

BMJ Open How do potentially inappropriate medications and polypharmacy affect mortality in frail and non-frail cognitively impaired older adults? A cohort study

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

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2018-026171>).

Received 10 September 2018
Revised 14 December 2018
Accepted 18 February 2019



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ABSTRACT

Objectives To test whether the use of potentially inappropriate central nervous system acting medications, proton pump inhibitors (PPIs) or polypharmacy are associated with mortality in cognitively impaired older adults and whether frailer people are at greater risk of harm.

Setting A cohort study nested within the Cognitive Function and Ageing Study II, a population representative cohort study of the older population in Cambridgeshire, Nottingham and Newcastle, UK.

Participants A total of 1154 cognitively impaired participants, aged 65 years or older.

Exposures Any use of antipsychotics, antidepressants, other anticholinergic medication, benzodiazepines or PPIs, polypharmacy (5–9) and hyperpolypharmacy (≥10 reported medications) were ascertained at baseline. Frailty was assessed using the Fried criteria.

Primary outcome Mortality up to 8 years follow-up. HRs associated with potentially inappropriate medication (PIM), frailty and their interaction were estimated adjusting for covariates.

Results Within the sample, 44% were taking one or more PIM. Apart from antipsychotics (adjusted HR=3.24, 95% CI 1.83 to 5.73), use of specific PIM was not associated with greater subsequent mortality. Polypharmacy (HR=1.17, 95% CI 0.95 to 1.45) and hyperpolypharmacy were associated with mortality (HR=1.60, 95% CI 1.16 to 2.22). Being frail (HR=1.90, 95% CI 1.32 to 2.72) or prefrail (HR=1.56, 95% CI 1.10 to 2.20) was associated with increased mortality. There was some evidence that the HR for polypharmacy on mortality was lower among frailer individuals, but the overall polypharmacy by frailty interaction was not statistically significant ($p=0.102$).

Conclusions For those with cognitive impairment, greater concern should be afforded to the number of medications than the prescription of specific classes. Frailer individuals may have a lower relative risk of mortality associated with polypharmacy than less frail individuals.

INTRODUCTION

More than 850 000 people live with dementia in the UK and many more have significant

Strengths and limitations of this study

- This study followed a large population-representative cohort of people with cognitive impairment for up to 8 years.
- All medication use was included, both over-the-counter and prescribed.
- Demographic-related and health-related confounding variables were included in the analysis.
- There was no loss to follow-up as each participant was flagged for notification of mortality with the Office for National Statistics.
- Medication use and frailty were only ascertained once at baseline, ascertainment of medications relied on self-report with interviewers checking packaging and prescriptions where available.

cognitive impairment.¹ Around 70% of people with dementia live with comorbidity and are prescribed multiple medications.² Polypharmacy, often defined as the regular use of five or more medications, is common among older adults and people with dementia, particularly as clinical prescribing guidelines often take a single disease focus, rarely accounting for patients with multimorbidity.³

Polypharmacy has been associated with incident frailty.⁴ Frailty is often used to describe low physiological reserve and individual susceptibility to stressors that may affect health^{5 6} and is an important determinant of health outcomes in older people, including hospitalisation and mortality.^{7–9} Incorporating frailty assessment into primary care is increasingly encouraged to identify individuals at greater risk of mortality, hospitalisation and susceptibility to adverse health outcomes.¹⁰ An important aspect of the validity of frailty measures is whether they can predict resilience or susceptibility to other potential risk factors.⁹ Recent findings

suggest that polypharmacy and frailty are associated with mortality, incident disability and hospitalisation compared with non-frail participants without polypharmacy.¹¹ However, the moderating role of frailty in the relationship between polypharmacy and adverse outcomes, hence whether ‘frailty’ can be used to identify those at particular risk from polypharmacy, is unknown.

All medications have associated risks; a medication is considered a ‘potentially inappropriate medication’ (PIM) when the potential harm outweighs potential benefit among a particular group. PIMs are associated with increased risk of hospitalisation, mortality and other adverse health outcomes^{12–14} and around 29% of older people and 64% of people with dementia are prescribed at least one PIM.^{15 16} Validated criteria can be used to identify potentially inappropriate prescribing, examples include the Beers criteria, which is primarily used in the USA, and the European Screening Tool for Older Persons Prescribing (STOPP).^{17 18} These criteria identify PIM for specific patient groups, where interaction with specific diseases, prescriptions or overuse may result in adverse effects.

