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Abstract

Polypharmacy has been linked to higher risks of hospitalisation and death in community samples. It is commonly present in people with dementia but these risks have rarely been studied in this population. We aimed investigate associations between polypharmacy and emergency department attendance, any and unplanned hospitalisation, and mortality in patients with dementia. Using a large mental health care database in South London, linked to hospitalisation and mortality data, we assembled a retrospective cohort of patients diagnosed with dementia. We ascertained number of medications prescribed at the time of dementia diagnosis and conducted a multivariate Cox regression analyses. Of 4,668 patients with dementia identified, 1,128 (24.2%) were prescribed 4-6 medications and 739 (15.8%) ≥7 medications. Compared to those using 0-3 medications, patients with dementia using 4-6 or ≥7 agents had an increased risk of emergency department attendance (hazard ratio 1.20 / 1.35), hospitalisation (hazard ratio 1.12 / 1.32), unplanned hospital admission (hazard ratio 1.12 / 1.25), and death within two years (hazard ratio 1.29 /1.39) after controlling for potential confounders. We found evidence of a dose response relationship with each additional drug at baseline increasing the risk of emergency department attendance and mortality by 5% and hospitalisation by 3%. In conclusion, polypharmacy at dementia diagnosis is associated with a higher risk of adverse health outcomes. Future research is required to elucidate which specific agents underlie this relationship and if reduction of inappropriate prescribing is effective in preventing adverse health outcomes in dementia.

Keywords: dementia; hospitalisation; mortality; emergency department; polypharmacy; pharmacoepidemiology

Highlights:

- Polypharmacy in patients with dementia is associated with an increased risk of emergency department attendance, hospitalisation, unplanned hospital admission and death.
- Risk of emergency department attendance is increased by 20% in those taking 4-6 medications and by 35% in patients taking ≥7 medications.
- Hospitalisation risk is increased by 12% in those taking 4-6 medications and by 32% in patients taking ≥7 medications.
- A dose-response relationship exists between the number of medications at dementia diagnosis and adverse health outcomes.

1. Introduction

Compared to the general older population, people with dementia have high rates of physical and psychiatric co-morbidity, often resulting in the prescription of multiple medications simultaneously (Andersen and others 2011; Clague and others 2016). Clinical practice guidelines and policies tend to provide advice for single conditions, such as dementia or cardiovascular disease, and their applicability to patients with multiple co-morbidities is often unclear. Individual medications, which are beneficial and well-evaluated in a single condition, may lose their effect or even be harmful when taken in combination with other medications, due to drug-drug interactions, and little evidence exists on the efficacy, safety and tolerability of medications used to manage co-morbidities in dementia (Duerden M 2013; Reeve and others 2015). People with dementia are often excluded from clinical trials, from which guideline-based treatments for long-term conditions commonly arise (Brauner and others 2000; Parsons 2017). Further, typical dementia symptoms, such as declining memory, executive function, language and agitation might prevent adverse drug events from being detected early and before they lead to more serious complications and subsequent hospitalisation (Onder and others 2011).

In community samples of older people, polypharmacy has been linked to inappropriate prescribing (Guthrie and others 2011), adverse drug events (Bourgeois and others 2010), preventable and unplanned hospitalisation (Leendertse and others 2008; Payne and others 2014), increased mortality (Gnjidic and others 2012; Richardson and others 2011), reduced adherence (Vik and others 2004), higher risk of falls (Richardson and others 2015) and frailty (Veronese and others 2017), and impaired quality of life (Fincke and others 1998). However, despite the reported high levels of polypharmacy in people with dementia very little is known about potential adverse health outcomes in this group (Parsons 2017), apart from one study

of nursing home residents with severe dementia, in whom the prescription of 10 or more medications was associated with a higher mortality risk (Onder and others 2013).

We sought to investigate if polypharmacy is associated with four important outcomes – emergency department attendance, any and unplanned hospital admissions, and mortality – in a large, naturalistic sample of people with dementia.

