starting anticholinergics, antipsychotics and tricyclic antidepressants, which suggests that there were considerations accounted for in the review which continued to lead to the prescription of these PIMs in people with dementia. Nevertheless, it is difficult to ascertain the nuances associated with prescribing decisions from routinely collected observational data.

The careful consideration of patient and practice level effects accounted for in the multivariate analyses can only go so far in understanding the within patient and within practice variation in prescribing practices. In addition, where the results have also corroborated with other studies in identifying increased prescription of PIMs in care homes, this could reflect greater disease and symptom severity in this population. Antipsychotics, for example, may be prescribed to people with dementia where behavioural symptoms are severe and distressing, and in care homes a prescription of antipsychotics may be prescribed to be used 'as needed'. What we cannot ascertain from these findings is how often an antipsychotic is actually used.

It is not the position of this thesis to argue that all prescriptions of PIMs are inappropriate but rather, given the evidence there is a potential for increased risk of harm, to highlight the clinical importance of carefully reviewing prescriptions of these medications regularly. The prescription choice may be considered appropriate after consideration of benefits and harms, patient and carer preferences, beliefs and values. It is important that researchers recognise and do not underestimate the care with which prescribing decisions are made.

8.10   Methodological discussion

My studies have used epidemiologic methods to understand potentially inappropriate medication use in people with dementia. Using these methods is a considerable strength particularly in these large, population-representative datasets because of the analytical power to investigate potential harms, which would be unethical to conduct in a clinical trial. In addition, these methods are able to supplement the gaps in the literature into our understanding of the safety of medicines in this

population due to exclusion from clinical trials [341]. However, using secondary datasets for these analyses has not come without challenges [342].

Data entry lacked standardisation in some of the CFAS II questions, including the timed Sit-To-Stand and gait-speed test. Having standardised validation at the point of data entry would improve the reliability of the operationalisation of the frailty variable.

In the CFAS II cohort, the original aim had been to complete the analyses in a sample of people with dementia. However, the sample was expanded to include people with severe cognitive impairment. A number of factors informed this decision. People without medication data were excluded. As were people with severe cognitive impairment, if they did not have a proxy to provide medication information. From the potential sample of people with dementia, after the inclusion criteria were applied this left a sample that would have been underpowered to detect associations. For many reasons throughout the CFAS II interviews the interviewer could skip questions. This would often occur when the individual being interviewed was unable to answer questions due to cognitive or physical impairment and these participants are more likely to have dementia than those able to answer the questions. Cognitive impairment with no dementia is a understudied group and it was interesting to observe that in a sample of people with MMSE scores equal to or less than 24 points, around 13% had a dementia diagnosis according to the CFAS algorithm. Often, MMSE of 24 is applied as marker of severe impairment or dementia and this may indicate that the CFAS algorithm used to diagnose dementia may be specific but lack some sensitivity in diagnosing dementia.

8.11   Strengths and limitations

My studies comprised two large, population representative cohorts, providing up-to-date estimates of the prevalence of polypharmacy and PIM use amongst people with cognitive impairment and dementia in primary care in England. My analyses demonstrated the successful application of the Fried frailty phenotype to the CFAS dataset. Through this I was able to uniquely examine the association of potentially inappropriate prescribing with adverse outcomes and understand the predictive validity of the frailty phenotype. While there are alternative measures of frailty that could have been used, applying the frailty phenotype enables the distinction between factors that are contributory to frailty. Including the distinction between frailty and other impairments that increase older adults vulnerability as they age, such as cognitive

impairment or comorbidities. In doing so, my results can be used to understand the predictive validity of frailty, compared with cognitive impairment and comorbidity on the outcome. Mortality was selected as an outcome measure in my analyses of CFAS II subsample as mortality is a valuable indicator of overall health, disease burden and the effectiveness of and access to health care. Moreover, mortality as the outcome indicator avoided any loss to-follow up as all participants were flagged for notification of death with the Office for National Statistics. Other key outcomes such as falls, hospitalisation, care home admission, activities of daily living and quality of life are important to patients and would have further strengthened the analysis if these outcomes were available in this cohort.

The PIMs used in my analyses are a specific selection of PIMs that are included in a number of criteria, including STOPP and Beers. These PIMs were identified from the scoping review and have been recognised as medications which prescribers have requested as priority medications for deprescribing guidance to be developed [246], however my finding challenges some assumptions regarding their harms. It has been common in previous studies to measure the association of PIMs with an outcome from any PIM prescription, from a long list of criteria. Using individual PIMs enabled an in-depth understanding of the role of individual PIMs on harms and prescribing in primary care rather than a general understanding of the prescription of a number of PIMs according to criteria. Benzodiazepines were not included in CPRD analyses and therefore estimates of use could not be compared with CFAS. Moreover, future studies would benefit from operationalising full PIM criteria to further understand the extent of inappropriate prescribing in this population.

A limitation of my research is that the beliefs, views and opinions of people with dementia, carers and prescribers could not be measured in terms of outcomes or predictors. A growing body of literature has sought to understand barriers and enablers to addressing PIM in older adults and a smaller number of studies in people with dementia which further highlight the complexities involved in prescribing. For prescribers, there are many factors that influence the prescription of PIMs. This includes awareness (or lack) of the problem and lower perceived value attached to ceasing compared to continuing PIMs. In addition, experience and confidence to change prescribing, particularly when going against the decisions of another prescriber. The feasibility of changing prescriptions without clinical guidelines, alternative therapeutic options and external constraints such as limited time and resource also impact self-perceived confidence and ability to manage PIMs [335]. While my studies could not measure the perspectives of prescribers, my findings did suggest a very small practice-level effect associated with stopping and starting PIMs.

This may suggest little variation across practices. However, this approach may not be sensitive enough to detect such individualised characteristics that influence prescribing in practice. The findings from previous qualitative studies are useful in understanding the multifactorial model previously discussed (Figure 30). Prescribing and deprescribing are complex multifactorial processes but there are clear opportunities for interventions such as training and clinical guideline development to improve prescriber confidence and awareness of PIMs in this population.

In CPRD analyses, the dose of medication use was not used and in CFAS II this detail was not available. Understanding the dose of a prescription may enlighten further understanding of the amount of PIM prescription that are associated with potential adverse effects. In CPRD the analyses were not designed to ascertain changes in dose of PIM, which may have indicated more deprescribing processes, including reducing dose or tapering medicines. Furthermore, medications are not always taken as prescribed and non-adherence to medication regimes is common. There are many barriers to adherence for patients [93] and cognitive impairment may further impede medication management and increase non-adherence in patients with dementia [343].

My findings are based on samples with prevalent medication use and on a population who may have been stable on the medications they were prescribed, as opposed to being new users. In studies applying a new-user design, where an individual is included in the study at the point at which they are first prescribed a medication, results vary compared to prevalent users [344]. Prevalent users are more likely to be representative of healthier users, as people who have an adverse reaction close to initiation of the drug may not survive or are likely to cease this medication due to the adverse reaction to it. Moreover, people who stop a drug or die soon after initiation of a drug may be living with greater comorbidity and vulnerability to adverse effects and as such these adverse events will not be picked up in the prevalent user sample. However, practically introducing a new-user cohort design would not have been feasible with the data available from CFAS II interviews as there was no data available on when a prescription was initiated or the duration of medication use.

My CPRD cohort analysis was strengthened by disaggregating the analysis into starting and stopping PIMs, rather than investigating the probability of PIM, which was originally considered as an approach to the analysis. In doing so, this separates people who are currently prescribed PIM from those who are not exposed to each PIM and reflects two important component parts of the

prescribing process. Moreover, the process of stopping and starting a medication, whilst occurring for different reasons, are both integral in the prescribing process.

While analyses were well adjusted for comorbidities, cognitive impairment and frailty there remains the possibility that a proportion of the observed association between polypharmacy and mortality may be biased by residual confounding. It is possible that the comorbidities adjusted for did not fully account for indications of prescribed medications. All possible comorbidities were adjusted for from the data that was recorded as part of the CFAS II interviews. By also adjusting for frailty this improved the analyses by adjusting for increased susceptibility to adverse effects.

The predominant focus of my analyses has been on the potential for harm associated with use of PIMs in people with cognitive impairment and dementia, which may overlook the potential benefits. While there is a clearly recognised need to understand the potential for harm in this vulnerable population it will also be important to consider the extent of benefits that can be accrued. Understanding both the benefits and harms of a medication is integral to prescribing decisions and since clinical trials of the efficacy and the safety of medicines will generally exclude these vulnerable populations, further research could be beneficial to supporting prescribers. Furthermore, for patients and carers, an understanding of the risks compared to the benefits will be important in enabling them to be effectively and confidently involved in prescribing decisions.

My analyses were unable to account for variation according to dementia subtype. It is possible that there may have been variation in the outcome from the CFAS II subsample analysis associated with dementia sub-type. Previous studies have found that potentially inappropriate prescribing can vary according to the sub-type of dementia. People with Lewy-body dementia had a higher exposure to PIMs, for example [345] although this may be expected due to common symptoms including hallucinations and sleep disturbance. However, although my analyses did not account for dementia sub-type the analyses did adjust for cognitive impairment, frailty and living situation as useful markers of severity.

8.12   Implications

- For clinicians and prescribers, my findings can be used as evidence to inform prescribers and increase awareness of the risk of harm associated with polypharmacy and particularly hyper-polypharmacy amongst older adults with cognitive impairment. Careful consideration should be afforded when making decisions to prescribe to patients with cognitive impairment and dementia and current medicines should be regularly reviewed in order to reduce unnecessary and potentially inappropriate medicines.

- My findings suggest that while particular caution should be applied when prescribing amongst the frailest individuals, even amongst people who are identified as not frail, caution should continue to be applied when considering prescribing of additional medicines.

- These results can be used to inform the development of prescribing guidelines amongst people with severe cognitive impairment and dementia.

- These findings can be used to inform the current national and local initiatives into the optimisation of medicines, particularly highlighting the importance of polypharmacy and ways to reduce polypharmacy in practice.

- For health service providers, these findings have implications for the future direction of the provision of dementia annual reviews. The reviews could provide a key opportunity for the ongoing care of the individual and the needs of their carers to be reviewed, alongside an opportunity to review and optimise medicines.

- Further research implications include the practical application of a multilevel modelling approach to estimate changes in medication use amongst populations that are more likely to be excluded from clinical trials, and to detect changes in rarer outcomes from large scale datasets.

- Frailty phenotype has been operationalised and the methodological approach detailed in publication which can then be replicated for future studies within the CFAS II cohort or as an example case for application in different cohort studies [269].

- Importantly, for people with dementia or people caring for someone with dementia, these findings can provide support for requesting a medication review and frailty assessment, as part of a comprehensive geriatric assessment in order to identify opportunities for intervention, including reducing PIMs and polypharmacy.

8.13 Suggestions for future research

My findings improve our understanding of polypharmacy and PIM use in people with dementia, however future research is needed to build on these findings. Future studies into the adverse effects of PIM in people with dementia should investigate the adverse effects of all medications included in STOPP criteria using new-user (incident user) designs in large, representative cohorts of electronic health records, such as the CPRD in order to operationalise STOPP fully. Previous studies suggest that new-user cohort studies may see different results to prevalent user studies [310]. These studies will benefit from matched-controls and an adequate 'wash-out' period, when the patient is prescribed a drug, however the feasibility of operationalising this for the entire STOPP criteria may be challenging.

Future studies should also evaluate the impact of polypharmacy and PIMs on outcomes other than mortality, including outcomes that are identified as important to people with dementia and their carers. Outcomes of interest for patients and carers can include risk of falls, hospitalisation, and quality of life, impact on activities of daily living, caregiving burden and medication burden. The impact of medication management for a person with dementia and their carer requires further research, particularly amongst carers who generally become increasingly responsible for medication management. Moreover, the impact of interventions to reduce polypharmacy or exposure to PIMs should also be evaluated in terms of the impact on patient and carer relevant outcomes.

In light of my findings, future research should assess the effectiveness of a medication review included into a dementia annual review. In a trial, the impact of a medication review incorporated into the required procedure of a dementia annual review across a cluster of general practices in different geographical locations could be used to assess the impact on total number of prescribed medications, where my findings identified potential for harm.

Moreover, further research is required to understand if dementia annual reviews and other pay-for-performance incentives have a beneficial impact on improved outcomes for patients. The fidelity of dementia annual reviews in practice should also be evaluated in order to inform the ongoing discussion into the effectiveness of pay-for-performance schemes, particularly on patient experience and quality of care provision.

8.14   Conclusion

The older adult population are the largest consumers of medications and are more likely to live with comorbidity, disability and frailty. Cognitive impairment and progressive decline in functioning as part of ageing also reduces independence and increases dependence on care and support from others. The older population is heterogeneous and the results from this thesis have also demonstrated important heterogeneity amongst people living with dementia. My findings have shown variation in prescribing across the frailty syndrome and care settings. In addition, prescribing and deprescribing practices vary. My research findings suggest that consideration of the number of medications, rather than specific medication classes may more effectively reduce potential adverse outcomes. In primary care, there was some evidence to suggest that prescribing practices around PIMs are well managed when medications are reviewed. Incorporating a medication review into the dementia annual review may improve standardisation of medicines management across this heterogeneous population. This may then improve quality prescribing, reduce medication burden, provide regular opportunity for medication review and to discuss opportunities for deprescribing when possible. However, given around half of people with dementia in primary care received a dementia annual review and the increasing dismay at the application of pay-for-performance schemes in primary care, adding additional work to the already sparsely applied dementia annual review could have counterproductive effects.

Optimising medications in people with dementia requires a carefully considered and holistic approach. Patients with dementia and their carers should feel able to have their perceived needs, preferences and values accounted for. Prescribers may be aware of the potential for adverse effects associated with potentially inappropriate prescribing but will be enabled through evidence-based guidance to recognise the evaluated need and support for safe and effective prescribing and deprescribing. While prescribing in people with dementia can be challenging due to the complexities and diversities of symptoms, comorbidities, disability and frailty, it is a mark of the quality of the care provided to people with dementia how medications are optimised, just as it is the mark of a civilised society how we aim to treat those who are most vulnerable.

IX.   References

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X.   Appendices

10.01 Appendix 1: Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	36
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	n/a within thesis chapter
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	36
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	36
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	-
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	40
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	40
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	Appendix 2
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	40
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	40
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	40-41

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	-
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	43
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	44-45
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	46
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	-
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	48 Appendix 3
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	51-53
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	53-69
Limitations	20	Discuss the limitations of the scoping review process.	70
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	71
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	n/a

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.

† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).

‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.

§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

10.02 Appendix 2: Search terms used in literature review

Table 32 Table of search terms used across three databases for the literature review

Database Searched	Search Terms
Cochrane	#1 MeSH descriptor: [Polypharmacy] #2 MeSH descriptor: [Inappropriate Prescribing] #3 MeSH descriptor: [Potentially Inappropriate Medication List] #4 MeSH descriptor: [Medication Errors] #5 polypharma*:ti,ab #6 ((concomitant* or concurrent* or inappropriat* or appropriat* or suboptim* or sub-optim* or unnecessary or incorrect* or excess* or multip* or inadvert* or discontinu*) near/1 (medicine* or medicat* or prescrib* or prescription* or drug*)):ti,ab #7 ((over near/1 (prescrib* or prescript*)) or (over-prescrib* or overprescrib*) or ("or more" near/1 (medication* or prescrib* or prescript*))):ti,ab #8 ((under near/1 prescrib*) or underprescrib* or under-prescrib*):ti,ab #9 (stopp criter* or stopp list?).ti,ab. #10 ((forta or rasp or priscus) adj3 (criter* or list? or instrument)).ti,ab. #11 (stopp frail criter* or stopp frail list?).ti,ab. #12 ("fit for the aged" adj3 (criter* or list? or instrument or classif*)).ti,ab #13 "medication appropriateness index*".ti,ab. #14 ((beer* or shan? or mcleod?) adj3 criter*).ti,ab. #15 (acb criter* or acb scale or "anticholinergic cognitive burden scale") #16 {or #1-#15} #17 MeSH descriptor: [Geriatrics] explode all trees #18 (elder* or geriatric*):ti,ab #19 ((old* or aged) near/1 (person* or adult* or people or patient* or inpatient* or outpatient*)):ti,ab #20 {or #17-#19} #21 #16 and #20 #22 (dement* or Alzheimer*) #23 MeSH descriptor: [Dementia] explode all trees #24 {or #22-#23} #25 #16 and #24 #26 #21 or #25
Medline (EBSCO)	((MH "Polypharmacy+") or (MH "Potentially Inappropriate Medication List") or (MH "Inappropriate Prescribing") or (MH "Medication Errors+") or (stopp criter* or stopp list*) or ((forta or rasp or priscus) (criter* or list? or instrument)) or (("fit for the aged" (criter* or list? or instrument or classif*)) or ((beers criter*) or (beers list*)) or ((mcleod criter*) or (mcleod list*))) AND (old* or age* or elder* or geriatric*) ((MH "Polypharmacy+") or (MH "Potentially Inappropriate Medication List") or (MH "Inappropriate Prescribing") or (MH "Medication Errors+") or (stopp criter* or stopp list*) or ((forta or rasp or priscus) (criter* or list? or instrument)) or (("fit for the aged" (criter* or list? or instrument or classif*)) or ((beers criter*) or (beers list*)) or ((mcleod criter*) or (mcleod list*))) AND (MH "Dementia") OR

(MH "Frontotemporal Dementia") OR (MH "Dementia, Vascular") OR (MH "Dementia, Multi-Infarct") OR (MH "AIDS Dementia Complex") OR (MH "Alzheimer Disease") OR (MH "Lewy Body Disease")