2. Methods

2.1 Data source:

Data were obtained from the South London and Maudsley NHS Foundation Trust (SLaM) Clinical Record Interactive Search (CRIS) application. SLaM is one of Europe's largest healthcare providers for dementia and other mental disorders, serving a population of over 1.2 million residents, and has adopted fully-electronic health records for all services since 2006. CRIS provides research access to more than 270,000 de-identified health records from SLaM within a robust governance framework (Perera and others 2016; Stewart and others 2009), and has received ethical approval as an anonymized data resource (Oxford Research Ethics Committee C, reference 08/H0606/71+5).

Data of interest were extracted either from structured fields or from clinical documents through bespoke natural language processing algorithms using General Architecture for Text Engineering (GATE) software (Cunningham 2002; Perera and others 2016). Further, CRIS has been linked to national data on hospitalisation (Hospital Episode Statistics; HES) and mortality, enabling relevant health outcome data to be extracted for the current analyses.

2.2 Sample:

CRIS was used to extract cases aged 65 years or older who received a first dementia diagnosis from SLaM outpatient services within the period between 1st Jan 2006 and 31st March 2011. This a allowed a two year follow-up period as hopitalisation (HES) data were avalible until 31st March 2013.

2.3 Polypharmacy (exposure):

Number of medications recorded in text fields (case notes, clinical correspondence) in a 6-month window around the dementia diagnosis was ascertained using a GATE-supported natural language processing algorithm previously described (Perera and others 2016). This serves as a measure for prevalent polypharmacy as patients' medication might not be

recorded in electronic health records at the same time as the diagnosis. There is no single agreed definition of polypharmacy (Guthrie and others 2011); hence we used the categorization suggested in the development of multidimensional prognostic index, applying three groups: 0-3 (reference group), 4-6 or ≥7 medications (Pilotto and others 2008). This scale has been applied in similar analyses, which also have been able to demonstrate dose-response relationships (Veronese and others 2017).

2.4 Outcomes:

From linked national data we ascertained any and unplanned hospitalisations for physical disorders, emergency department attendances and mortality in the two years after dementia diagnosis using Hospital Episode Statistics (HES; NHS Digital). The HES database records all admissions to all National Health Service (NHS) hospitals in England, and includes diagnoses and procedures. Within the NHS, HES allows tracking of patients between different hospitals and across different years. To determine the causes of hospitalisation and death we extracted the ten most common primary discharge diagnoses and causes of death according to ICD-10 codes (World Health Organisation 2010) from HES and Office of National Statistics records.

2.5 Covariates:

We extracted data on a range of potential confounders which we ascertained at the time of dementia diagnosis (baseline). These comprised socio-demographic factors (age, gender, marital status, ethnicity, and a neighbourhood-level index of multiple deprivation (Noble and others 2007)), level of cognitive impairment as measured by Mini-Mental State Examination (MMSE) (Folstein and others 1975) score closest to the diagnosis and two measures of general physical health and co-morbidity: i) hospitalisation in the two years prior to dementia diagnosis, and ii) the 'Problems related to physical illness or disability' subscale of the Health of the Nation Outcome Scales (HoNOS65+) instrument. The HoNOS65+ is a standard measure of patient wellbeing used in UK (Burns and others 1999) mental health and dementia

services whose performance has been previously reported (Pirkis and others 2005) and subscales are each rated 0 (no problem) to 4 (severe or very severe problem). To determine the burden of co-morbid neuropsychiatric symptoms, we established the number of mental health subscales in HoNOS65+ (behavioural disturbance, non-accidental self-injury, substance use, hallucinations and/or delusions, depressive symptoms) in which the patient was scored to have at least a mild problem (score of 2 to 4). From structured fields and free-text documents we ascertained the dementia subtype diagnosis (Alzheimer's disease, vascular dementia, mixed-type dementia, Lewy body dementias, unspecified dementia).

2.6 Statistical analysis

Analyses were conducted using STATA 13 software (Stata Corp LP, College Station, TX, USA). Differences in the study population across the three levels of prescribing (0-3, 4-6, 7+ medications) were examined using linear regression models for continuous and logistic regression models for binary variables. Multivariable Cox regression models were used to calculate associations between polypharmacy and the aforementioned outcomes, with patients receiving 0-3 medications defined as the reference group. Censoring point was either the date of emergency department attendance/hospitalisation, date of death or the two-year mark after dementia diagnosis. Results are reported as hazard ratios (HR) with 95% confidence intervals (CIs). Analyses were initially adjusted for age, gender and MMSE score, and then for age, gender, ethnicity, marital status, MMSE score, deprivation score, HoNOS65+ 'Problems related to physical illness or disability' subscale (all at time of dementia diagnosis), hospitalisation in the two years prior to dementia diagnosis and any recorded vascular dementia diagnosis. As medications prescribed specifically for dementia (Lau and others 2010) contribute to the burden of polypharmacy and might pose their own hazards in this population, we carried out sensitivity analyses accounting for prescription of antipsychotics, antidepressants, hypnotics, or anticholinergic medications within six months before or after the dementia diagnosis date.

3. Results

We identified 6,253 patients diagnosed with dementia in SLaM outpatient services within the observation period. After excluding 413 (6.6%) patients who were under the age of 65 at the time of dementia diagnosis, 909 (14.5%) without recorded MMSE score and 262 (4.2%) lacking information on physical health, the sample consisted of 4,668 patients.

Of these, 64.2% were female and 18.2% from a minority ethnic group. Mean age at dementia diagnosis was 81.7 (SD ±6.9) years. Mean MMSE score was in the mild to moderate dementia range (18.4 ± 6.3). In the entire sample, median number of medications prescribed was 3 (range: 0-24).

Patient characteristics according to medication use are presented in Table 1. Participants using 7 or more medications were younger, more likely to be male and from a minority ethnic group; moreover, they resided in more deprived neighbourhoods, had more neuropsychiatric problems and worse physical health, mirrored in a higher physical illness HoNOS65+ score and a higher likelihood of hospitalisation in the previous two years. Diagnoses of vascular or mixed-type dementia, as well as Lewy body dementias, were associated with higher levels of polypharmacy.

Across the entire sample, 2,828 (60.6%) participants attended an emergency department in the follow-up period of two years after dementia diagnosis, 3,105 (66.5%) had at least one hospitalisation, 2,718 (58.2%) at least one unplanned admission and 1,142 (24.5%) died. Associations between medication use and these outcomes are presented in Table 2. Taking those using up to three medications as a reference group, patients prescribed 4-6 and ≥7 agents showed progressively increased risks of hospitalisation, emergency department attendance and mortality over the two-year follow-up. The age-, gender- and MMSE-adjusted hazard ratios lay between 1.21 to 1.37 for patients prescribed 4-6 medications and between

1.54 to 1.63 for patients prescribed 7 or more medications for these negative health outcomes, and remained statistically significant and relatively strong after adjustment for a broad range of potential confounders including physical illness severity scores and hospitalisations prior to the dementia diagnosis. Figure 1 shows Kaplan-Meier curves comparing time to first hospitalisation between the exposure groups. On further analysis applying the count of medications as an ordinal variable, each additional drug at baseline increased the risk of emergency department attendance and death within two years (each by 5%) and any and unplanned hospitalisation (by 3%). Sensitivity analyses accounting for potentially hazardous medications (see Supplementary Table 1) as co-variates, did not affect risks for the four outcomes substantially. Compared to those taking 0-3 medications, patients taking 4-6 medications were more frequently admitted due to pneumonia and other lower respiratory tract infections and this was also significantly more often recorded as cause of death in this group ($p=0.034$). Patients taking 7 or more medications were more frequently admitted due to ischaemic heart disease. Frequency of other common causes of hospitalisation, including hip fractures and head injuries, and mortality didn't differ between groups (see Supplementary Tables 1 & 2).