((MH "Polypharmacy+") or (MH "Potentially Inappropriate Medication List") or (MH "Inappropriate Prescribing") or (MH "Medication Errors+") or (stopp criter* or stopp list*) or ((forta or rasp or priscus) (criter* or list? or instrument)) or (("fit for the aged" (criter* or list? or instrument or classif*)) or ((beers criter*) or (beers list*)) or ((mcleod criter*) or (mcleod list*))) AND (dementia or alzheimers or vascular dementia or lewy body or frontotemporal)

Embase (OVID)	(polypharmacy* or "potentially inappropriate prescr*" or "inappropriate prescr*").ab. polypharmacy.mp. or exp polypharmacy/ inappropriate prescribing.mp. or exp inappropriate prescribing/ or exp elderly care/ prescription.mp. or exp prescription/ exp drug safety/ or exp medication error/ old.mp. or exp aging/ geriatric.mp. or geriatrics/ geriatric.mp. or exp geriatrics/ stopp criteria.mp. "(stopp criter* or stopp list*) or ((forta or rasp or priscus) (criter* or list* or instrument)) transformed to (stopp criter* or stopp list*) or ((forta or rasp or priscus) (criter* or list* or instrument))".af. (stopp criter* or stopp list*).af.
	(forta criteria list* or rasp criteria* list* or priscus criteria* list*).af. (forta or "fit for the aged").af. ("beers criter*" or "beers list*").af. ("mcleod criter*" or "mcleod list*").af. exp Alzheimer disease/ or demenita.mp. or exp dementia/

10.03 Appendix 3: Scoping review tables of included studies

(a) Table of review aims and key findings from scoping review

Table 33 Table of review aims and key findings of reviews included in the scoping review

Citation, population, setting	Review aims	Key findings
Bokhof & Junius-Walker (2016). Older adults, community	Explore the perspectives of GPs and older patients in reducing polypharmacy and identify approaches already being practiced	• Patients felt unprepared to deal with complex medication regimes. GPs felt pressurized to prescribe or to follow evidence-based guidelines. • Deprescribing was not deemed easy because there was no guidance available and when their patients were older, multimorbid and more complex to manage. • System-wide factors such as multiple prescribers and inadequate consultation time impacted prescribers and patients.
Chang & Chan (2010) Older adults, mixed setting	Summarize and compare criteria for PIMs to enable informed choices about their use	• Seven criteria were identified. • Explicit criteria to define PIMs were varied across the world; benzodiazepines and tricyclic antidepressants were consistently identified as PIMs across criteria. • Beers, Rancourt and Wint-Watjana criteria were most similar. • Prevalence of PIMs was varied and the association of PIMs and health outcomes was inconclusive.
Corsonello et al., (2012) Older adults, mixed setting	Summarize the evidence about the use of explicit criteria for PIMs to reduce the risk of adverse drug reactions (ADRs) in older people.	• Some evidence of association between Beers and mortality, healthcare utilisation, adverse drug events, quality of life and functional decline. • Beers criteria were not applicable to European countries due to variation in prescribing practices. • STOPP/START address many limitations of Beers by also including prescribing omissions, are classified by physiological systems and empathises drug-drug interactions.
Corsonello et al., (2009). Older adults, hospital	Reviewing evidence of the application of Beers criteria in elderly hospitalized patients and Italian studies that have focused on the role of PIMs as potential predictors of negative hospital outcomes.	• The application of Beers criteria may be limited in reliability in hospital settings, particularly in European countries. • Prevalence of PIMs was high in hospital settings and some evidence that Beers identified PIMs were associated with ADRs and length of hospital stay.
Cullinan et al., (2014). Older adults, mixed	Synthesise qualitative studies exploring PIM in older patients to understand why it happens from a prescriber perspective and to generate new theory to guide future interventions aimed at minimising it in older people	• Factors associated with reasons for prescribing PIMs included the need to please the patient, feeling forces to prescribe, tension between prescribing experience and guidelines and prescriber self-perceived restrictions.
Ćurković et al., (2016) Older adults, mixed settings	To describe the prevalence and prevention of inappropriate prescribing and risk factors associated with psychotropic medications	• PIM prescription and the prescription of psychotropic drugs was higher amongst nursing home residents. • Polypharmacy was associated with PIM and psychotropic drug prescription.

Citation, population, setting	Review aims	Key findings
Dimitrow et al., (2011) Older adults, mixed setting	To systematically review articles prescribing criteria for assessing PIM in individuals ages 65 years or older and to define circumstances of their use (explicit and implicit), origins, development processes and content	- Fourteen criteria were identified, seven originating in the US. Most criteria were explicit, consensus validated and often based on Beers. - Explicit criteria need to be updated regularly but implicit criteria also require up-to-date knowledge and prescriber skill. - Most criteria measure appropriateness of medicines, Australian and MAI also assess the medication management process. - Most require clinical information to be implemented, NORGEP was the only criteria that did not require clinical information.
Disalvo et al (2016) Older adults and people with dementia, mixed setting	To identify and synthesise published systems for identifying PIM and make recommendations for identifying PIM in advanced dementia.	- One system was in place to identify PIMs in patients with advanced dementia where palliative care was appropriate. - Patient comfort and symptom management was emphasised when reducing polypharmacy and preventative treatments. - Lack of evidence based guidelines and difficulties identifying advanced dementia were cited as reasons for inappropriate medication use in advanced dementia.
Fulton et al., (2005). Older adults, primary care	To review literature addressing polypharmacy in adults 60 years and older to 1) determine primary care providers definition of polypharmacy 2) explore how polypharmacy was assessed in primary care and 3) seek tested interventions that address polypharmacy	Polypharmacy is a considerable issues and little research has been conducted into the methods primary care providers use to assess polypharmacy and interventions used.
Gallagher et al., (2007) Older adults, mixed setting	Overview of the literature on potentially inappropriate prescribing in the elderly and to review explicit criteria that have been designed to detect potentially inappropriate prescribing in the elderly	- Prescription of PIMs in older people was prevalent in UK and Europe, ranking from 12% in the community to 40% in nursing home residents. - PIMs were associated with adverse drug events but limited evidence on health outcomes.
Guaraldo et al., (2011). Older adults, community	To describe studies using information from insurance company and social security administrative databases to assess PIM among community dwelling elderly and present risk factors most often associated with PIM	- Prevalence of PIMs was high among community-dwelling elderly - PIM use was associated with being female, advanced age and number of prescribed drugs. - PIM prevalence's varied depending on criteria used but ranged from 11.5% to 62.5%.
Hajjar et al., (2007) Older adults, mixed setting	Describe observational studies examining the epidemiology of polypharmacy and review RCTs designed to reduce polypharmacy in older adults	- Polypharmacy has increased and is a risk factor for mortality and morbidity. - There were few rigorous interventions that have shown to reduce unnecessary polypharmacy in older adults.
Hill-Taylor et al,. (2013) Older adults, mixed setting	Conduct a systematic review of studies to describe the application of STOPP/START criteria and examine evidence of the impact of STOPP/START on clinical, humanistic and economic outcomes in older adults	- STOPP/START were more sensitive than Beers in six studies but less sensitive in identifying adverse reactions. - Limited evidence of STOPP/START as effective in optimising prescribing. - STOPP can be used to identify avoidable adverse drug events but the evidence is not robust.
Hyttinen et al., (2016) Older adults, mixed setting	Evaluate recent evidence on health care utilization and health care costs associated with PIM use in older adults.	Most studies found a significant effect on health care service use, including hospitalisation, among older adults. Findings on the impact of length of hospital stay were inconclusive.
Johnell (2015)	To identify, assess and summarize available studies about potentially inappropriate drug use in cognitive impairment and dementia and to present	Prevalence of inappropriate drug use among people with cognitive impairment or dementia ranged from 10.2% to 56.4%.

Citation, population, setting	Review aims	Key findings
People with cognitive impairment or dementia, mixed setting	findings about whether cognitive impairment and dementia are associated with inappropriate drug use.	• A lower likelihood of inappropriate drug use in people with cognitive impairment or dementia in 6/8 studies. The remaining two articles showed no statistically significant association between cognitive impairment or dementia and inappropriate drug use.
Kouladjian et al., (2014). Older adults, mixed setting	Evaluate and summarize the theoretical and practical aspects of Drug Burden Index (DBI), the effect of anticholinergic and sedative medications in older adults, discuss evidence supporting utilisation in practice and compares DBI with other pharmacologically developed models measuring anticholinergic or sedative exposure in older adults	• The Drug Burden Index is a method used to identify anticholinergic and sedative drug burden, the DBI has been associated with poorer physical function, falls, frailty, hospitalisation and mortality.
Kroger et al., (2015). Dementia, nursing home	Identify categories of appropriateness for medications as well as successful interventions or elements of to improve medication use in nursing home residents with severe dementia, suitable for use in Canada.	• Including healthcare professionals is important for improving medication use among nursing home residents with severe dementia • Interventions should include education, medication review or multidisciplinary teamwork. • Evidence for outcomes other that appropriate prescribing is mixed and it is unclear what the impact is on quality of life.
Levy et al., (2010). Older adults, mixed	To provide a comparative overview of explicit criteria that have been developed since 2003 for inappropriate prescribing and to contrast these newer criteria with Beers 2003 criteria	• Criteria developed since 2003 include Beers, the French Consensus Panel list, STOPP/START, the Australian Prescribing Indicators tool and the Norwegian General Practice Criteria. • More recent criteria offer improvements on Beers, including around drug-drug interactions, prescribing omissions and wider application, with STOPP/START showing improvements in the application of criteria more widely.
Matanović et al., (2012). Older adults, mixed	To review and critically evaluate available protocols for detecting PIMs in the elderly and summarize these into a new comprehensive and widely applicable protocol	• Many strategies are there to improve drug prescribing in older adults, who are at greater risk of adverse effects.
Morin et al., (2016) Older adults, nursing home	To systematically review the prevalence of potentially inappropriate medication use in nursing home residents	• Pooled point prevalence estimates were 43.2% (95% CI 37.3%-49.1%) in nursing homes • Prevalence increased from 30% in studies from 1990-1999 to 49.8% in studies conducted after 2005. • Prevalence was higher in European countries compared to North America. • The total number of prescribed medications was consistently reported as the main driving factor for PIM use.
Motter et al., (2018). Older adults, mixed	To provide summaries and comparisons of validated PIMs lists published between 1991 and 2017 and summarize the medications and drug-disease and drug-drug interactions listed in different PIM lists	• Approaches to identify PIM have increased (over 36 different PIM criteria) however there was limited overlap between the different PIM lists and some do not provide considerations of use or alternative therapies to use.
Muhlack et al., (2017). Older adults, mixed	To identify, evaluate and meta-analyse cohort studies reporting the association of PIM intake with mortality and cardiovascular events	• When restricted to new user designs, the association between PIM use and mortality was statistically significant (RR 1.59 95% CI 1.45-1.75). • One study focused on cardiovascular events and there was no significant association
Opondo et al., (2012).	To quantify the extent of inappropriate prescription to elderly persons in the primary care setting	• Around 1/5 prescriptions to elderly primary care is inappropriate, despite the attention to quality of prescribing.

Citation, population, setting	Review aims	Key findings
Older adults, primary care		
Pérez-Jover et al., (2018). Older adults, mixed	Review published literature on the inappropriate use of medicines and to articulate recommendations on how to reduce it in chronic patients, particularly those who are elderly, poly-medication or multi-pathological.	• Most older adults take 5 or more medications daily • Older people with polypharmacy are at a greater risk of medication error • Tools can be used to reduce prescribing errors.
Peron et al., (2011). Older adults, mixed	To critically review articles that have examined the relationship between medication use and functional status decline in the elderly.	• No relationship between Beers criteria and functional status • Polypharmacy was associated with functional status decline.
Redston et al., (2018) Older adults with and without cognitive impairment	To quantify and compare the prevalence of PIMs in older inpatients with and without cognitive impairment.	• High prevalence of PIMs in older inpatients with and without cognitive impairment
Rodrigues et al.,(2016). Older adults, mixed	to identify and summarize studies examining both drug-drug interactions and adverse drug reactions in older poly-medicated adults	• Polypharmacy is multifactorial and is associated with negative health outcomes, drug-disease interactions and adverse drug reactions.
Salahudeen et al., (2015). Older adults	To compare anticholinergic burden quantified by the anticholinergic risk scales and evaluate associations with adverse outcomes in older people.	• There were 7 expert-based anticholinergic rating scales identified, ACB scale was the most frequently validated scale for adverse outcomes. • Cohort studies show that higher anticholinergic burden is associated with negative brain effects, poorer cognitive and functional outcomes. • Rating of anticholinergic activity for medicines was not consistent across scales.
Santos et al,. (2015). Older adults, mixed	Assess the tools used to detect PIMs in various studies and to determine which terms are used to refer to potentially inappropriate drug therapy in practice.	• Beers criteria was the most commonly used and there were more than 50 different terms used to identify potentially inappropriate drug therapy. There was no consensus for a term used to describe this.
Skinner (2015). Older adults, primary care	To critically evaluate evidence-based protocols on polypharmacy in elderly patients in primary care.	• No standardized protocol for addressing polypharmacy in primary care was found although there were a range of practice guidelines, algorithms and clinical strategies that were employed across various settings.
Storms et al,. (2017) Older adults, care home	assess the prevalence of inappropriate medication use in residential long-term care facilities	• Beers and STOPP were most frequently used to determine PIM in long-term care facilities, prevalence varied depending on the criteria used and the study.
Tommelein, et al,. (2015).	To determine prevalence and type of PIM in community dwelling older people across Europe as well as identifying risk factors for PIM.	• 1/5 older adults are exposed to PIM in Europe (overall weighted prevalence 22.6%). • Prevalence was varied with various criteria that are used across studies.

Citation, population, setting	Review aims	Key findings
Older adults, community		• Polypharmacy, low functional status, depression, economic situation, comorbidity and reduced cognition are associated with higher risk of PIM. Age was associated in around half of studies that investigated age as a risk factor for PIM.
Villalba-Moreno, et al., (2016) Older adults, mixed	to identify anticholinergic scales described in the literature that are applicable to polypathological patients and analyse their clinical outcomes	• 10 scales were identified, exposure to anticholinergics was linked to cognitive disorders but the evidence associated with mortality was not clear.
Wang et al,. (2018). Older adults, care home	To systematically review the association between medication or prescribing patterns and hospitalizations from long-term care facilities.	• In care homes, polypharmacy and PIM were consistently associated with increased hospital admission

(b) Table of reviews of intervention studies included in the scoping review

Table 34 Table of reviews of intervention studies included in the scoping review

Reviews of interventions

Authors (year)	Types of studies included	Population, Setting	*n* studies (participants)	Review aims	Types of interventions	Key findings
Alldred et al., (2016)	RCTs	Older adults, care home	12 (10,953)	Evaluate evidence for interventions to address suboptimal prescribing in care homes to identify how care can be improved in this frail and vulnerable population.	• Medication review • Multifaceted interventions, including education of care home staff, clinical decision support technology, multi-disciplinary case conferences, pharmacist medication review	o In care homes, medication review may improve medication appropriateness and the identification and resolution of medication related problems. o There was no evidence of an effect of interventions on mortality and adverse drug events. o Uncertain whether medication review improved hospital admissions or quality of life. o Robust conclusions could not be drawn due to the quality of the evidence.
Christensen & Lundh (2016)	RCTs	Older adults	10 (3,575)	Evaluate whether a medication review leads to improvement in health outcomes of hospitalised adult patients compared with standard care.	• Medication review in hospital setting	o In hospitals, there was no evidence that medication review reduced mortality or hospital readmissions o Some evidence that medication review may reduce the number of emergency department contacts compared with standard care.
Clyne et al., (2012)	RCTs, cluster RCTs, cohort studies, interrupted time series	Older adults, ambulatory care, nursing home, hospital	14	To identify studies on the effectiveness of assistive prescribing technologies for older people.	• e-prescribing • computerised decision support systems • Drug-specific alters on prescribing systems with recommendations on dose and alternatives.	o 11/14 studies identified that the use of prescribing technologies (e-prescribing and computerised decision support systems) lowered inappropriate prescribing and polypharmacy. o In nursing homes, implementing prescribing technologies was more challenging.
Clyne et al., (2016).	RCTs	Older adults, community-dwelling	12 (156,529)	Identify and determine the effectiveness of interventions to reduce PIM in community dwelling older adults	• Organisational – changing structure of services • Professional – targeting professionals to improve practice, including education • Multifaceted interventions e.g. computerised decision support systems and academic detailing	o Organisational interventions, including pharmacist medication review, showed a reduction in PIM. o The evidence of effectiveness of multidisciplinary teams was weak. o Computerised clinical decision support systems were effective in reducing new PIM prescriptions but did not impact existing PIMs. o Some evidence that multifaceted approaches were effective. o Overall, effect sizes were modest and the impact on clinically relevant patient outcomes is unclear.
Cooper et al., (2015)	RCTs, cluster RCTs, controlled before and after studies	Older adults	12 (22,438)	To update a review of interventions aimed at improving the appropriate use of polypharmacy in older adults	• Organisational interventions – multifaceted pharmaceutical-care based interventions • Medication review • patient education • health professional education • Computerised decision support	o Interventions showed a reduction in PIMs and improvements in appropriate polypharmacy. o Clinically relevant effects were unclear, evidence was conflicting on the effect of interventions on hospital admissions and medication related problems. o No evidence associated with health related quality of life.
Forsetlund et al., (2011)	RCTs	Older adults, nursing home	20	To identify and summarise the effect of interventions aimed at reducing PIM in nursing homes	• Education interventions • medication review by pharmacists • Multidisciplinary teams	o In nursing homes, education interventions and pharmacist medication review may reduce PIMs, however the evidence was low quality. o Contextual factors within nursing homes influence the effect of interventions. o The evidence was limited on the impact of health-related outcomes.
Johansson et al., (2016)	RCTs, non-randomised	Older adults, mixed	25 (10,980)	Explore the impact of strategies to reduce polypharmacy on mortality, hospitalization and change in number of drugs	• Pharmacist-led interventions • Education • Discussion with patients	o Meta-analysis showed no effect of interventions to reduce polypharmacy overall on mortality.

Author	Study types	Population	N	Aim	Interventions	Findings
	controlled trials				• Medication review by physicians • Multidisciplinary teams	o Some evidence of an association with reduced hospital admissions but the evidence was not robust and due to heterogeneity of studies results could not be compared. o There was no robust evidence of a reduction in polypharmacy or subsequent impact on mortality or hospitalisation.
Kaur et al., (2009)		Older adults, mixed	24 (56-124,802)	Identify interventions and strategies that can significantly reduce inappropriate prescribing in the elderly.	• Education • Medication review • Multidisciplinary teams • Computerised decision support systems • regulatory policies • Regulatory policies	o Various interventions showed a positive effect on reducing PIM, o Combined efforts not relying on primary care prescribers (e.g. including pharmacists) are required. o Education interventions showed mixed effects. o Computerised decision support showed positive effects and majority of studies involving pharmacists showed positive effects. o Mixed effects of multidisciplinary teams.
Page et al., (2016)	Experimental and observational studies	Older adults	116 (34,14, 6,090 people with dementia)	To determine whether or not deprescribing is safe, effective and feasible intervention to modify mortality and health outcomes in older adults	• Deprescribing single medications • Deprescribing polypharmacy • Education	o Deprescribing reduced the number of medicines and PIMs prescribed and was not associated with an increase in adverse drug events. o In non-randomised studies, deprescribing polypharmacy was significantly associated with decreased mortality, however there was no evidence of an association in randomised studies. o Interventions involving medication reviews were associated with significant reduction in mortality however general prescriber education interventions were not. o Deprescribing did not change cognitive function, risk of falls or quality of life.
Page et al., (2016)		Older adults, mixed		To describe the genesis of deprescribing as an increasingly accepted medical and pharmaceutical intervention (to manage polypharmacy and PIM) and an overview of deprescribing	• Deprescribing: The process of supervised withdrawal of inappropriate medications with the goal of managing polypharmacy • Medication review • Education	o Medications should be review to ensure appropriate and optimal use. o Deprescribing is the process of supervised medication withdrawal, with the aim of managing polypharmacy and improving outcomes. o There is evidence suggesting that deprescribing is effective in managing polypharmacy and PIMs and used in combination with other interventions, could also improve health outcomes.
Rankin et al., (2018)	RCTs, non-randomised controlled trials, controlled before and after studies and interrupted time series	Older adults, mixed	32 (28,672)	To determine which interventions, alone or in combination, are effective in improving the appropriate use of polypharmacy and reducing medication-related problems in older people.	• Computerised decision support • Multifaceted pharmaceutical-care e.g. including medication review, education of patient or prescriber	o Results were unclear whether pharmaceutical care improved appropriate polypharmacy and number of PIMs. o Some evidence that pharmaceutical care reduces potential prescribing omissions, however risk of bias high. o Little or no evidence of impact on hospital admissions, quality of life and medication-related problems.
Rollason & Vogt (2003)	RCTs, controlled trials	Older adults, nursing home and hospital	14	Examine the effectiveness of interventions led by pharmacists in reducing polypharmacy	• Pharmacist-led or included interventions • Medication review • case conferencing • Education interventions • Some interventions involved patients, multidisciplinary teams	o Whilst the number of medications reduced was often small, the studies were in favour of the effectiveness of pharmacist-led interventions overall. o An intervention of any kind by or involving a pharmacist could reduce the number of drugs in older adults.
Thillainadesan (2018)	RCTs	Older adults, hospital	9 (2,522)	To investigate the efficacy of deprescribing interventions in older inpatients in hospital to reduce PIMs and impact on clinical outcomes	• Deprescribing interventions • Pharmacist-led • Physician-led • Multidisciplinary teams • Tools to identify PIMs • medication review • Computerised decision support	o Deprescribing interventions in hospitals are effective at reducing overall number of PIMs, however the evidence of the impact on clinical outcomes was not well measured and was unclear.

Author (year)	Study types	Population	N (participants)	Aim	Interventions	Findings
Thiruchelvam et al., (2017).	RCTs and observational studies	Older adults, care homes	22	Assess the impact of medication reviews in aged care facilities with additional focus on types of medication reviews, using RCTs and observational studies	• Medication reviews by pharmacists or multidisciplinary teams involving pharmacists	o In care homes, medication reviews conducted by a pharmacist as part of a team or independently appeared to improve quality of medicines. o Medication reviews may slightly reduce number of medicines prescribed and PIMs. o There was some evidence to suggest a positive effect of medication review on mortality, hospitalisation and disability.
Tjia et al., (2013)	RCTs, pre-post interventions, case series	Older adults, mixed	36 (13,906)	Identify unnecessary medications, the intervention process of medication reduction and the effectiveness of these interventions	• Medication review • Education interventions • Pharmacists involvement	o 22/26 studies reported a significant reductions or differences associated with interventions to reduce unnecessary medicines. o Pharmacist involvement in medication reviews was important but clinician-led reviews were more consistently associated with a positive outcome across studies.
Walsh et al., (2016)	RCTs and non-randomised controlled trials	Older adults, hospital	4 (1,164)	Collate available evidence on the effectiveness of pharmacist interventions on the quality of prescribing to older hospitalised patients.	• Pharmacist included in ward teams • Clinical pharmacists in multidisciplinary teams	o Evidence that interventions involving pharmacists were associated with reduction in PIMs. o In hospitalised older adults, multidisciplinary teams involving pharmacists may improve the appropriate of medicines.
Wilsdon et al., (2017)	RCTs and non-randomised controlled trials	Older adults, mixed	21	determine the effectiveness of interventions to deprescribe inappropriate Proton Pump Inhibitors (PPIs) in older adults	• Population-wide education strategy • Academic detailing for general practitioners • in-patient geriatrician-led deprescribing • discharge letters • education • medication review	o Some interventions were effective in reducing PPIs, including population-wide education and deprescribing promotion strategies, academic detailing and geriatric assessment. o Whether the impact of these interventions translates into clinical outcomes is unclear.

(c) Table of criteria for identifying potentially inappropriate medications in older adults from 1991-2017

Table 35 criteria for identifying potentially inappropriate medications from 1991-2017

Criteria for identifying PIM	Year	Country of origin	Reference
2017			
Khodykov criteria	2017	USA	Khodyakov et al (2017)
Mazhar criteria	2017	Pakistan	Mazhar et al (2017)
2016			
Chilean criteria	2016	Chile	Passi et al (2016)
GheOP(3)S-tool	2016	Belgium	Tommelein et al (2016)
2015			
EU(7) PIM list	2015	Germany	Renom-Guiteras et al. 2015
Korean Criteria	2015	South Korea	Kim et al (2015)
NORGEP-NH	2015	Norway	Nyborg et al (2015)
Beers	2015	USA	Beers 2015
Swedish National Board of Health and Welfare	2015	Sweden	Fastborn & Johnell (2015)
STOPP/START	2015	Ireland	Gallagher 2015
2014			
Fit for the Aged (FORTA) (2014)	2014	Germany	Kuhn-Thiel et al (2014)
Galan-Retamal criteria	2014	Spain	Retamal et al (2014)
2013			
Czech national Criteria (CNC)	2013	Czech Republic	Fialova et al (2013)
Castillo-Paramo criteria	2013	Spain	Castillo-Paramo et al., 2013
OPTI-SCRIPT	2013	Ireland	Clyne et al (2013)
2012			
Beers	2012	USA	
Australian Prescribing Indicators Tool (APIT)	2012	Australia	Basger et al (2012)
New Mexico criteria	2012	New Mexico	Bachyrycz et al (2012)
Taiwan criteria	2012	Taiwan	Chang et al (2012)
2010			
PRISCUS	2010	Germany	Holt et al (2010)
Korean criteria	2010	South Korea	Kim et al (2010)
Italian criteria	2010	Italy	Maio et al (2010)
2000-2009			
Beers	2003	USA	
STOPP/START	2008	Ireland	
Assessing Care of Vulnerable Elders (ACOVE)	2001	USA	Wenger & Shekelle (2001)
Hyperpharmacotherapy Assessment Tool (HAT)	2008	USA	Bushardt et al (2008)
Association of Nursing Home Surveyors Interpretative Guidelines	2007	USA	(Lapane et al (2007)
French Consensus panel List	2007	France	(Laroche et al., 2007
Improved Prescribing in the Elderly Tool (IPET)	2000	Canada	Naugler et al (2000)
Phadke criteria	2004	India	Phadke (1998)
Rancourt criteria	2004	Canada	Rancourt et al (2004)
Norwegian General Practice Criteria (NORGEP)	2009	Norway	Rognstad et al (2009)
Zhan criteria	2001	USA	Zhan et al (2001)
Healthcare Effectiveness and Data Information Set (HEDIS)	2006	USA	Pugh et al (2006)
Lindblad criteria	2006	USA	Lindblad et al (2006)
Japanese Beers criteria	2008	Japan	Imai et al (2008)
Thailand Criteria	2008	Thailand	Winit-Watjana et al (2008)
1991-1999			
Beers	1991	USA	
Beers	1997	USA	
Medication Appropriateness Index (MAI)	1992	USA	(Hanlon et al., 1992)
Assessment of Underutilization of medication (AOU)	1999	USA	Jeffrey et al (1999)
McLeod Criteria	1997	Canada	McLeod et al (1997)
Stuck	1994	USA	Stuck et al (1994)
Lipton implicit criteria	1993	USA	Lipton et al (1993)

10.04 Appendix 4: ISAC application form: Protocol for Research using CPRD

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A. Study Title[§]

Potentially inappropriate prescribing in people with dementia in England: a prospective cohort study.

B. Lay Summary (Max. 200 words)[§]

People with dementia are often prescribed many different medicines for symptoms of dementia or other health conditions. Some medicines may be inappropriate if they have been used for too long or their harms outweigh their benefits.

Doctors are expected to manage medications and are paid to hold an annual dementia care review with every patient. We do not know what effect these opportunities to review medication have on quality of care, an important part of which is reducing the amount of medicines that may be harmful in people with dementia.

Detailed medication recommendations have been created to help health professionals reduce harmful prescriptions. We have used these guides to select four groups of medications that may be inappropriate for people with dementia. They are antipsychotic medications, tricyclic antidepressants, anticholinergics (defined according to Anticholinergic Cognitive Burden scale score = 3) and proton pump inhibitors. We will look at how often these medicines are prescribed and the impact of dementia annual reviews and other medication reviews on their use, using GP records of all people with dementia available in the Clinical Practice Research Datalink in 2014 and 2015.

C. Technical Summary (Max. 200 words)[§]

[§]*Please note: This information will be published on CPRD's website as part of its transparency policy*

Objective: To estimate the (i) prevalence of potentially inappropriate medication use, and overall medication burden among people with dementia between 2015 and 2017 (ii) and the factors associated with potentially inappropriate medication use, in particular the effect of medication reviews and dementia annual review.

Methods. A 2-year cohort study following all prevalent cases of dementia at the start date of 01/01/2015, and incident cases between the start date and the study end date of 30/04/2017. Prescriptions of four classes of potentially inappropriate medications (antipsychotics, tricyclic antidepressants, anticholinergics and proton pump inhibitors) will be extracted, as well as any medication review or dementia annual review (exposures) during that period and potentially confounding variables.

Statistical analysis. We will estimate the prevalence of potentially inappropriate medication use in people with dementia across the study period. McNemar and Wilcoxon signed rank tests will test the change in each outcome before and after a medication review or dementia annual review. Multilevel logistic regression analyses will then be used to estimate the factors associated with each outcome, and in particular the effect of medication review or dementia annual review on subsequent prescriptions controlling for age, sex, time varying comorbidity, area-level deprivation, GP practice and exception from QOF dementia indicators.

D. Objectives, Specific Aims and Rationale

Objectives

1. To estimate the (i) prevalence of potentially inappropriate medication (PIM) prescription among people with dementia (ii) factors associated with PIM, in particular the effect of medication review (MR) and dementia annual review (DAR) on PIM.

Specific aims

1. To estimate the prevalence of PIM use in people with dementia in primary care in England between 2015 and 2017.
2. To estimate the change in probability of being prescribed a potentially inappropriate medication before and after a MR or DAR.
3. To estimate the patient and practice level factors associated with each PIM in people with dementia, including the effect of age, sex, comorbidity, recent review, area-level deprivation, residual between practice variation and exception from QOF dementia indicators.

The potentially inappropriate medications are selected through consultations with experienced prescribers and from explicit criteria (Beer's, STOPP) as those specifically implicated in people with dementia. Specifically the prescription of:

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a. Any antipsychotic (vs no antipsychotic prescription)
b. Tricyclic antidepressants (vs no tricyclic antidepressant)
c. Any definite anticholinergic (defined using Anticholinergic Cognitive Burden score=3 [254] vs no ACB=3 anticholinergic)
d. Any inappropriate PPI (defined as use for >8 weeks at maximum therapeutic dose [232, 243]) (vs no PPI prescription).
e. Overall medication burden as measured by a continuous variable for the total number of prescribed medications. Excluding devices, dressings and topical preparations.

Rationale

By addressing the aims identified above, we will be able to estimate the prevalence of potentially inappropriate prescribing in people with dementia in England. We will be able to understand the impact of MR and DAR on these prescriptions. This will provide a means of assessing the extent of the problem of PIM in people with dementia and impact that contact with GP services through medication reviews and QOF incentives have on specific patient-focused outcomes such as appropriate prescribing.

E. Study Background

'Dementia' refers to a syndrome of terminal decline in multiple aspects of cognitive function and consequent independence in daily functioning, caused by one of a number of different underlying neurodegenerative diseases. In the UK there are over 800,000 people living with dementia [28]. People with dementia often have many comorbid conditions for which they are prescribed medications. However the harms of many commonly used medications can outweigh the benefits in people with dementia and much of this prescribing is considered 'potentially inappropriate'.

One of the most commonly used criteria for identifying potentially inappropriate prescribing is Beer's criteria for use in older adults [232]. Beer's includes medications or classes that should be avoided and disease-specific drugs to avoid and has been applied across healthcare settings [346]. However, a large proportion of medicines in Beer's are unavailable in the UK and Europe [106]. An alternative criteria, validated in the UK and Europe, is the Screening Tool of Older Person's Prescriptions (STOPP). This consists of 80 physiological systems-based criteria for screening inappropriate medication use in older adults [243]. Despite their differences in approach there is overlap in the medications and classes that are identified as potentially inappropriate in older people [347]. In people with dementia, antipsychotics, antidepressants and anticholinergics are implicated in both criteria for their potential adverse harms or for worsening cognitive impairment.

Increasing awareness of harms, including stroke and excess mortality, has led to a decrease in the prescription of antipsychotic medications following a dementia diagnosis in primary care in the UK (19.9% to 7.4%), whereas the use of antidepressant medications (10.7% to 26.3%) has risen across the same time period (1995 – 2011) [204]. During 2013 in Northern Ireland, 25.2% of people with dementia were being prescribed an anticholinergic medication [189] and in 2007 around 29% of people with dementia in the UK were prescribed any potentially inappropriate medication [291].

Potentially inappropriate medication use occurs where the associated harms outweigh potential benefit and in people with dementia there are a number of medications that are associated with particular adverse effects. The use of anticholinergic mediations is associated with delirium, sedation, urinary retention and increased cognitive impairments in people with dementia [213, 225]. Tricyclic antidepressants also have a high anticholinergic load and it is recommended that they are avoided in people with dementia due to their associated harms [232]. Tricyclics are also associated with orthostatic hypotension, sedation and cognitive impairment [213, 215, 348, 349]. All antidepressants have the potential for multiple adverse effects and the side effect profiles differ between the different types [348].

Used to treat acid related indigestion and peptic ulcers, proton pump inhibitors (PPIs) are one of the most frequently prescribed medications in the world [233] and are generally associated with few adverse effects, however they are costly and their frequent use significantly impacts NHS budgets, with over £100 million spent annually on PPIs in England [244]. In STOPP, PPIs are deemed inappropriate when used for peptic ulcer disease at maximum therapeutic dosage for >8 weeks. There have been several serious adverse effects associated with long-term PPI use, the strongest evidence is for Clostridium difficile infection and increased risk of bone fractures and there is some evidence for increased risk of pneumonia [238, 244, 350, 351]. Monitoring long-term PPI use could have implications on prescribing costs and appropriate and safe prescribing for patients. The prevalence of inappropriate PPI use

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ranges from 3.7% using UK Clinical Practice Research Datalink in 2007 (CPRD) to 22.9% using the Northern Ireland Enhanced Prescribing Database in 2013 [189, 291].