Table 1: Characteristics of patients with dementia classified according to medication usage

	0-3 medications (n=2,801; 60.0%)	4-6 medications (n=1,128; 24.2%)	≥7 medications (n=739; 15.8%)	P[1] (4-6 vs 0-3)	P[1] (≥7 vs 0-3)
Socio-demographics[2]					
Age (years, mean, SD)	81.8 (6.9)	82.0 (6.8)	81.2 (6.7)	0.347	0.034
Female (%)	64.8%	64.8%	60.8%	0.985	0.040
Non-White Ethnicity (%)	17.6%	17.9%	21.0%	0.500	<0.001
Married or cohabiting (%)	34.9%	36.9%	32.4%	0.580	0.220
Deprivation score (mean, SD)	26.4 (11.3)	26.9 (11.2)	28.7 (10.4)	0.178	<0.001
MMSE score (mean, SD)	18.7 (6.3)	18.1 (6.3)	18.1 (6.5)	0.008	0.020
Physical illness or disability[3]					
0-1 (no or minor problem)	57.9%	47.9%	35.3%	<0.001	<0.001
2 (mild problem)	21.5%	25.8%	31.8%	0.004	<0.001
3-4 (moderately severe to very severe problem)	20.6%	26.3%	32.9%	<0.001	<0.001
Co-morbid non-cognitive mental health problems[4]					
No additional mental health problems	70.8%	59.4%	44.2%	<0.001	<0.001
One additional mental health problems	21.6%	28.8%	35.3%	<0.001	<0.001
Two or more additional mental health problems	7.6%	11.8%	20.5%	<0.001	<0.001
Hospitalisation[5]					
Any (planned and unplanned) hospitalisation	51.5%	58.5%	72.5%	<0.001	<0.001
Unplanned hospitalisation	39.3%	48.2%	65.0%	<0.001	<0.001
Dementia subtype					
Alzheimer's disease	44.2%	36.0%	24.6%	<0.001	<0.001
Vascular dementia	17.9%	25.4%	30.0%	<0.001	<0.001
Mixed-type dementia (including Alzheimer's disease and Vascular dementia)	22.5%	25.4%	29.%	0.052	<0.001
Lewy body dementias (Dementia with Lewy bodies or Parkinson's disease dementia)	2.1%	4.2%	7.0%	<0.001	<0.001
Unspecified dementia	11.7%	7.5%	6.1%	<0.001	<0.001

[1] using linear regression for continuous and logistic regression for ordinal variables
[2] at the time of dementia diagnosis
[3] ascertained via HoNOS65+ 'Problems related to physical illness or disability' subscale
[4] Number of HoNOS65+ subscales with score of 2 or more (behavioural disturbance, non-accidental self-injury, substance use, hallucinations and/or delusions, depressive symptoms)
[5] hospitalisations in the 2 years prior to dementia diagnosis from Hospital Episode Statistics