Primary care provides an integral role in the detection, diagnosis, management and support of people with dementia and their carers [352]. GPs are important in prescribing, managing and reviewing potentially harmful medications, such as the regular review of antipsychotic medications. The use of antipsychotic medications in people with mild-moderate dementia is not advised due to serious adverse effects [203, 353, 354]. When antipsychotics are used to manage severe and distressing behavioural and psychological symptoms it is recommended that they are used at the lowest dose for a limited time and regularly reviewed (every 3 months) [355].

Potentially, every GP consultation provides an opportunity for medications to be reviewed and changes to be implicated. Medication review (MR) is a term that encompasses a range of interventions that may be carried out by GPs, prescribing nurses or pharmacists, with and without the patient being present and can range from a token check to a full clinical review [356]. For older adults, government policy documents, such as the National Service Framework for Older People advocate that medications are reviewed at least annually and every 6 months for patients taking four or more medications [357].

In 2006, the dementia annual review (DAR) was introduced as a Quality Outcomes Framework (QOF) indicator for dementia care, providing a payment-based reward for quality GP practice care. The DAR is a yearly comprehensive review of the patients' physical, mental health and social review, access to support services, and a carer's assessment [111]. Variation in practice implementation means that the number of patients receiving a DAR ranges from around 50% - 86% [114] and previous research suggests that the quality and comprehensiveness of the reviews being conducted are variable [113]. Although not explicitly implicated, the DAR provides an opportunity to review and reduce potentially inappropriate medications implicated in people with dementia. The impact of DAR as an effective means of achieving this is unknown.

This study will estimate the recent prevalence of potentially inappropriate prescribing in people with dementia in primary care in England and the effect of medication review and DAR on these prescriptions. Specifically we will describe the prescription of four exemplar classes of PIM use including antipsychotics, anticholinergics, antidepressants and proton pump inhibitors, as well as the overall medication load.

F. Study Type

Prospective cohort study.

G. Study Design

The study period is 01/01/2015 to 30/04/2017. People with dementia diagnosed before or during the study period will be followed until death, leaving the practice or the end of the study period. A prospective cohort study method will be used to estimate the prevalence of a prescription of the selected potentially inappropriate medication in people with dementia between January 2015 and April 2017.

Within this period we will use longitudinal modelling to estimate the effect of the exposures (DAR and MR) on the prescription of potentially inappropriate medications in months following review, to determine how DAR and medication reviews affect inappropriate prescribing.

H. Feasibility counts

Using a restricted set of the most common diagnosis codes, there are 32,970 people with dementia in CPRD GOLD (October 2016 version) at some point during 2014 or 2015 period. Between 01/01/2014 – 31/12/15, 3434 of these were prescribed a tricyclic antidepressant on at least one occasion.

This is one of the rarer medication classes we are investigating, suggesting that all PIM groups in this cohort will be sufficiently frequent to permit our analysis. There are also an estimated 9,000 people with dementia who have a record of both a DAR and MR.

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I. Sample size considerations

There are an estimated 33,000 patients with dementia based in English CPRD GOLD registered practices at the start of the study period (01/01/2015) (sample size estimated from October 2016 version of CPRD GOLD). There are around 14000 patients with a dementia annual review and 16000 with a medication review Read code (CPRD GOLD 2015).

Our primary objective is the effect of DAR or MR on changing prescription of PIM classes. We have estimated the number of participants needed to demonstrate a change in potentially inappropriate medication (PIM) prevalence, using data from a recent RCT of medication reviews in the general older population [268], and considering a relatively rare PIM.

This has provided an illustrative example of the expected change in prescribing. The paired changes in PIM prescriptions before and after exposure (a medication review) are given in the table below.

Table 1. Proportion of rare PIM prescriptions, such as tricyclic antidepressants post-medication review, based upon Milos et al. (2013).

		Post-review		Total
		1	**0**	
Pre-review	**1**	0.03	0.02	0.05
	0	0.01	0.94	0.95
	Total	0.04	0.96	**1**

n.b. Odds Ratio = 2, Proportion of discordant pairs = 0.03

For a rare PIM, where baseline prevalence is around 5%, with a 2% reduction in PIM and 1% starting a PIM, to detect a difference following a exposure with 90% power (at significance level of $p = <0.05$) we will require a sample 2600 patients (for rare PIM, such as tricyclic antidepressant medications). To reflect the multiple testing correction with a significance level of $p=<0.005$ at 90% power we will require 4400 patients. More common PIM will require fewer participants, and this is comfortably within the 14000 patients with a dementia annual review code available in CPRD.

J. Data Linkage Required (if applicable):§

§*Please note that the data linkage/s requested in research protocols will be published by the CPRD as part of its*

transparency policy

IMD. Index of multiple deprivation quintile at the practice level is needed as a potential confounder.

K. Study population

All cases will be selected who meet the following criteria:

Diagnosis of dementia as defined by the presence of a record of a dementia diagnosis (see Appendix 1) or a prescription of a cognitive enhancer (i.e. memantine, donepezil, rivastigmine, or galantamine) before the start date (01/01/2015) or during the study period (01/01/2015 – 30/04/17). Including new diagnoses will maintain a representative sample of dementia patients throughout the study period.

- • Dementia diagnosis using similar definitions has been validated in CPRD with a positive predictive value (PPV) of 95% [252].

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- • Cognitive enhancers as a diagnosis of dementia will be used with caution. In some cases rivastigmine is used in patients with Parkinson's, without a clear diagnosis of dementia. However a limited number of diagnoses are identified through rivastigmine (approximately 0.3%) so this is unlikely to be a problem.
- • The study period has been selected in order to provide the most current estimate of the prevalence of medication use within this population and to account for at least one dementia annual review in every eligible patient.
- • Patients excepted from the QOF indicator for dementia annual review will also be included in analyses. On average 12.7% of patients were excepted for dementia QOF indicators (2015-2016). Any potential confounding effect of QOF exception will be controlled for by adding a covariate indicating QOF exception at or before any point during each time period into the analysis. Exceptions will be defined using Read Codes 9hD..00 (Exception reporting: dementia quality indicators), 9hD0.00 (Excepted from dementia quality indicators: Patient unsuitable) 9hD1.00 (Excepted from dementia quality indicators: Informed dissent) and 8CMZ200, 8IAe000, 8IAe200 and 8CMZ300.

Registered with an 'Up To Standard' (research quality) practice in England for 1 year before study entry. This will allow for appropriate measurement of baseline covariates.

- • We will restrict to practices in England to ensure the quality of DAR recording, as QOF guideline agreements are different in England compared to agreements in Scotland, Northern Ireland and Wales [358].

The study population included in the analysis addressing aim 2, estimating the change in probability of being prescribed a potentially inappropriate medication before and after a MR or DAR, will by necessity only include patients with dementia who have a record of i) dementia annual review ii) medication review iii) dementia annual review and medication review.

- • Dementia annual review will be defined by the presence of the Read Code 6AB..00 within the defined follow-up time points.

- • The presence of a Read code identifying that a medication review took place within the follow-up time points (see Appendix 2 for codes).

L.   Selection of comparison group(s) or controls

There are no controls or comparison groups in this study.

M. Exposures, Health Outcomes§ and Covariates
§*Please note: Summary information on health outcomes (as included on the ISAC application form above)will be published on CPRD's website as part of its transparency policy*

Exposures:
Dementia Annual Review: Dementia annual review will be defined by the presence of the Read Code 6AB..00 within the defined follow-up time points.

Medication review: The presence of a Read code identifying that a medication review took place within the follow-up time points (see Appendix 2 for codes).

*Incident cases for the first year since diagnosis, another code of newly diagnosed – may not always be possible

Health outcomes:
We will extract the presence of a prescription for the selected potentially inappropriate medications, defined using World Health Organisation Anatomical Therapeutic Chemical Classification System (ATC) codes.

The presence of each of the following PIMs will be coded within each of 12 2-month time periods between January 2015 and April 2017 for each patient conditional on their inclusion in the study for the whole of that period.

1.   Antipsychotic medication will be defined using ATC code N0A5A (see Appendix 3a).

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2. Tricyclic antidepressants will be defined using ATC codes. Antidepressants (ATC N06A) are grouped into tricyclic antidepressant sub-type, according to ATC cross-referenced with the British National Formulary (BNF) to identify those used in UK practice (ATC N06AA02, N06AA03, N06AA04, N06AA06, N06AA07, N06AA09, N06AA10, N06AA12, N06AA16, N06AX03 and N06AX05) (see Appendix 3b).

3. Definite anticholinergic medication will be defined as any medication with an Anticholinergic Cognitive Burden (ACB) score of 3. An ACB=3 score indicates medications with definite anticholinergic activity and severe negative cognitive effects [254] (see Appendix 3c).

4. Proton pump inhibitors are implicated as potentially inappropriate, according to Beer's and STOPP criteria when they are used to treat peptic ulcer disease at maximum therapeutic dose for >8 weeks. Their use will be defined using ATC code A02BC (see Appendix 3d), at maximum dose and the presence of a Read code indicating peptic ulcer disease (J13y200, J13z.00, 12E1.00, 14C1.00, J130200, J13y100, J13..00).

5. A binary indicator representing the use of any of the above PIMs

6. A continuous indicator of the total number of prescribed medicines within the 2-month time periods. This will include all prescribed medications but exclude devices, dressings and topical preparations.

All health outcomes will be measured as the presence of a prescription at any point within the 2-month time periods.

Covariates
Potentially confounding variables will be coded at the date of study entry. Demographic factors including **age, sex, comorbidity, IMD and GP practice** were selected on the basis of factors that are potentially linked to the prescription of potentially inappropriate medications and use of DAR.
- Comorbidity will be defined using the Charlson Comorbidity Index (CCI) [258]. The CCI is the most widely validated and used comorbidity score [260]. Comorbidity score will be calculated using Read Codes that have been validated for use in CPRD [259, 261].
  - IMD for England [359] is based on levels of income, employment, health, education, crime, access to services and living environment. Differential prescribing according to area-level deprivation has been identified in people with dementia [360].
  - GP practice-level variation in safe prescribing has previously identified in CPRD [116].

An additional covariate to account for **QOF exception patients** will also be included at each time point.
- Between 2015-2016 an average of 12.7% of patients in England were excepted from QOF dementia indicators. Exceptions to QOF indicators can occur when a patient is deemed clinically unsuitable or the patient declines.
- Exceptions will be defined using Read Codes 9hD..00 (Exception reporting: dementia quality indicators), 9hD0.00 (Excepted from dementia quality indicators: Patient unsuitable) 9hD1.00 (Excepted from dementia quality indicators: Informed dissent) and 8CMZ200, 8IAe000, 8IAe200 and 8CMZ300.

An additional covariate to account for care home residence will be included to account for variation in prescribing in care homes compared to patients with dementia living in the community. Whether a patient is resident in a care home will be defined using Med Codes indicating care/nursing/residential home and Consultation Type codes indicating that the consultation took place in a care home.

N. Data/ Statistical Analysis

Aim 1) To estimate the prevalence of PIM use in people with dementia in primary care in England between 2015 and 2017. The prevalence of each health outcome (antipsychotics, tricyclic antidepressants, definite anticholinergics and proton pump inhibitors) and the mean number will be estimated in each 2 month period across the study period. For each period we will include patients with a dementia diagnosis at or before the start of that period and who remained in the study for its duration.

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Aim 2) To estimate the change in probability of being prescribed a potentially inappropriate medication before and after a MR or DAR. For each participant the first DAR and first medication review within the study period will be identified. The presence of each binary outcome, and the number of prescriptions will be described in the 2 month period preceding the one including the index review and in the two month period after the period including index review. The DAR and medication review will be treated separately in analyses.

The presence of PIM will be described in the 2 month period preceding and post the index review to reliably capture the effect of the review on changes in prescriptions, comparing the prescriptions before and after the review.

McNemar tests will be used to test the hypothesis of no change in binary outcomes PIM (antipsychotics, tricyclic antidepressants, definite anticholinergics, proton pump inhibitors) before and after the review. Wilcoxon signed rank tests will test the hypothesis of no change in the number of prescriptions in the periods before and after the review.

Aim 3) To estimate the patient and practice level factors associated with each PIM in people with dementia, including the effect of age, sex, comorbidity, area-level deprivation, residual between practice variation and QOF exception. Multilevel mixed effects logistic regression models will be used to estimate patient and practice level factors associated with each PIM (antipsychotic, tricyclic antidepressants, definite anticholinergics and proton pump inhibitors) during each 2 month period. The regression models will include fixed effects of age, sex, comorbidities, area-level deprivation, DAR in the previous period and MR in the previous period, care home residence and as well as random effects of GP practice and within-patient variation. The DAR and MR will be treated separately in analyses.

For primary outcomes we will set the threshold for significance following the Benjamini-Hochberg (41, 42) procedure to control the false discovery rate at 0.05, using 12 tests corresponding to six primary outcomes and two primary exposures.

Analyses will be stratified by care home residence to account for confounding.

Sensitivity analyses

Sensitivity analyses will be performed repeating analyses addressing **Aim 1) Estimating the prevalence of PIM use in people with dementia in primary care in England between 2015 and 2017.** The analysis will be repeated in 1 month and 3 month time periods, instead of 2 months as per primary analysis.

O. Plan for addressing confounding

Using logistic regression analyses we will be able to adjust for age, sex, comorbidity, deprivation and random practice and individual variation. Patients will be censored at the time-period in which they leave the practice, die or at the end of the study period (30/04/2017). The main effect of interest will be estimated primarily based on within-patient comparisons and so the potential for patient-level confounders to affect results is limited. Dementia review should be scheduled annually irrespective of patient-level factors. It is likely that practice level variation exists so we will adjust for random effect of practice in our analysis.

Potential confounding may occur due to the patients living in a care/nursing/residential home. This will be adjusted for by stratifying analyses by care home residence to explore the confounding role of residential status on PIM prescription.

P. Plans for addressing missing data

Since the exposure of a DAR or medication review, the outcomes of potentially inappropriate prescriptions and comorbidity will be treated as binary variables (present in the patient record or not), there is no potential for data to be 'missing'. We will only include patients from practices with practice level IMD available. Patients with no information on age or sex will be excluded.

The residential status of the patients is often unclear, we will be able to ascertain if a patient has had a consultation in a care home using Consultation Type codes. These provide an indication that the patient was resident in a care

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home. An alternative assumption will be that if there is no record of 'care home' then the patient is resident in their own home or at least, not in a care home. Therefore, whilst there will be data missing, this will be recorded as 'not care home' and will be assumed they are resident in their own home.

Q. Patient or user group involvement (if applicable)

Carers of people with dementia and health professionals working with people with dementia have been involved in various projects within the pharmacoepidemiology research group at the University of East Anglia and will continue to be involved in separate advisory groups throughout this study. The advisory groups and Alzheimer's Society Research Network Volunteers have assisted in the development of the protocol and will continue to inform the study and the dissemination of the findings.

R. Plans for disseminating and communicating study results, including the presence or absence of any restrictions on the extent and timing of publication

We will be working towards publication and dissemination by January 2018. We plan to present the work in academic papers and at international (such as Alzheimer's Disease International 2017 and UK dementia conferences (Alzheimer's Society Research conference 2017) and one health professionals conference (e.g. British Society of Gerontology, 2017).

S. Limitations of the study design, data sources, and analytic methods

Study design: We cannot measure and so cannot account for the potential confounder of the patient's residential status (community or care home). Medicine use can vary across these settings and there is likely to be more potentially inappropriate prescribing in care homes [361–363]. Additionally, the use of DAR may be less in care homes as exceptions can be made, making the patient exempt from the review if the patient is terminally ill, extremely frail or the severity of their condition may inhibit their engagement with the review [111].

We have selected medications using advice from prescribers and used STOPP and Beer's to identify medications that are specifically implicated in people with dementia. This provides a means of focusing on medications that can be targeted and are indicative of an overall pattern of prescribing quality, however these are not exhaustive and we will not be accounting for the range of potentially inappropriate prescribing that may exist in primary care in this population.

Inappropriate PPI use is implicated when it is used to treat peptic ulcer disease at maximum therapeutic for >8 weeks. We will measure PPI use as a single prescription within each 2 month period however we will not know whether the PPI use is continuous for 8 weeks across this time. Additionally, we may not have the full comorbidity information that is required to implement the STOPP or Beer's Criteria for PPI use. Inappropriate PPI use in this case is indicated for peptic ulcer disease. We will account for this by identifying patients who also have a Read code for 'peptic ulcer disease', but it may be difficult to account for the duration of use in relation to this disease and the duration of medication use.

Data sources: We will not know the severity of the dementia, which would be implicated in the prescription of antipsychotic medications which are used to manage severe behavioural and psychological symptoms of dementia. We will not know the indications for most medications so we will be unable to make individual judgments about whether a medication is appropriate or not. PIM criteria are an indication that medications are likely to be inappropriate, and so are useful to judge the quality of prescribing in a population rather than within individuals.

Analytic methods: By using binary outcomes to assess the presence or not of particular PIM we may miss subtle changes in medication dosage that may change as a result of the medication review. However, the selected medications are implicated in criteria that suggest stopping rather than reducing the dosage.