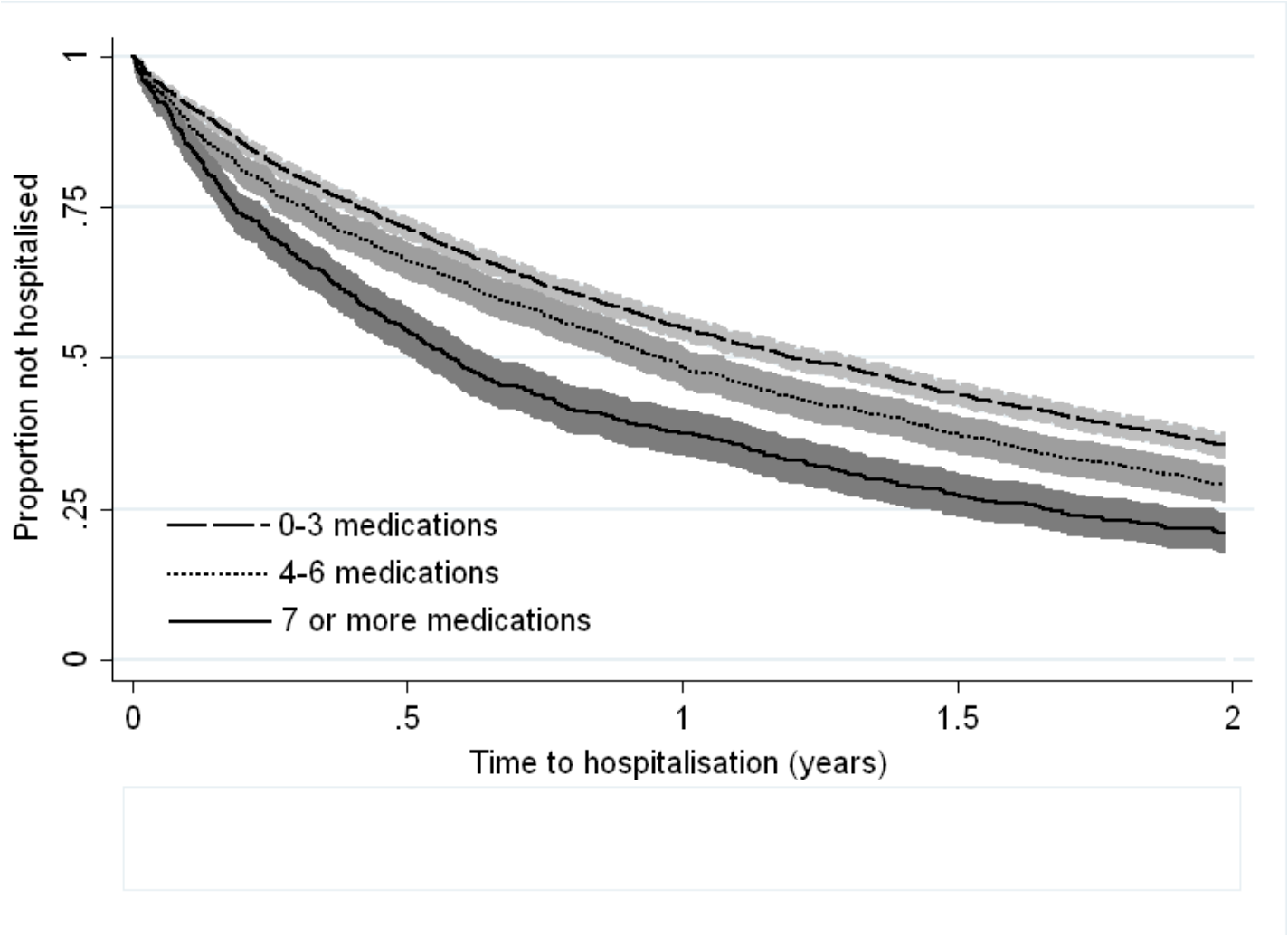
Table 2: Adjusted hazard ratios for categories of medication use and outcomes using multivariable cox regression in patients with dementia

	Emergency department attendance			Hospitalisation			Unplanned hospitalisation			Mortality		
	Cumulative incidence (%)	Age & gender, MMSE adjusted HR (95% CI)	Fully adjusted HR± (95% CI)	Cumulative incidence (%)	Age & gender, MMSE adjusted HR (95% CI)	Fully adjusted HR± (95% CI)	Cumulative incidence (%)	Age & gender, MMSE adjusted HR (95% CI)	Fully adjusted HR± (95% CI)	Cumulative incidence (%)	Age & gender adjusted HR (95% CI)	Fully adjusted HR± (95% CI)
0-3 medications	57.1%	1 [reference]	1 [reference]	63.0%	1 [reference]	1 [reference]	54.6%	1 [reference]	1 [reference]	21.2%	1 [reference]	1 [reference]
4-6 medications	64.6%	**1.27 (1.16-1.39)***	**1.20 (1.09-1.31)***	69.2%	**1.21 (1.11-1.32)***	**1.12 (1.02-1.22)#**	61.4%	**1.21 (1.11-1.33)***	**1.12 (1.02-1.23)#**	28.2%	**1.37 (1.20-1.57)***	**1.29 (1.11-1.49)***
≥ 7 medications	67.5%	**1.54 (1.39-1.71)***	**1.35 (1.21-1.51)***	75.9%	**1.63 (1.48-1.79)***	**1.32 (1.19-1.47)***	67.1%	**1.56 (1.41-1.72)***	**1.25 (1.11-1.40)***	31.1%	**1.61 (1.38-1.87)***	**1.39 (1.17-1.66)**
Risk increase per additional medication		**1.06 (1.05-1.07)***	**1.05 (1.03-1.06)***		**1.06 (1.04-1.07)***	**1.03 (1.02-1.04)***		**1.05 (1.04-1.07)***	**1.03 (1.02-1.04)***		**1.06 (1.05-1.08)***	**1.05 (1.03-1.07)***