10.05 Appendix 5 Medication coding lists

(a) Anticholinergics

ATC	Anticholinergic drug	ACB
		3
N06AA09	Amitriptyline	3
A06AA17	Amoxapine	
N06AA09	Amitriptyline	3
N06AA09	Amitriptyline	3
A03BA01	Atropine	3
A03BA01	Atropine	3
N04Ac01	Benztropine	
R06AB01	Brompheniramine	3
R06AA08	Carbinoxamine	
R06AB04	Chlorphenamine	3
R06AB04	Chlorphenamine	3
N05AA01	Chlorpromazine	3
R06AA04	Clemastine	3
N06AA04	Clomipramine	3
N05AH02	Clozapine	3
G04BD10	Darifenacin	3
N06AA01	Desipramine	
A03AA07	Dicyclomine	3
R06AA52	Dimenhydrinate	3
R06AA02	Diphenhydramine	3
N06AA12	Doxepin	3
R06AA09	Doxylamine	3
G04BD011	Fesoterodine fumarate	3
G04BD02	Flavoxate	3
A02BX03	Homatropine	3
N05BB01	Hydroxyzine	3
N05BB01	Hydroxyzine	3
A03BA03	Hyoscymine	3
N06AA02	Imipramine	3
R06AE05	Meclizine	
M03BA03	Methocarbamol	3
N06AA10	Nortriptyline	3
N06AA10	Nortriptyline,flupenazine	3
N05AH03	Olanzapine	3
M03BC01	Orphenadrine	3
G04BD04	Oxybutynin	3
N06AB05	Paroxetine	3
N05AB03	Perphenazine	3
R06AD02	Promethazine	3
A03AB05	Propantheline	3
G04BD06	Propiverine hydrochloride	3
N05AH04	Quetiapine	3
G04BD08	Solifenacin succinate	3
G04BD05	Terodiline	3
N05AC02	Thioridazine	3
G04BD07	Tolterodine	3
G04BD07	Tolterodine	3

N05AB06	Trifluoperazine	3
N04AA01	Trihexyphenidyl	3
N06AA06	Trimipramine	3
G04BD09	Trospium chloride	3

(b) Proton Pump Inhibitors

Proton Pump Inhibitors

CIMETIDINE	*CIMETIDINE+ALGINIC chew tabs	RANITIDINE 150mg/10mL s/f syr
TAGAMET 200mg tablets	*CIMETIDINE+ALGINIC chew tabs	RANITIDINE 150mg/10mL s/f soln
TAGAMET 400mg tablets	*CIMETIDINE+ALGINATE susp	RANITIDINE 150mg tablets
TAGAMET 800mg tablets	*CIMETIDINE+ALGINATE susp	*RANITIDINE 150mg disp tabs
TAGAMET 200mg/5mL syrup	CIMETIDINE 200mg tablets	RANITIDINE 300mg tablets
*TAGAMET 200mg/2mL injection	CIMETIDINE 400mg tablets	RANITIDINE 50mg/2mL injection
*TAGAMET 4mg/mL i-v inf 100mL	CIMETIDINE 800mg tablets	PIRENZEPINE
*DYSPAMET CHEWTAB 200mg tabs	CIMETIDINE 200mg/5mL syrup	*GASTROZEPIN 50mg tablets
*DYSPAMET 200mg/5mL suspension	*CIMETIDIN 200mg/2mL injection	*PIRENZEPINE 50mg tablets
*CIMETIDNE 200mg/5mL sus 600mL	*CIMETIDINE 4mg/mL i-v inf	BISMUTH CHELATE
*GALENAMET 200mg tablets	RANITIDINE	*DE-NOL 120mg/5mL liquid 100mL
*GALENAMET 400mg tablets	ZANTAC 150mg tablets	*DE-NOL 120mg/5mL liquid 560mL
*GALENAMET 800mg tablets	*ZANTAC 150mg disp tabs	DE-NOLTAB 120mg tablets
*CIMETIDINE 400mg eff tabs	ZANTAC 300mg tablets	*BISMUTH CHELATE 120mg/5mL liq
*CIMETIDINE 200mg chew tabs	ZANTAC 50mg/2mL injection	BISMUTH CHELATE 120mg tablets
*PHIMETIN 200mg tablets	ZANTAC 150mg/10mL sf syr 300mL	SUCRALFATE
*PHIMETIN 400mg tablets	ZANTAC EFFERVESCENT 150mg tabs	ANTEPSIN 1g tablets
*PHIMETIN 800mg tablets	ZANTAC EFFERVESCENT 300mg tabs	ANTEPSIN 1g/5mL suspension
CIMETIDINE 200mg/5mL s/f soln	RANITIDINE 150mg eff tabs	SUCRALFATE 1g/5mL suspension
*CIMETIDINE 400mg/100mL inf	RANITIDINE 300mg eff tabs	SUCRALFATE 1g tablets
*ZITA 200mg tablets	*RACIRAN 150mg tablets	CARBENOXOLONE SODIUM [GI]
*ZITA 400mg tablets	*RACIRAN 300mg tablets	*BIOGASTRONE 50mg tablets
*ZITA 800mg tablets	*ZAEDOC 150 tablets	*DUOGASTRONE 50mg tablets
*ULTEC 200mg tablets	*ZAEDOC 300 tablets	*PYROGASTRONE chewable tablets
*ULTEC 400mg tablets	*RANTEC 150mg tablets	*PYROGASTRONE liquid
*ULTEC 800mg tablets	*RANTEC 300mg tablets	*CARBENOXOLONE SOD 50mg tabs
*ACITAK-200 tablets	RANITIC 150mg tablets	LIQUORICE DEGLYCYRRHIZINISED
*ACITAK-400 tablets	RANITIC 300mg tablets	*CAVED-S tablets
*ACITAK-800 tablets	HISTAC 150mg tablets	*RABRO tablets
*TAGAMET DUAL ACTION liq 200mL	HISTAC 300mg tablets	FAMOTIDINE
*TAGAMET DUAL ACTION liq 600mL	RANITIL 150mg tablets	FAMOTIDINE 20mg tablets
*ALGITEC 200mg/500mg chew tabs	RANITIL 300mg tablets	FAMOTIDINE 40mg tablets
*ALGITEC 100mg/250mg/5mL susp	ZANTAC 75 DISSOLVE eff tabs	PEPCID 20mg tablets
*CIMETIDINE COMPOUND susp	RANITIDINE 75mg tablets	PEPCID 40mg tablets
*TAGAMET EFFERVESC 400mg tabs	GAVILAST-P 75mg tablets	NIZATIDINE
*PEPTIMAX 200mg tablets	RANZAC 75mg tablets	NIZATIDINE 150mg capsules
*PEPTIMAX 400mg tablets	ZANTAC 75 tablets	NIZATIDINE 300mg capsules

*PEPTIMAX 800mg tablets	RANITIDINE 75mg eff tablets	AXID 150mg capsules
		AXID 300mg capsules
		*AXID 100mg/4mL injection
*NIZATIDINE 100mg/4mL inj	*NIZATIDINE 100mg/4mL inj	*OMEPRAZOLE 20mg e/c tablets
*ZINGA 150mg capsules	*ZINGA 150mg capsules	*OMEPRAZOLE 40mg e/c tablets
*ZINGA 300mg capsules	*ZINGA 300mg capsules	OMEPRAZOLE 10mg tablets
MISOPROSTOL	MISOPROSTOL	OMEPRAZOLE 20mg tablets
MISOPROSTOL 200mcg tablets	MISOPROSTOL 200mcg tablets	OMEPRAZOLE 40mg tablets
CYTOTEC 200micrograms tablets	CYTOTEC 200micrograms tablets	LANSOPRAZOLE
*CYTOTEC 200microgram tablets	*CYTOTEC 200microgram tablets	*ZOTON 30mg capsules
OMEPRAZOLE	OMEPRAZOLE	LANSOPRAZOLE 30mg capsules
OMEPRAZOLE 20mg e/c capsules	OMEPRAZOLE 20mg e/c capsules	LANSOPRAZOLE 15mg capsules
*LOSEC 20mg capsules x28	*LOSEC 20mg capsules x28	*ZOTON 15mg capsules
LOSEC 20mg capsules	LOSEC 20mg capsules	*LANSOPRAZOLE 30mg suspension
LOSEC 40mg capsules	LOSEC 40mg capsules	*ZOTON 30mg oral suspension
OMEPRAZOLE 40mg e/c capsules	OMEPRAZOLE 40mg e/c capsules	LANSOPRAZOLE 15mg disp tabs
LOSEC 10mg capsules	LOSEC 10mg capsules	LANSOPRAZOLE 30mg disp tabs
OMEPRAZOLE 10mg e/c capsules	OMEPRAZOLE 10mg e/c capsules	ZOTON FASTAB 15mg disp tabs
OMEPRAZOLE 40mg inj pdr+solv	OMEPRAZOLE 40mg inj pdr+solv	ZOTON FASTAB 30mg disp tabs
LOSEC 40mg inj powder+solvent	LOSEC 40mg inj powder+solvent	RANITIDINE BISMUTH CITRATE
OMEPRAZOLE 40mg i-v inf powder	OMEPRAZOLE 40mg i-v inf powder	RANITIDINE BISMUTH CITRATE
LOSEC 40mg i-v infusion powder	LOSEC 40mg i-v infusion powder	*RANITIDINE BISMUTH 400mg tabs
LOSEC MUPS 10mg tablets	LOSEC MUPS 10mg tablets	*RANITIDINE BISMUTH 400mg tabs
LOSEC MUPS 20mg tablets	LOSEC MUPS 20mg tablets	*PYLORID 400mg tablets
LOSEC MUPS 40mg tablets	LOSEC MUPS 40mg tablets	PANTOPRAZOLE
*OMERAN 10mg e/c tablets	*OMERAN 10mg e/c tablets	PANTOPRAZOLE 40mg e/c tablets
*OMERAN 20mg e/c tablets	*OMERAN 20mg e/c tablets	PROTIUM 40mg e/c tablets
*OMERAN 40mg e/c tablets	*OMERAN 40mg e/c tablets	PANTOPRAZOLE 40mg inj powder
ZANPROL 10mg e/c tablets	ZANPROL 10mg e/c tablets	PROTIUM I.V 40mg inj powder
*GALPHARM HEARTBURN 10mg tabs	*GALPHARM HEARTBURN 10mg tabs	PANTOPRAZOLE 20mg e/c tablets
*GALPHARM HEARTBURN 10mg tabs	*GALPHARM HEARTBURN 10mg tabs	PROTIUM 20mg e/c tablets
UNICHEM HRTBRN RELIEF 10mg tab	UNICHEM HRTBRN RELIEF 10mg tab	RABEPRAZOLE SODIUM
UNICHEM HRTBRN RELIEF 10mg tab	UNICHEM HRTBRN RELIEF 10mg tab	RABEPRAZOLE NA 10mg e/c tabs
VANTAGE HRTBURN RELF 10mg tabs	VANTAGE HRTBURN RELF 10mg tabs	RABEPRAZOLE NA 20mg e/c tabs
CARE HEARTBURN RELIF 10mg tabs	CARE HEARTBURN RELIF 10mg tabs	PARIET 10mg e/c tablets
NUMARK HEARTBURN RLF 10mg tabs	NUMARK HEARTBURN RLF 10mg tabs	PARIET 20mg e/c tablets
MEPRADEC 10mg e/c capsules	MEPRADEC 10mg e/c capsules	COMBINATION ULCER HEALING DRUG
MEPRADEC 20mg e/c capsules	MEPRADEC 20mg e/c capsules	*CLARITHROMY+LANSOPRZ+AMOX pck
	OMEPRAZOLE 10mg e/c tablets	*HELICLEAR triple pack
*CLARITH+LANSOPRZ+METRONID pck	NEXIUM 20mg tablets	ESOMEPRAZOLE 40mg i-v inj pdr
*HELIMET triple pack	NEXIUM 40mg tablets	ESOMEPRAZOLE 40mg tablets
ESOMEPRAZOLE	NEXIUM 40mg i-v inj powder	ESOMEPRAZOLE 20mg tablets

(c)   CFAS Medication categorisation: drugs lists used to define exposure groups.

Antipsychotics

d411.	Chlorpromazine
d412.	Chlorpromazine
d413.	Chlorpromazine
d414.	Chlorpromazine
d415.	Chlorpromazine
d41a.	Chlorpromazine
d41b.	Chlorpromazine
d41c.	Chlorpromazine
d41d.	Chlorpromazine
d4b1.	Perphenazine
d4e1.	PROMAZINE
d4ex.	PROMAZINE
d4g..	Thioridazine
d4g1.	Thioridazine
d4g2.	Thioridazine
d4g3.	Thioridazine
d4g5.	Thioridazine
d4g7.	Thioridazine
d4gp.	Thioridazine
d4gt.	Thioridazine
d4gu.	Thioridazine
d4gv.	Thioridazine
d4gw.	Thioridazine
d4gz.	Thioridazine
d4h..	Trifluoperazine
d4h1.	Trifluoperazine
d4h2.	Trifluoperazine
d4h3.	Trifluoperazine
d4h4.	Trifluoperazine
d4hs.	Trifluoperazine
d4ht.	Trifluoperazine
d4hu.	Trifluoperazine
d4hx.	Trifluoperazine
d4l2.	CLOZAPINE
d4r1.	OLANZAPINE
d4r3.	OLANZAPINE
d4r7.	OLANZAPINE
d4s1.	QUETIAPINE
d4s2.	QUETIAPINE
d4s3.	QUETIAPINE
d4s5.	QUETIAPINE
d4ss.	QUETIAPINE
d4sx.	QUETIAPINE

Tricyclic antidepressants

d7...	
d71..	Amitriptyline
d711.	Amitriptyline
d712.	Amitriptyline
d713.	Amitriptyline
d719.	Amitriptyline
d71a.	Amitriptyline
d71b.	Amitriptyline
d71c.	Amitriptyline
d71d.	Amitriptyline
d71e.	Amitriptyline
d71f.	Amitriptyline
d71u.	Amitriptyline
d71v.	Amitriptyline
d71w.	Amitriptyline
d71y.	Amitriptyline
d71z.	Amitriptyline
d73..	Clomipramine
d731.	Clomipramine
d732.	Clomipramine
d733.	Clomipramine
d736.	Clomipramine
d73s.	Clomipramine
d73t.	Clomipramine
d73u.	Clomipramine
d73v.	Clomipramine
d73w.	Clomipramine
d73z.	Clomipramine
d75..	DOSULEPIN
d751.	DOSULEPIN
d752.	DOSULEPIN
d755.	DOSULEPIN
d756.	DOSULEPIN
d75y.	DOSULEPIN
d75z.	DOSULEPIN
d761.	Doxepin
d762.	Doxepin
d765.	Doxepin
d76w.	Doxepin
d76x.	Doxepin
d76y.	Doxepin
d76z.	Doxepin
d77..	Imipramine

d771.	Imipramine
d772.	Imipramine
d775.	Imipramine
d776.	Imipramine
d79..	Lofepramine
d791.	Lofepramine
d79z.	Lofepramine
d7a2.	Maprotiline
d7a3.	Maprotiline
d7b..	MIANSERIN
d7b1.	MIANSERIN
d7b3.	MIANSERIN
d7b4.	MIANSERIN
d7b7.	MIANSERIN
d7b9.	MIANSERIN
d7c1.	Nortriptyline
d7c3.	Nortriptyline
d7c6.	Nortriptyline
d7c8.	Nortriptyline
d7cy.	Nortriptyline
d7d3.	Protriptyline
d7f1.	Trimipramine
d7f2.	Trimipramine
d7f3.	Trimipramine
d7fx.	Trimipramine
d7fy.	Trimipramine
d7fz.	Trimipramine
d911.	Amitriptyline
d913.	Nortriptyline,flupenazine
d914.	Nortriptyline,flupenazine
d916.	Amitriptyline
d917.	Amitriptyline

Other anticholinergics

Code	Drug
A4...	
A41..	Atropine
A451.	Dicyclomine
A453.	Dicyclomine
A454.	Dicyclomine
A455.	Dicyclomine
A45x.	Dicyclomine
A45y.	Dicyclomine
A471.	HYOSCINE
A473.	HYOSCINE
A47y.	HYOSCINE
A4b1.	Poldine methyl
A4by.	Poldine methyl
A4c1.	Propantheline
A4c2.	Propantheline
A821.	Atropine
A823.	Atropine
Bf2f.	HOMATROPINE
C831.	Brompheniramine
C833.	Brompheniramine
C84..	Chlorphenamine
C841.	Chlorphenamine
C843.	Chlorphenamine
C84x.	Chlorphenamine
C84y.	Chlorphenamine
C851.	Clemastine
C85y.	Clemastine
C88	Diphenhydramine
C882.	Diphenhydramine
C885.	Diphenhydramine
C888.	Diphenhydramine
C8a..	Hydroxyzine
C8i1.	Promethazine
C8i2.	Promethazine
C8i9.	Promethazine
C8iu.	Promethazine
C8iv.	Promethazine
C8iw.	Promethazine
Ch2h.	Diphenhydramine
Ci1l.	CHLORPHENAMINE
D28..	Hydroxyzine
D284.	Hydroxyzine
D281.	Hydroxyzine
D282.	Hydroxyzine
D28x.	Hydroxyzine
D28y.	Hydroxyzine
Da6..	Paroxetine
Da61.	Paroxetine
Da62.	Paroxetine
Da63.	Paroxetine
Da64.	Paroxetine
Da65.	Paroxetine
Da67.	Paroxetine
Da68.	Paroxetine
Dh51.	Dimenhydrinate
Dias.	Promethazine
Dr11.	Trihexyphenidyl
Dr12.	Trihexyphenidyl
Dr13.	Trihexyphenidyl
Dr14.	Trihexyphenidyl
Dr1w.	Trihexyphenidyl
Dr1x.	Trihexyphenidyl
Dr22.	Orphenadrine
Dr2y.	Orphenadrine
Dr51.	Anti-muscarinic
Dr6..	Procyclidine
Dr63.	Procyclidine
Dr6w.	Procyclidine
Dr6y.	Procyclidine
Gd...	Tolterodine
Gd21.	
Gd41.	Flavoxate
Gd42.	Flavoxate
Gd4y.	Flavoxate
Gd4z.	Flavoxate
Gd92.	Terodiline
Gd9z.	Terodiline
Gda..	Oxybutynin
Gda1.	Oxybutynin
Gda1.	TOLTERODINE
Gda5.	Oxybutynin
Gda6.	Oxybutynin
Gda7.	Oxybutynin
Gda9.	Oxybutynin
Gdaa.	Oxybutynin
Gdag.	Oxybutynin
Gdai.	Oxybutynin
Gdax.	Oxybutynin
Gday.	Oxybutynin
Gdaz.	Oxybutynin
Gdb1.	TROSPIUM CHLORIDE
Gdby.	TROSPIUM CHLORIDE
Gdbz.	TROSPIUM CHLORIDE
Gdc1.	PROPIVERINE HYDROCHLORIDE
Gdc2.	PROPIVERINE HYDROCHLORIDE
Gdc4.	PROPIVERINE HYDROCHLORIDE
Gdd1.	SOLIFENACIN SUCCINATE
Gdd2.	SOLIFENACIN SUCCINATE
Gddy.	SOLIFENACIN SUCCINATE
Gddz.	SOLIFENACIN SUCCINATE
Gdfz.	DARIFENACIN
Gdg2.	FESOTERODINE FUMARATE
Gdgy.	FESOTERODINE FUMARATE
Gdgz.	FESOTERODINE FUMARATE
J851.	METHOCARBAMOL
J85y.	METHOCARBAMOL
O311.	Atropine
O522.	Chlorpromazine
Gda2.	TOLTERODINE
Gda2.	Oxybutynin
Gda3.	Oxybutynin
Gda4.	Oxybutynin
Gda4.	TOLTERODINE
Gda5.	TOLTERODINE
Gda6.	TOLTERODINE
Ci1p.	CHLORPHENAMINE
Ci1q.	CHLORPHENAMINE

Other antidepressants			Benzodiazepines	
D8...	monoamine-oxidase inhibitors		D14..	Flunitraze
D8...	monoamine-oxidase inhibitors		d141.	Rohypnol
D81..	phenelzine		d14z.	Flunitraze
D811.	nardil 15mg tablets		d15..	Flurazepam
D81z.	phenelzine 15mg tablets		d151.	Dalmane
D82..	*iproniazid		d152.	Dalmane
D821.	*marsilid 25mg tablets		d153.	Paxane
D822.	*marsilid 50mg tablets		d154.	Paxane
D82y.	*iproniazid 25mg tablets		d15y.	Flurazepam
D82z.	*iproniazid 50mg tablets		d15z.	Flurazepam
D83..	isocarboxazid		d16..	Loprazolam
D831.	*marplan 10mg tablets		d161.	Loprazolam
D83z.	isocarboxazid 10mg tablets		d162.	Dormonoct
D84..	tranylcypromine		d17..	Lormetazep
D841.	*parnate 10mg tablets		d171.	Lormetazep
D84z.	tranylcypromine 10mg tablets		d172.	Lormetazep
D85..	moclobemide		d173.	
D851.	manerix 150mg tablets		d174.	
D852.	moclobemide 150mg tablets		d18..	Nitrazepam
D853.	manerix 300mg tablets		d181.	Nitrazepam
D854.	moclobemide 300mg tablets		d182.	Nitrazepam
D9...	compound antidepressant drugs		d183.	Nitrazepam
D91..	compound antidepressants a-z		d184.	Nitrazepam
D911.	*limbitrol 5 capsules		d185.	Mogadon
D912.	*limbitrol 10 capsules		d186.	Mogadon
D913.	*motipress tablets x28cp		d187.	Nitrados
D914.	*motival tablets		d188.	
D915.	*parstelin tablets		d189.	Remnos
D916.	triptafen tablets		d18a.	Remnos
D917.	triptafen-m tablets		d18b.	
Da2..	tryptophan		d18c.	Somnite
Da21.	optimax 500mg tablets		d18d.	
Da22.	*optimax 1g/6g powder		d18e.	Unisomnia
Da23.	*optimax wv 500mg tablets		d18f.	Nitrazepam
Da24.	*pacitron 500mg tablets		d1a..	Temazepam
Da2y.	tryptophan 500mg tablets		d1a1.	Temazepam
Da2z.	*tryptophan 1g/6g powder		d1a2.	Temazepam
Da3..	fluvoxamine maleate		d1a3.	Temazepam
Da31.	faverin 50mg tablets		d1a4.	Temazepam
Da32.	fluvoxamine maleate 50mg tabs		d1a5.	Temazepam
Da33.	faverin 100mg tablets		d1a6.	Normison
Da34.	fluvoxamine maleate 100mg tabs		d1a7.	Normison
Da4..	fluoxetine hydrochloride		d1a8.	Temazepam
Da41.	fluoxetine 20mg capsules		d1a9.	Temazepam
Da42.	*prozac 20mg capsules x30		d1aa.	Temazepam
Da43.	fluoxetine 20mg/5ml oral liq		d1ab.	Temazepam
Da44.	prozac 20mg/5ml oral liquid		d1ac.	Temazepam
Da45.	prozac 20mg capsules		d1ad.	Temazepam
Da46.	fluoxetine 60mg capsules		d1ae.	Temazepam
Da47.	*prozac 60mg capsules		d1af.	Temazepam
Da48.	*felicium 20mg capsules		d1ag.	Temazepam
Da49.	oxactin 20mg capsules		d1ah.	Temazepam
Da4a.	ranflutin 20mg capsules		d1ai.	Temazepam
Da4b.	prozit 20mg/5ml oral solution		d1aj.	Temazepam
Da4c.	prozep 20mg/5ml oral solution		d1ak.	Temazepam
Da5..	sertraline hydrochloride		d1al.	Euhypnos
Da51.	sertraline 50mg tablets		d1am.	Euhypnos
Da52.	sertraline 100mg tablets		d1an.	Euhypnos
Da53.	lustral 50mg tablets		d1ao.	Temazepam
Da54.	lustral 100mg tablets		d1b..	Triazolam
Da6..	paroxetine hydrochloride		d1b1.	Triazolam
Da61.	paroxetine 20mg tablets		d1b2.	Triazolam
Da62.	seroxat 20mg tablets x30		d1b3.	Halcion
Da63.	paroxetine 30mg tablets		d1b4.	Halcion
Da64.	seroxat 30mg tablets x30		d21..	Diazepam
Da65.	paroxetine 10mg/5ml s/f liq		d211.	Diazepam
Da66.	seroxat 10mg/5ml s/f liq		d212.	Diazepam
Da67.	paroxetine 10mg tablets		d213.	Diazepam
Da68.	seroxat 10mg tablets		d214.	Diazepam
Da7..	venlafaxine		d215.	Diazepam

Da71.	venlafaxine 37.5mg tablets	d216.	Diazepam
Da72.	venlafaxine 75mg tablets	d217.	
Da73.	efexor 37.5mg tablets	d218.	
Da74.	efexor 75mg tablets	d219.	
Da75.	*venlafaxine 50mg tablets	d21a.	Diazepam
Da76.	*efexor 50mg tablets	d21b.	Rimapam
Da77.	venlafaxine 75mg m/r capsules	d21c.	Rimapam
Da78.	efexor xl 75mg m/r capsules	d21d.	Rimapam
Da79.	venlafaxine 150mg m/r capsules	d21e.	Dialar
Da7a.	efexor xl 150mg m/r capsules	d21f.	Dialar
Da8..	nefazodone	d21g.	Valclair
Da81.	*nefazodone hcl 100mg tabs	d21j.	Diazepam
Da82.	*nefazodone hcl 200mg tabs	d21a.	Atensine
Da83.	*dutonin 100mg tablets	d21b.	Atensine
Da84.	*dutonin 200mg tablets	d21c.	Atensine
Da85.	*nefazodone initiation tabs pk	d21d.	Diazemuls
Da86.	*dutonin initiation tabs pack	d21e.	
Da9..	citalopram	d21f.	
Da91.	citalopram 20mg tablets	d21g.	
Da92.	cipramil 20mg tablets	d21h.	
Da93.	citalopram 10mg tablets	d21i.	
Da94.	cipramil 10mg tablets	d21j.	
Da95.	citalopram 40mg tablets	d21k.	Stesolid
Da96.	cipramil 40mg tablets	d21l.	Stesolid
Da97.	cipramil 40mg/ml drops 15ml	d21m.	Tensium
Da98.	paxoran 10mg tablets	d21n.	Tensium
Da99.	paxoran 20mg tablets	d21o.	Tensium
Da9a.	paxoran 40mg tablets	d21p.	
Da9z.	citalopram 40mg/ml oral drops	d21q.	
Daa..	REBOXETINE	D21r.	VALIUM
Daa1.	REBOXETINE 4mg tablets	D21s.	VALIUM
Daa2.	EDRONAX 4mg tablets	D21t.	VALIUM
Dab..	MIRTAZAPINE	D21u.	VALIUM
Dab1.	MIRTAZAPINE 30mg tablets	D21v.	VALIUM
Dab2.	*ZISPIN 30mg tablets	D21w.	
Dab3.	MIRTAZAPINE 30mg disp tabs	D21x.	
Dab4.	ZISPIN SOLTAB 30mg disp tabs	D21y.	VALIUM
Dab5.	MIRTAZAPINE 15mg disp tabs	D21z.	DIAZEPAM
Dab6.	ZISPIN SOLTAB 15mg disp tabs	D22..	ALPRAZOLAM
Dab7.	MIRTAZAPINE 45mg disp tabs	D221.	XANAX
Dab8.	ZISPIN SOLTAB 45mg disp tabs	D222.	XANAX
Daby.	MIRTAZAPINE 45mg tablets	D22y.	ALPRAZOLAM
Dabz.	MIRTAZAPINE 15mg tablets	D22z.	ALPRAZOLAM
Dac..	ESCITALOPRAM	D23..	BROMAZEPAM
Dac1.	ESCITALOPRAM 10mg tablets	D231.	LEXOTAN
Dac2.	CIPRALEX 10mg tablets	D232.	LEXOTAN
Dac3.	ESCITALOPRAM 20mg tablets	D23y.	BROMAZEPAM
Dac4.	CIPRALEX 20mg tablets	D23z.	BROMAZEPAM
Dac5.	ESCITALOPRAM 5mg tablets	D24..	CHLORDIAZE
Dac6.	CIPRALEX 5mg tablets	D241.	CHLORDIAZE
Dac7.	ESCITALOPRAM 10mg/ml oral dps	D241.	CHLORDIAZE
Dac8.	CIPRALEX 10mg/ml oral drops	D242.	CHLORDIAZE
		D242.	CHLORDIAZE
Du6..	bupropion	d243.	Chlordiaze
Du6..	amfebutamone	d244.	Chlordiaze
Du61.	zyban 150mg m/r tablets	d245.	Chlordiaze
Du6z.	bupropion hcl 150mg m/r tabs	d246.	Chlordiaze
Du6z.	amfebutamon hcl 150mg m/r tabs	d247.	Chlordiaze
		D248.	CHLORDIAZE
Gde..	duloxetine	d249.	Librium
Gde1.	yentreve 20mg g/r capsules	d24a.	Librium
Gde2.	yentreve 40mg g/r capsules	d24b.	Librium
Gde3.	cymbalta 30mg g/r capsules	d24c.	Librium
Gde4.	*cymbalta 60mg g/r capsules	d24d.	Librium
Gdew.	*duloxetine 60mg g/r capsules	d24e.	
Gdex.	duloxetine 30mg g/r capsules	d24f.	Tropium
Gdey.	duloxetine 20mg g/r capsules	d24g.	Tropium
Gdez.	duloxetine 40mg g/r capsules	d24h.	Tropium
		D24i.	TROPIUM
Dq6..	selegiline	d24j.	Tropium
Dq61.	eldepryl 5mg tablets	d26..	Clobazam

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Dq62.	eldepryl 10mg tablets	d261.	Clobazam
Dq63.	eldepryl 10mg/5ml syrup	d262.	Frisium
Dq64.	*vivapryl 5mg tablets	d263.	Clobazam
Dq65.	*vivapryl 10mg tablets	d264.	Frisium
Dq66.	*stilline 5mg tablets	d27..	Clorazepat
Dq67.	*stilline 10mg tablets	d271.	Tranxene
Dq68.	*centrapryl 5 tablets	d272.	Tranxene
Dq69.	*centrapryl 10 tablets	d27y.	Clorazepat
Dq6a.	zelapar 1.25mg tablets	d27z.	Clorazepat
Dq6w.	selegiline hcl 1.25mg tablets	d29..	Ketazolam
Dq6x.	selegiline hcl 10mg/5ml syrup	d291.	
Dq6y.	selegiline hcl 10mg tablets	d292.	
Dq6z.	selegiline hcl 5mg tablets	d29y.	
		D29z.	
		D2a..	LORAZEPAM
		D2a1.	LORAZEPAM
		D2a2.	LORAZEPAM
		D2a3.	
		D2a4.	
		D2a5.	ATIVAN
		D2a6.	ATIVAN
		D2a7.	ATIVAN
		D2ax.	
		D2az.	LORAZEPAM
		D2b..	MEDAZEPAM
		D2b1.	NOBRIUM
		D2b2.	NOBRIUM
		D2by.	MEDAZEPAM
		D2bz.	MEDAZEPAM
		D2d..	OXAZEPAM
		D2d1.	OXAZEPAM
		D2d2.	OXAZEPAM
		D2d3.	OXAZEPAM
		D2d4.	OXAZEPAM
		D2d5.	
		D2d6.	
		D2d7.	
		D2e..	PRAZEPAM
		D2e1.	
		D2ez.	

10.06 Appendix 6: Charlson Comorbidity Index

Charlson disease category	Charlson score weight
AIDS	6
Cancer	2
Cerebrovascular disease	1
Chronic pulmonary disease	1
Congestive heart disease	1
Dementia	1
Diabetes	1
Diabetes with complications	2
Hemiplegia	2
Metastatic tumour	6
Mild liver disease	1
Mod liver disease	3
Myocardial infarction	1
Peptic ulcer disease	1
Peripheral vascular disease	1
Renal Disease	2
Rheumatological disease	1

Charlson Comorbidity Index, adapted version from Khan et al (2010) for use with Read Coded databases. The index includes over 2,300 comorbidities classified with individual Read Codes, falling into 17 categories listed.

10.07 Appendix 6: McNemar test results comparing PIM before and after the first record of a review: Tables

(a) Anticholinergics

Table 36 McNemar 2x2 contingency table presenting the number of patients who stopped or started anticholinergic medications after the first record of a review

		After first dementia annual review	
		PIM	No PIM
Before first dementia annual review	PIM	622	**106**
	No PIM	**112**	3523

		After first medication review	
		PIM	No PIM
Before first medication review	PIM	1141	**188**
	No PIM	**195**	5959

Dementia annual review	*Medication review*
OR 1.01 95% CI 0.97 – 1.05	OR 1.01 95% CI 0.98-1.01
McNemar test statistic is: $x^2 = \frac{(b-c)^2}{b+c}$	McNemar test statistic is: $x^2 = \frac{(b-c)^2}{b+c}$
$x^2 = (106\text{-}112)^2 / (106+112)$	$x^2 = (188\text{-}195)^2 / (168+195)$
$x^2 = 0.17$, df(1) p=0.685	$x^2 = 0.13$, df(1) p = 0.759

n = number of individual patients

Starting anticholinergics across study period n=2,277
Starting anticholinergics after any medication review n=433 (2.6%), without medication review n=1,844 (2.1%)
Starting anticholinergics after any dementia review n=159 (1.8%), without dementia review n=2,118 (2.2%)
Stopping anticholinergics across study period n= 2,344
Stopping anticholinergics after any medication review n=473 (11.8%), without medication review n=1,871 (10.4%)
Stopping anticholinergics after any dementia review n=146 (8.0%), without dementia review n=2,198 (10.9%)

McNemar Chi-squared test estimating the ratio between the disconcordant pairs, where the outcome (record of a PIM prescription) has changed after a review. Comparing the total number of patients who stopped a PIM with the total number of patients who started a PIM. The remaining two cells represent the number of patients who did not change after the first record of a review.

(b) Antipsychotics

Table 37 McNemar 2x2 contingency table presenting the number of patients who stopped or started antipsychotic medications after the first record of a review

		After first dementia annual review	
		Antipsychotic	No Antipsychotic
Before first dementia annual review	Antipsychotic	320	**52**
	No Antipsychotic	**64**	3927

		After first medication review	
		Antipsychotic	No Antipsychotic
Before first medication review	Antipsychotic	536	**80**
	No Antipsychotic	**128**	6739

Dementia annual review	*Medication review*
OR 1.03 95% CI 0.97 – 1.09	OR 1.08 95% CI 1.03-1.12
McNemar test statistic is: $x^2 = \frac{(b-c)^2}{b+c}$	McNemar test statistic is: $x^2 = \frac{(b-c)^2}{b+c}$
x^2= (52-64)^2 / (52+64)	x^2= (80-128)^2 / (80+128)
x^2= 1.24, df(1), p=0.265	x^2= 11.08, df(1) p = >0.001

n = number of individual patients

Number of patients starting antipsychotic across study period n=1,496
Number of patients starting antipsychotics after any medication review n=285 (1.56%), starting without medication review n=1,211 (1.26%)
Number of patients starting antipsychotics after dementia review n= 98 (1.07%), starting without dementia review n=1,398 (1.33%)

Number of patients stopping antipsychotics across study period n=1,138
Number of patients stopping antipsychotics after any medication review n= 224 (10.8%), number of patients stopping antipsychotics without medication review n=914 (10.3%)
Number of patients stopping antipsychotics after dementia review n=73 (7.5%), stopping without dementia review 1,065 (10.7%)

McNemar Chi-squared test estimating the ratio between the disconcordant pairs, where the outcome (record of a PIM prescription) has changed after a review. Comparing the total number of patients who stopped a PIM with the total number of patients who started a PIM. The remaining two cells represent the number of patients who did not change after the first record of a review.