* $p<0.01$
# $p<0.05$

±Fully adjusted model included as covariates: age, gender, ethnicity, marital status, MMSE score, deprivation score, HoNOS65+ physical illness problem score, number of co-morbid non-cognitive mental health problems (all at time of dementia diagnosis); if hospitalised in two years prior to dementia diagnosis; dementia subtype

Figure 1: Kaplan-Meier curves displaying time to first hospitalisation after dementia diagnosis by number of medications prescribed



4. Discussion

In this study of more than 4,000 patients diagnosed in a specialist dementia care and assessment provider we demonstrated that polypharmacy is associated with an increased risk of emergency department attendance, and both any and unplanned hospitalisation, as well as mortality over a two-year follow-up period. We further demonstrated a dose-response relationship between number of medications prescribed and negative outcomes in all four outcomes.

Hospitalisation is a common and unwanted event for people with dementia (Rao and others 2016) and may increase the risk of delirium, functional decline and death itself (Mathews and others 2014). Thus, understanding potentially modifiable factors for hospitalisation is essential. However, little is known about polypharmacy and hospitalisation in dementia (Russ and others 2015). To our knowledge, previous studies have been almost entirely restricted to community samples of unselected older populations. In an elderly all male community-dwelling population, Beer and colleagues (Beer and others 2011) found a 4% increased risk of hospitalisation per additional medication prescribed. In a smaller study, with less rigorous adjustment for chronic illness, Jensen and colleagues (Jensen and others 2001) found 3.8 times increased odds for hospitalisation in older community-dwelling Medicare beneficiaries using three or more medications. In residential settings, an Italian study (Cherubini and others 2012) of 1,466 nursing home residents, of whom 70% suffered from cognitive impairment, reported that polypharmacy (defined as the concurrent use of 5 or more medications) was associated with hospitalisation in a mixed-effects logistic regression model adjusted for co-morbidity (effect size: 0.54; $p<0.01$). Similarly, an Australian long-term care study (Lalic and others 2016) demonstrated an increased risk of hospitalisation in relation to being prescribed 9 or more medications (hazard ratio 1.84; $p<0.01$). Thus, our data expand the previous literature to dementia populations and confirms that the higher hospitalisation risk described in general older populations is also applicable in people with dementia. Further, our study

shows that polypharmacy is associated with an increased risk of emergency department attendance, which is inherently related to hospitalisation.

Mortality is the only outcome which has been previously evaluated in dementia in relation to polypharmacy. The SHELTER care home study found that excessive polypharmacy, defined as being prescribed 10 or more medications, was associated with at 119% increased risk of death in those with limited life expectancy (Onder and others 2013). Although important, the SHELTER study (Onder and others 2013) has some limitations, such as only including participants from nursing homes and including a relatively small sample size (only 822 residents). Studies on polypharmacy-related mortality in community-dwelling older adults have only been carried out in unselected general populations. Two studies (Beer and others 2011; Gnjidic and others 2012), which had good adjustment for chronic illness (Fried and others 2014), found the risk of death increased by 4% - 9% for each additional medication prescribed. Defining polypharmacy as the concomitant prescription of 5 or more medications, Richardson and colleagues (Richardson and others 2011) found a 42% increased risk of two-year mortality for men and 30% for women. Although we cannot distinguish between community-dwelling and institutionalised participants, our study is the first to examine mortality in relation to polypharmacy in a wider group of dementia patients from both settings and better representativeness of the source population.

Several factors could explain why polypharmacy is linked to higher risk of adverse health outcomes in dementia populations. Possible mediators of this interaction are adverse drug events which are associated with polypharmacy (Bourgeois and others 2010), preventable medication related hospitalisation in older people (Leendertse and others 2008) and mortality (Pardo Cabello and others 2016). Further, the link between polypharmacy and inappropriate prescribing is well established (Guthrie and others 2011), which has in turn been implicated in higher hospitalisation risk (Hamilton and others 2011). Specifically, in dementia antipsychotics and antidepressants have been associated with increased risk of mortality (Corbett and others

2014; Mueller and others 2017). In our study, risk of hospitalisation and mortality remained significantly related to polypharmacy after accounting for potentially hazardous medications (see Supplementary Table 1), indicating that other potentially inappropriate medications or polypharmacy itself remain independent risk factors. Few significant differences were detected in reasons for hospitalisation and mortality in this study, indicating that polypharmacy might exert its primary effect by hastening the occurrence of these outcomes.

Strengths of the current study include the broad range of data available for our large sample. This allowed adjustment for a number of confounders, including cognitive and deprivation scores, a physical illness problem score and previous hospitalisation as a measure of multi-morbidity, vascular disease, psychotropic and anticholinergic medication.

Our study has a number of limitations. First, while data from a specialist dementia assessment and care provider ensures an expert diagnosis, we cannot rule out under-recording of physical health medications. This would however imply that patients in our 0-3 medications references group are potentially taking more medication and we are underestimating the hazards of polypharmacy. Second, the software ascertained prescribed medication in a 6-month window around dementia diagnosis, which means that that medications prescribed as a consequence of the dementia diagnosis or an early hospitalisation would be captured. Nevertheless, those dementia-specific medications do also contribute to the polypharmacy burden. Third, multi-morbidity was captured through recoding of hospitalisation prior to dementia diagnosis and the HoNOS65+ physical illness subscale. Despite being a widely used routine measure of clinical outcome in mental health and dementia services in the UK (Pirkis and others 2005), the scale is relatively brief without details on the specific long-term conditions determining its score. Finally, in observational studies there always remains the possibility of residual unmeasured confounders which may affect outcomes, although we have adjusted for wide range of social, pharmacoepidemiological and mental and physical health factors.

4.1 Conclusions

Polypharmacy at the time of dementia diagnosis is associated with an at least 20% increased risk of emergency department attendance, at least 12% increased risk of any or unplanned hospitalisation and least 29% increased risk of early mortality. Given that almost 50 million people have dementia world-wide, with an expected increase of close to 10 million cases every year (Prince and others 2013), and growing levels of polypharmacy reported (Qato and others 2016), these relatively small, but consistent, increased risks may have considerable public health and healthcare delivery consequences. Future analyses could explore this association in more detail using inappropriate prescribing criteria (e.g. Beers (By the American Geriatrics Society Beers Criteria Update Expert 2015) or STOPP (O'Mahony and others 2015) criteria) or assess the wanted and unwanted effects of medications on certain receptor groups (e.g. using the Anticholinergic Effect on Cognition (AEC) scale (Bishara and others 2017)). The 'Medication Appropriateness Tool for Comorbid Health conditions during Dementia' (MATCH-D) developed by Page and colleagues using the Delphi technique [12] advocates an individualised treatment approach, giving guidance on treatment goals and use of preventative medications according to dementia severity stage, as well as on symptomatic, psychotropic and antidementia medications. If such a tool enables reduction of polypharmacy, the related hazards described in this analysis, and ultimately improves outcomes, requires further evaluation.

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