(c) Tricyclic antidepressants

Table 38 McNemar 2x2 contingency table presenting the number of patients who stopped or started tricyclic antidepressant medications after the first record of a review

		After first medication review	
		Tricyclic	No Tricyclic
Before first medication review	Tricyclic	512	**70**
	No Tricyclic	**79**	6822
	Total		

		After first dementia annual review	
		Tricyclic	No Tricyclic
Before first dementia annual review	Tricyclic	292	**44**
	No Tricyclic	**53**	3974

Dementia annual review
OR 1.03 95% CI 0.97 – 1.09

McNemar test statistic is: $x^2 = \frac{(b-c)^2}{b+c}$

x^2= (44-53)² / (44+53)
x^2= 0.84, df(1) p=0.361

Medication review
OR 1.02 95% CI 0.97-1.06 9

McNemar test statistic is: $x^2 = \frac{(b-c)^2}{b+c}$

x^2= (70-79)² / (70+79)
x^2= 0.54, df(1) p=0.471

n = number of individual patients

Number of patients starting tricyclic medication n=837
Number of patients starting tricyclic after any medication review n=173 (0.9%), n starting without review n=664 (0.7%)
Number of patients staring after dementia review n=64 (0.7%), n staring without dementia review n=773 (0.7%)

Number of patients stopping tricyclic medication n=925
Number of patients stopping after medication review n= 185 (10.6%), n stopping without review n=740 (9.2%)
Number of patients stopping after dementia review n=58 (7.2%), n stopping without review n=867 (9.7%)

McNemar Chi-squared test estimating the ratio of disconcordant pairs, where the outcome (record of a PIM prescription) has changed after a review. Comparing the total number of patients who stopped a PIM with the total number of patients who started a PIM. The remaining two cells represent the number of patients who did not change after the first record of a review.

(d) Proton Pump Inhibitors

Table 39 McNemar 2x2 contingency table presenting the number of patients who stopped or started PPI for more than 8 weeks after the first record of a dementia annual review

		After first dementia annual review	
		PPI	No PPI
Before first dementia annual review	PPI	662	**38**
	No PPI	**62**	1397

		After first medication review	
		PPI	No PPI
Before first medication review	PPI	1324	**85**
	No PPI	**104**	2900

Dementia annual review	*Medication review*
OR 1.03 95% CI 1.01-1.06	OR 1.01 95% CI 0.99-1.03
McNemar test statistic is: $x^2 = \frac{(b-c)^2}{b+c}$	McNemar test statistic is: $x^2 = \frac{(b-c)^2}{b+c}$
x^2= (38-62)^2 / (38+62)	x^2= (85-104)^2 / (85+104)
x^2= 5.76 df(1) p=0.016	$x^2 = 1.91$, df(1) p=0.167

n = number of individual patients

Number of patients prescribed a PPI for 8 weeks or more n=1,662
Number of patients prescribed a long-term PPI after a medication review n= 259 (1.81%), number of patients not prescribed PPI or prescribed for less than 8 weeks after a review n=1,403 (1.83%)
Number of patients prescribed long-term PPI after dementia review n=91 (1.26%), n=1571 (1.87%) prescribed PPI for more than 8 weeks without dementia review.

Number of patients stopping a long-term PPI n=1,274
Number of patients stopping after a medication review n=261 (2.6%), number of patients stopping without a review n=1,013 (2.1%)
Number of patients stopping after a dementia review n=68 (1.0%), patients stopping without a dementia review n=1,206 (2.3%)

Long-term PPI (prescribed for more than 8 weeks)
McNemar Chi-squared test estimating the ratio of disconcordant pairs, where the outcome (record of a PIM prescription) has changed after a review. Comparing the total number of patients who stopped a PIM with the total number of patients who started a PIM. The remaining two cells represent the number of patients who did not change after the first record of a review.

10.08 Appendix 7: Relationship between a review, clinical and demographic factors and odds of stopping PIMs: Tables

Table 40 Mixed effects logistic regression model estimating the relationship between a review, clinical and demographic factors and odds of stopping anticholinergic medication, stratified by living situation, in people with a dementia diagnosis in England. Clinical Practice Research Datalink (n=2,344)

VARIABLES	Unadjusted model Stopping anticholinergics	Adjusted mixed effects model Stopping Anticholinergics (n=2,344)	Home residence stratification	
			Care Home (n=1,339)	Not in Care Home (n=3,172)
Age (years)		1.01*	1.03*	1.00
		(1.00 - 1.02)	(1.01 - 1.05)	(0.99 - 1.01)
Female		0.82*	0.83	0.81*
		(0.70 - 0.95)	(0.60 - 1.15)	(0.68 - 0.96)
Previous review				
Medication review	1.19*	1.21*	1.64*	1.04
	(1.06 - 1.32)	(1.06 - 1.38)	(1.31 - 2.07)	(0.88 - 1.22)
Dementia annual review	0.69*	0.58*	0.66*	0.55*
	(0.58 - 0.82)	(0.48 - 0.71)	(0.47 - 0.94)	(0.42 - 0.70)
Total CCI score		1.00	1.04	0.98
		(0.96 - 1.04)	(0.96 - 1.12)	(0.94 - 1.03)
IMD				
3-4		1.05	1.06	1.04
		(0.80 - 1.38)	(0.62 - 1.81)	(0.77 - 1.41)
5-6		0.96	0.87	1.01
		(0.73 - 1.26)	(0.51 - 1.48)	(0.75 - 1.36)
7-8		0.90	0.86	0.95
		(0.68 - 1.20)	(0.50 - 1.50)	(0.70 - 1.29)
9-10, least deprived		1.02	1.11	0.97
		(0.77 - 1.34)	(0.66 - 1.88)	(0.72 - 1.31)
Care home		0.99		
		(0.84 - 1.16)		
Polypharmacy				
5-9		0.84*	1.11	0.77*
		(0.73 - 0.98)	(0.82 - 1.51)	(0.65 - 0.91)
10+		0.84*	1.05	0.79*
		(0.70 - 1.00)	(0.74 - 1.50)	(0.64 - 0.97)
Constant coefficient	-2.13	-2.31	-2.90	-2.13
	(-2.18, 2.08)	(-2.59,-2.04)	(-3.47,-2.33)	(-2.43,-1.83)
Random effects[1]				
Practice		0.09	0.22	0.76
		(0.41-0.20)	(0.08-0.64)	(0.03-0.23)
Patients nested in practice		2.14	2.53	2.06
		(1.87-2.46)	(1.96-3.26)	(1.65-2.32)

OR (95% CI) *p<0.05

Stopping anticholinergics across study period n= 2,344 : Stopping anticholinergics after any medication review n=473 (11.8%), without medication review n=1,871 (10.4%): Stopping anticholinergics after any dementia review n=146 (8.0%), without dementia review n=2,198 (10.9%) Total number of observations n=21,975, n=2,344 stopping anticholinergic medications

Analyses included patients transitioning into care home n=66

Number of GP practices n=268

[1]estimated variance components of the random effects equations. Variance components are estimates of the amount of variance in the dependant variable that is attributable to the random effects. There are two random effects equations, the first is a random intercept (constant only) at the practice level and the second is the random intercept at the patient level, with patients nested within practices.

Age: centred around the sample mean age (82 years) CCI: Charlson Comorbidity Index Score: higher scores = worse comorbidity

IMD: Indices of Multiple Deprivation Polypharmacy excluding PIMs

Collinearity between covariates tested, mean VIF=1.05

Conditional on the fixed effects, the latent response within patient have a correlation of 0.40 (95% CI 0.38-0.44), whereas within practice correlation was 0.02 (95% CI 0.01-0.04). Model with random effects compared to model without random effects. Significant difference between the models and random effects remained included (LR test x^2 =767.92 df(2), p=>0.001)

Table 41 Mixed effects logistic regression model estimating the relationship between a review, clinical and demographic factors and odds of stopping antipsychotic medication, stratified by living situation, in people with a dementia diagnosis in England. Clinical Practice Research Datalink (n=1,138)

VARIABLES	Unadjusted model Stopping antipsychotics	Adjusted mixed effects model Stopping antipsychotics (n=1,138)	Home Residence Stratification	
			Care Home (n=1,053)	Not in Care Home (n=1,434)
Age (years)		1.02*	1.01	1.03*
		(1.01 - 1.04)	(0.99 - 1.03)	(1.01 - 1.04)
Female		0.99	1.26	0.88
		(0.80 - 1.22)	(0.84 - 1.89)	(0.69 - 1.13)
Previous review				
Medication review	1.08	1.07	1.45*	0.86
	(0.93 - 1.27)	(0.89 - 1.29)	(1.09 - 1.94)	(0.67 - 1.10)
Dementia annual review	0.67*	0.55*	0.70	0.45*
	(0.52 - 0.86)	(0.41 - 0.73)	(0.46 - 1.08)	(0.30 - 0.66)
Total CCI score		1.09*	1.10	1.08*
		(1.04 - 1.15)	(1.00 - 1.21)	(1.01 - 1.16)
IMD				
3-4		0.96	0.86	1.12
		(0.66 - 1.39)	(0.42 - 1.76)	(0.76 - 1.64)
5-6		0.84	0.85	0.88
		(0.58 - 1.21)	(0.41 - 1.74)	(0.60 - 1.28)
7-8		1.04	0.73	1.34
		(0.71 - 1.52)	(0.34 - 1.58)	(0.92 - 1.97)
9-10, least deprived		0.80	0.83	0.84
		(0.55 - 1.16)	(0.41 - 1.69)	(0.57 - 1.25)
Care home		0.68*		
		(0.55 - 0.83)		
Polypharmacy				
5-9		0.83	0.84	0.82
		(0.68 - 1.02)	(0.59 - 1.20)	(0.64 - 1.05)
10+		0.75*	0.72	0.77
		(0.58 - 0.96)	(0.47 - 1.12)	(0.57 - 1.04)
Constant coefficient	-2.14	-2.36	-3.24	-2.19
	(-2.21, -2.07)	(-2.73, -1.98)	(-3.98, -2.49)	(-2.59, -1.80)
Random effects[1]				
Practice		0.14	0.59	-
		(0.06-0.36)	(0.25-1.35)	-
Patients nested in practice		1.93	2.62	1.61
		(1.57-2.38)	(1.90-3.63)	(1.22-2.12)

OR (95% CI) *p<0.05

Number of patients stopping antipsychotics across study period n=1,138: Number of patients stopping antipsychotics after any medication review n= 224 (10.8%), number of patients stopping antipsychotics without medication review n=914 (10.3%) Number of patients stopping antipsychotics after dementia review n=73 (7.5%), stopping without dementia review 1,065 (10.7%) Number of observations n=2,387, n=1,138 stopping antipsychotics

Number of GP practice n=256 Number of patients transition into care home n=100

[1]estimated variance components of the random effects equations. Variance components are estimates of the amount of variance in the dependant variable that is attributable to the random effects. There are two random effects equations, the first is a random intercept (constant only) at the practice level and the second is the random intercept at the patient level, with patients nested within practices.

Age: centred around the sample mean age (82 years), CCI: Charlson Comorbidity Index Score: higher scores = worse comorbidity, IMD: Indices of Multiple Deprivation, Polypharmacy excluding PIMs,

Collinearity between covariates tested, mean VIF=1.05

Conditional on the fixed effects, the latent response within patient have a correlation of 0.39 (95% CI 0.34-0.43, there was little effect of within practice correlation, correlation was 0.03 (95% CI 0.01-0.06). Model with random effects compared to model without random effects. Significant difference between the models (LR test $x^2 = 318.20$ df(2), p=>0.001)

Table 42 Mixed effects logistic regression model estimating the relationship between a review, clinical and demographic factors and odds of stopping tricyclic antidepressant medication, stratified by living situation, in people with a dementia diagnosis in England. Clinical Practice Research Datalink (n=925)

VARIABLES	Unadjusted model	Adjusted mixed effects model	Home Residence stratification	
	Stopping tricyclic	Stopping tricyclic (n=925)	Care Home (n=654)	Not in Care Home (n=1,372)
Age (years)		1.00 (0.99 - 1.02)	1.02 (0.99 - 1.06)	1.00 (0.98 - 1.02)
Female		0.68* (0.52 - 0.87)	0.68 (0.39 - 1.18)	0.68* (0.51 - 0.91)
Previous review				
Medication review	1.20* (1.01 - 1.42)	1.25* (1.01 - 1.54)	1.62* (1.12 - 2.36)	1.10 (0.86 - 1.42)
Dementia annual review	0.70* (0.53 - 0.93)	0.62* (0.45 - 0.86)	0.81 (0.46 - 1.43)	0.56* (0.38 - 0.83)
Total CCI score		1.03 (0.97 - 1.09)	1.08 (0.95 - 1.22)	1.01 (0.94 - 1.08)
IMD				
3-4		0.93 (0.64 - 1.34)	0.69 (0.34 - 1.42)	1.04 (0.67 - 1.61)
5-6		0.88 (0.60 - 1.28)	0.66 (0.31 - 1.41)	1.01 (0.64 - 1.59)
7-8		0.99 (0.68 - 1.46)	0.55 (0.24 - 1.25)	1.19 (0.76 - 1.86)
9-10, least deprived		1.02 (0.70 - 1.49)	0.86 (0.40 - 1.84)	1.09 (0.70 - 1.70)
Care home		0.79 (0.61 - 1.02)		
Polypharmacy				
5-9		0.87 (0.69 - 1.11)	0.70 (0.45 - 1.10)	0.96 (0.72 - 1.26)
10+		0.99 (0.74 - 1.32)	0.84 (0.49 - 1.43)	1.08 (0.77 - 1.53)
Constant coefficient	-2.27 (-2.35, -2.19)	-2.50 (-2.92, -2.08)	-2.80 (-3.66, -1.94)	-2.56 (-3.04, -2.08)
Random Effects[1]				
Practice		-	0.15	-
		-	(0.01-3.45)	-
Patient nested in practice		2.61 (2.13-3.21)	3.09 (2.08-4.61)	2.47 (1.93-3.16)
Number of patients		1,964	654	1,372
Observations	9,793	9,790	3,254	6,536
Number of groups		254	175	249

OR (95% CI) ** p<0.05

Number of patients stopping tricyclic medication n=925, Number of patients stopping after medication review n= 185 (10.6%), n stopping without review n=740 (9.2%), Number of patients stopping after dementia review n=58 (7.2%), n stopping without review n=867 (9.7%), Number of observations =1,964, n stopping tricyclics n=925

Number of patients transition into care home n=62, Number of GP practices n=254

[1]estimated variance components of the random effects equations. Variance components are estimates of the amount of variance in the dependant variable that is attributable to the random effects. There are two random effects equations, the first is a random intercept (constant only) at the practice level and the second is the random intercept at the patient level, with patients nested within practices.

Age: centred around the sample mean age (82 years) CCI: Charlson Comorbidity Index Score: higher scores = worse comorbidity IMD: Indices of Multiple Deprivation Polypharmacy excluding PIMs

Collinearity between covariates, mean VIF=1.05

Conditional on the fixed effects, the latent response within patient have a correlation of 0.69 (95% CI 0.65-0.71), whereas within practice correlation was 0.07 (95% CI 0.05-0.10). Model with random effects compared to model without random effects. Significant difference between the models and random effects remained included (LR test x^2 =1-83.43 df(2), p=>0.001)

Table 43 Mixed effects logistic regression model estimating the relationship between a review, clinical and demographic factors and odds of stopping long-term PPI, stratified by living situation, in people with a dementia diagnosis in England. Clinical Practice Research Datalink (n=1,274)

VARIABLES	Unadjusted Model Stopping long-term PPI	Adjusted mixed effects model Stopping long-term PPI (n= 1,274)	Home Residence stratification	
			Care Home (n= 5,028)	Not in Care Home (n=12,112)
Age (years)		0.98*	0.98	0.97*
		(0.96 - 0.99)	(0.95 - 1.00)	(0.96 - 0.99)
Female		0.81*	1.13	0.76*
		(0.67 - 1.00)	(0.70 - 1.82)	(0.61 - 0.95)
Previous review				
Medication review	1.33*	1.39*	1.54*	1.31*
	(1.16 - 1.53)	(1.18 - 1.65)	(1.12 - 2.13)	(1.07 - 1.60)
Dementia annual review	0.42*	0.39*	0.31*	0.42*
	(0.33 - 0.54)	(0.30 - 0.52)	(0.18 - 0.55)	(0.31 - 0.58)
Total CCI score		1.11*	1.15*	1.11*
		(1.06 - 1.17)	(1.03 - 1.28)	(1.04 - 1.17)
IMD				
3-4		1.25	0.92	1.34
		(0.75 - 2.10)	(0.39 - 2.17)	(0.79 - 2.28)
5-6		1.09	1.29	0.97
		(0.65 - 1.81)	(0.56 - 2.98)	(0.57 - 1.65)
7-8		1.08	0.52	1.22
		(0.63 - 1.83)	(0.21 - 1.33)	(0.71 - 2.10)
9-10, least deprived		1.06	1.03	0.99
		(0.63 - 1.77)	(0.44 - 2.42)	(0.58 - 1.68)
Care home		1.03		
		(0.83 - 1.29)		
Polypharmacy				
5-9		0.58*	0.59*	0.58*
		(0.48 - 0.69)	(0.40 - 0.87)	(0.47 - 0.71)
10+		0.36*	0.34*	0.36*
		(0.28 - 0.45)	(0.21 - 0.55)	(0.27 - 0.48)
Constant coefficient	-3.79	-6.05	-6.68	-5.86
	(-3.85, -3.73)	(-6.57, -5.53)	(-7.70, -5.67)	(-6.41, -5.31)
Random Effects[1]				
Practice		0.80	0.96	0.74
		(0.54-1.20)	(0.45-2.04)	(0.47-1.16)
Patients nested within practice		4.97	6.09	4.79
		(4.32-5.72)	(4.59-8.08)	(4.06-5.64)
Number of patietns		16,802	5,028	12,112
Observations	58,523	58,492	17,317	41,175
Number of groups		272	252	272

OR (95% CI) ** p<0.05

Number of patients stopping a long-term PPI n=1,274, Number of patients stopping after a medication review n=261 (2.6%), number of patients stopping without a review n=1,013 (2.1%), Number of patients stopping after a dementia review n=68 (1.0%), patients stopping without a dementia review n=1,206 (2.3%), Number of observations n=16,802, number stopping long-term PPI n= 1,274, Number of patients transition into care home n=338, Number of GP practices n=272

[1]estimated variance components of the random effects equations. Variance components are estimates of the amount of variance in the dependant variable that is attributable to the random effects. There are two random effects equations, the first is a random intercept (constant only) at the practice level and the second is the random intercept at the patient level, with patients nested within practices.

Age: centred around the sample mean age (82 years), CCI: Charlson Comorbidity Index Score: higher scores = worse comorbidity, IMD: Indices of Multiple Deprivation, Polypharmacy excluding PIMs

Collinearity between covariates, mean VIF=1.05

Conditional on the fixed effects, the latent response within patient have a correlation of 0.64 (95% CI 0.60-0.67), whereas within practice correlation was 0.09 (95% CI 0.06-0.13). Model with random effects compared to model without random effects. Significant difference between the models and random effects remained included (LR test x^2 =1197.09 df(2), p=>0.001)

10.09 Appendix 8: Relationship between a review, clinical and demographic factors and odds of starting PIMs: Tables

Table 44 Mixed effects logistic regression model estimating the relationship between a review, clinical and demographic factors and odds of starting anticholinergic medication, stratified by living situation, in people with a dementia diagnosis in England. Clinical Practice Research Datalink (n=2,277)

VARIABLES	Unadjusted model Starting anticholinergics	Adjusted mixed effects model Starting anticholinergics (n= 2,277)	Home residence stratification Care Home (n=5,835)	Not in Care Home (n=14,676)
Age (years)		0.98*	1.00	0.97*
		(0.97 - 0.99)	(0.99 - 1.02)	(0.96 - 0.98)
Female		0.97	0.89	0.98
		(0.85 - 1.11)	(0.69 - 1.16)	(0.84 - 1.14)
Previous review				
Medication review	1.27*	1.20*	0.99	1.31*
	(1.14 - 1.41)	(1.06 - 1.36)	(0.80 - 1.24)	(1.13 - 1.51)
Dementia annual review	0.82*	0.77*	0.75	0.77*
	(0.70 - 0.97)	(0.64 - 0.92)	(0.54 - 1.04)	(0.62 - 0.96)
Total CCI score		0.99	0.97	1.01
		(0.96 - 1.03)	(0.91 - 1.03)	(0.97 - 1.05)
IMD				
3-4		1.01	0.88	1.08
		(0.76 - 1.33)	(0.56 - 1.39)	(0.78 - 1.48)
5-6		0.85	1.01	0.81
		(0.65 - 1.13)	(0.65 - 1.57)	(0.59 - 1.11)
7-8		1.05	1.00	1.08
		(0.79 - 1.39)	(0.63 - 1.59)	(0.79 - 1.49)
9-10, least deprived		0.89	0.90	0.88
		(0.68 - 1.18)	(0.57 - 1.40)	(0.64 - 1.21)
Care home		1.15*		
		(1.00 - 1.33)		
Polypharmacy				
5-9		1.40*	1.99*	1.29*
		(1.23 - 1.61)	(1.48 - 2.68)	(1.10 - 1.50)
10+		3.16*	6.08*	2.45*
		(2.70 - 3.71)	(4.39 - 8.43)	(2.03 - 2.96)
Constant coefficient	-3.86	-5.68	-5.80	-5.70
	(-3.90-3.81)	(-5.97, -5.39)	(-6.35, -5.25)	(-6.03, -5.37)
Random effects[1]				
Practice		0.16	0.23	0.20
		(0.11-0.28)	(0.10-0.49)	(0.12-0.34)
Patient nested in practice		3.19	3.02	3.30
		(2.85-3.57)	(2.42-3.76)	(2.89-3.76)

OR (95% CI) *p<0.05

Starting anticholinergics across study period n=2,277, Starting anticholinergics after any medication review n=433 (2.6%), without medication review n=1,844 (2.1%), Starting anticholinergics after any dementia review n=159 (1.8%), without dementia review n=2,118 (2.2%), Total number of observations n=19,819, 2,277 started anticholinergics over the study period. Analysis included patients transitioning into care home n=692 and therefore contributing to n of both stratified analyses. Number of GP practices n=272

[1]estimated variance components of the random effects equations. Variance components are estimates of the amount of variance in the dependant variable that is attributable to the random effects. There are two random effects equations, the first is a random intercept (constant only) at the practice level and the second is the random intercept at the patient level, with patients nested within practices. Age: centred around the sample mean age (82 years) CCI: Charlson Comorbidity Index Score: higher scores = worse comorbidity, IMD: Indices of Multiple Deprivation, Polypharmacy excluding PIMs. Collinearity between variables: mean VIF= 1.04

Conditional on the fixed effects covariates, the latent responses within the same patient have a correlation of 0.51 (95%CI 0.48-0.53) and of 0.03 (95% CI 0.02-0.04) within the same practice.

Table 45 Mixed effects logistic regression model estimating the relationship between a review, clinical and demographic factors and odds of starting antipsychotic medication, stratified by living situation, in people with a dementia diagnosis in England. Clinical Practice Research Datalink (n=1,496)

VARIABLES	Unadjusted model Starting antipsychotic	Adjusted mixed effects model Starting antipsychotic (n=1,496)	Home Residence Stratification	
			Care Home (n= 5,835)	Not in Care Home (n= 14,688)
Age (years)		0.98*	0.99	0.98*
		(0.97 - 0.99)	(0.97 - 1.00)	(0.97 - 1.00)
Female		1.03	0.94	1.06
		(0.86 - 1.22)	(0.68 - 1.32)	(0.87 - 1.30)
Previous review				
Medication review	1.27*	1.19*	1.01	1.30*
	(1.11 - 1.45)	(1.03 - 1.39)	(0.78 - 1.31)	(1.08 - 1.56)
Dementia annual review	0.77*	0.68*	0.76	0.62*
	(0.63 - 0.95)	(0.54 - 0.86)	(0.52 - 1.12)	(0.47 - 0.83)
Total CCI score		0.95*	1.01	0.93*
		(0.91 - 1.00)	(0.94 - 1.09)	(0.88 - 0.98)
IMD				
3-4		1.01	1.16	0.98
		(0.72 - 1.42)	(0.68 - 1.97)	(0.67 - 1.45)
5-6		1.08	1.13	1.09
		(0.77 - 1.50)	(0.67 - 1.90)	(0.75 - 1.60)
7-8		1.04	1.01	1.08
		(0.74 - 1.46)	(0.58 - 1.74)	(0.73 - 1.59)
9-10, least deprived		0.74	0.87	0.70
		(0.52 - 1.04)	(0.51 - 1.48)	(0.47 - 1.04)
Care home		1.38*		
		(1.16 - 1.65)		
Polypharmacy				
5-9		1.58*	2.11*	1.45*
		(1.33 - 1.87)	(1.48 - 2.99)	(1.19 - 1.77)
10+		3.32*	4.60*	2.93*
		(2.70 - 4.08)	(3.10 - 6.83)	(2.28 - 3.76)
Constant coefficient	-4.35	-6.81	-6.86	-6.75
	(-4.40, -4.29)	(-7.20, -6.43)	(-7.56, -6.15)	(-7.19, - 6.31)
Random Effects[1]				
Practice		0.21	0.20	0.23
		(0.12-0.36)	(0.07-0.61)	(0.12-0.44)
Patients nested in practice		4.61	4.43	4.81
		(4.09-5.19)	(3.55-5.52)	(4.18-5.54)

OR (95% CI) *p<0.05

Number of patients starting antipsychotic across study period n=1,496

Number of patients starting antipsychotics after any medication review n=285 (1.56%), starting without medication review n=1,211 (1.26%)

Number of patients starting antipsychotics after dementia review n= 98 (1.07%), starting without dementia review n=1,398 (1.33%)

Total number of observations n=19,819, n=1,496 starting antipsychotic medication

Number of patients transition into care home n=704

Number of GP practice n=272

[1]estimated variance components of the random effects equations. Variance components are estimates of the amount of variance in the dependant variable that is attributable to the random effects. There are two random effects equations, the first is a random intercept (constant only) at the practice level and the second is the random intercept at the patient level, with patients nested within practices.

Age: centred around the sample mean age (82 years)

CCI: Charlson Comorbidity Index Score: higher scores = worse comorbidity

IMD: Indices of Multiple Deprivation

Polypharmacy excluding PIMs

Collinearity between covariates included in model, mean VIF=1.05

Conditional on the fixed effects, the within patient correlation was 0.59 (95% CI 0.56-0.62), the within practice correlation was 0.03 (95% CI 0.02-0.04). Model tested without random effects (LR test x^2= 1110.88 df(2) p=>0.001

Table 46 Mixed effects logistic regression model estimating the relationship between a review, clinical and demographic factors and odds of starting tricyclic antidepressant medication, stratified by living situation, in people with a dementia diagnosis in England. Clinical Practice Research Datalink (n=837)

VARIABLES	Unadjusted model Starting tricyclic	Adjusted mixed effects model Starting tricyclic (n=837)	Home Residence Stratification	
			Care Home (n=5,835)	Not in Care Home (n=14,715)
Age (years)		0.96*	0.99	0.96*
		(0.95 - 0.98)	(0.96 - 1.03)	(0.94 - 0.97)
Female		1.38*	2.27*	1.28
		(1.08 - 1.78)	(1.15 - 4.47)	(0.98 - 1.68)
Previous review				
Medication review	1.39*	1.36*	1.18	1.44*
	(1.17 - 1.64)	(1.12 - 1.67)	(0.75 - 1.84)	(1.15 - 1.81)
Dementia annual review	0.89	0.90	1.33	0.78
	(0.69 - 1.16)	(0.67 - 1.21)	(0.76 - 2.31)	(0.54 - 1.11)
Total CCI score		1.07*	1.13	1.06
		(1.01 - 1.14)	(0.98 - 1.31)	(0.99 - 1.14)
IMD				
3-4		1.00	0.96	1.05
		(0.58 - 1.73)	(0.31 - 3.02)	(0.60 - 1.83)
5-6		0.69	0.47	0.77
		(0.40 - 1.20)	(0.14 - 1.53)	(0.44 - 1.36)
7-8		0.97	0.76	1.04
		(0.56 - 1.69)	(0.23 - 2.46)	(0.59 - 1.83)
9-10, least deprived		0.88	0.69	0.97
		(0.51 - 1.51)	(0.22 - 2.19)	(0.55 - 1.68)
Care home		0.80		
		(0.61 - 1.04)		
Polypharmacy				
5-9		1.00	1.83*	0.88
		(0.80 - 1.24)	(1.05 - 3.17)	(0.69 - 1.12)
10+		1.19	2.05*	1.09
		(0.90 - 1.58)	(1.06 - 3.98)	(0.79 - 1.51)
Constant coefficient	-4.97	-8.32	-10.23	-8.12
	(-5.04, -4.89)	(-8.91, -7.72)	(-11.76, -8.69)	(-8.75, -7.48)
Random Effects[1]				
Practice		0.76	2.10	0.65
		(0.50-1.16)	(1.10-4.02)	(0.39-1.08)
Patients nested in practice		6.40	7.85	6.22
		(5.56-7.34)	(5.86-10.52)	(5.32-7.28)

Number of patients starting tricyclic medication n=837, Number of patients starting tricyclic after any medication review n=173 (0.9%), n starting without review n=664 (0.7%), Number of patients staring after dementia review n=64 (0.7%), n staring without dementia review n=773 (0.7%) Number of observations n=19,819, n starting tricyclic n=837

Number of GP practices n=272 Number of patients transition into care home n=731

[1]estimated variance components of the random effects equations. Variance components are estimates of the amount of variance in the dependant variable that is attributable to the random effects. There are two random effects equations, the first is a random intercept (constant only) at the practice level and the second is the random intercept at the patient level, with patients nested within practices.

Age: centred around the sample mean age (82 years) CCI: Charlson Comorbidity Index Score: higher scores = worse comorbidity IMD: Indices of Multiple Deprivation Polypharmacy excluding PIMs

Collinearity between covariates tested, mean VIF=1.07

Conditional on the fixed effects, the latent response within patient have a correlation of 0.44 (95% CI 0.39-0.49, there was little effect of within practice correlation, within practice correlation was less than 0. Model with random effects compared to model without random effects. Significant difference between the models (LR test $x^2 = 352.09$ df(1), p=>0.001)

Table 47 Mixed effects logistic regression model estimating the relationship between a review, clinical and demographic factors and odds of being prescribed a long-term PPI, stratified by living situation, in people with a dementia diagnosis in England. Clinical Practice Research Datalink (n=1,662)

VARIABLES	Unadjusted model	Adjusted mixed effects model	Home residence stratification	
	Starting Long-term PPI	Starting Long-Term PPI (n=1,662)	Care Home (n=5,853)	Not in Care Home (n=14,534)
Age (years)		0.97*	0.96*	0.98*
		(0.96 - 0.98)	(0.93 - 0.99)	(0.97 - 0.99)
Female		0.78*	0.80	0.78*
		(0.65 - 0.94)	(0.51 - 1.27)	(0.64 - 0.95)
Previous review				
Medication review	1.01	0.95	0.91	0.95
	(0.89 - 1.16)	(0.81 - 1.11)	(0.64 - 1.27)	(0.79 - 1.14)
Dementia annual review	0.67*	0.65*	0.42*	0.72*
	(0.54 - 0.83)	(0.51 - 0.83)	(0.24 - 0.75)	(0.55 - 0.95)
Total CCI score		1.10*	1.15*	1.08*
		(1.04 - 1.15)	(1.04 - 1.28)	(1.02 - 1.14)
IMD				
3-4		1.09	1.29	1.00
		(0.72 - 1.67)	(0.61 - 2.73)	(0.66 - 1.53)
5-6		1.09	0.88	1.10
		(0.72 - 1.65)	(0.41 - 1.88)	(0.73 - 1.67)
7-8		0.95	0.79	0.94
		(0.62 - 1.47)	(0.36 - 1.75)	(0.61 - 1.45)
9-10, least deprived		0.92	0.74	0.90
		(0.60 - 1.41)	(0.34 - 1.59)	(0.59 - 1.37)
Care home		0.73*		
		(0.60 - 0.90)		
Polypharmacy				
5-9		2.00*	1.60*	2.11*
		(1.69 - 2.36)	(1.07 - 2.39)	(1.75 - 2.55)
10+		3.00*	2.26*	3.23*
		(2.43 - 3.69)	(1.41 - 3.62)	(2.56 - 4.09)
Constant coefficient	-3.96	-6.95	-7.59	-6.80
	(-4.01, -3.01)	(-7.39, -6.51)	(-8.53, -6.65)	(-7.25, -6.34)
Random Effects				
Constant		0.47	0.52	0.38
		(0.30-0.75)	(0.18-1.50)	(0.22-0.64)
Constant		5.30	6.60	5.07
		(4.75-5.93)	(5.28-8.27)	(4.47-5.76)

OR (95% CI) ** p<0.05

Number of patients prescribed a PPI for 8 weeks or more n=1,662, Number of patients prescribed a long-term PPI after a medication review n= 259 (1.81%), number of patients not prescribed PPI or prescribed for less than 8 weeks after a review n=1,403 (1.83%), Number of patients prescribed long-term PPI after dementia review n=91 (1.26%), n=1571 (1.87%) not prescribed PPI for more than 8 weeks. Number of observations n=19,819, n=1,662 prescribed PPI for 8 weeks or more. Number of patients transition into care home n=568 Number of GP practices n=272

[1]estimated variance components of the random effects equations. Variance components are estimates of the amount of variance in the dependant variable that is attributable to the random effects. There are two random effects equations, the first is a random intercept (constant only) at the practice level and the second is the random intercept at the patient level, with patients nested within practices.

Age: centred around the sample mean age (82 years) CCI: Charlson Comorbidity Index Score: higher scores = worse comorbidity IMD: Indices of Multiple Deprivation Polypharmacy excluding PIMs

Collinearity between covariates, mean VIF=1.05

Conditional on the fixed effects, the latent response within patient have a correlation of 0.62 (95% CI 0.59-0.65), whereas within practice correlation was 0.04 (95% CI 0.03-0.07). Model with random effects compared to model without random effects. Significant difference between the models and random effects remained included (LR test x^2 =1569.10 df(2), p=>0.001)