Proton pump inhibitors (PPIs) are considered potentially inappropriate after 8 weeks in older adults according to STOPP criteria. PPIs are prescribed extensively and although generally considered safe and effective, recent evidence has linked PPIs with potential adverse events, including hip and spine fractures, community-acquired pneumonia, *Clostridium difficile* infections, and vitamin and mineral deficiencies.^{19–26} PPIs are considerable contributors to polypharmacy, with 27% of patients using PPIs being prescribed them long-term, despite long-term effects being unknown.²⁷ Understanding the long-term effect of PPI use may improve patient safety, reduce unnecessary polypharmacy and have significant financial implications for health services.

The STOPP criteria also identify groups of PIM with central nervous system effects, and PIMs that are particularly inappropriate for people with dementia. People with dementia may be exposed to central nervous system acting medications, including antipsychotics, antidepressants, benzodiazepines (BZDs) and medications with anticholinergic effects in order to treat comorbidities and manage behavioural and psychological symptoms. However, these medications are associated with adverse cardiovascular effects,²⁸ hypotension, falls^{29–31} confusion, detrimental effects on cognition³² and mortality,³³ and are considered potentially inappropriate in both STOPP and Beers criteria. People with dementia may be more susceptible to adverse effects of central nervous system acting medications due to age-related and disease-related pharmacokinetic and pharmacodynamic changes, including alterations in the blood–brain barrier permeability associated with Alzheimer’s disease.^{34–36}

Being frail may also increase susceptibility to adverse effects of PIM and polypharmacy, since frailty is defined as increased vulnerability to risk factors and lack of physiological reserve.⁵ Using frailty criteria may, therefore,

enable the identification of those at particular risk from PIM and polypharmacy, although whether frailty exacerbates any adverse effects of PIM is not known.

This study seeks to understand the effect of potentially inappropriate use of central nervous system acting drugs, PPIs and polypharmacy among cognitively impaired older adults, and whether any risk varies with increasing frailty. We used the Cognitive Function and Ageing Study II (CFAS II) to estimate (a) the association between PIMs and polypharmacy at baseline and survival up-to 8 years, and (b) the moderating role of frailty in this relationship.

METHODS

CFAS II is a cohort study of ageing in England. The design and methods have been described in detail elsewhere.³⁷ In short, participants were randomly sampled from primary care lists within three geographic centres representing urban and rural areas (Nottingham, Cambridgeshire and Newcastle) between 2008 and 2011. In England, the vast majority of people are registered with a single primary care provider, and so primary care patient lists form sampling frames that are close to enumerations of the populations of specific areas. Approximately, 2500 participants were recruited from each geographic area. All participants were aged 65 years or older at baseline and were interviewed in their usual place of residence, whether this was their own home or a long-term care facility, by a trained interviewer. The CFAS interview included questions on health and lifestyle, demographics, and current medication use, as well as a range of cognitive tests and algorithmic dementia assessment. This was repeated at a two-year follow-up assessment.

Sample

For the present study, we used data from all participants with a baseline Mini-Mental State Examination (MMSE) score of 24 or lower, indicating clinically significant cognitive impairment.³⁸ Participants were excluded if medication data were not recorded or were deemed unreliable, that is, if MMSE was less than 18 and proxy-reported medication data were unavailable.

Exposures

Medication use

Information on medication use was ascertained from the question: ‘Do you take any medicine, tablets or injections of any kind, that either you buy yourself or that are prescribed by your doctor?’ To improve data accuracy, reported medications were cross-checked with medication packs by the interviewer. In care homes, staff cross-checked with medication lists. Medications were coded using Read Codes and Application Dictionary.³⁹

Potentially inappropriate medications

PIMs were identified using STOPP criteria.¹⁸ We focused primarily on medications from Section D: Central Nervous System Criteria of STOPP, including antidepressants,

antipsychotics, other anticholinergics (ie, anticholinergics other than antidepressants and antipsychotics) and BZDs. Acetylcholinesterase inhibitors, inappropriate in patients with vascular dementia, were not included in this study due to specific dementia subtype diagnosis information being unavailable. PPIs, indicated as potentially inappropriate in long-term use, contributors to polypharmacy and a priority of deprescribing, were also included.^{19 40}

Anticholinergic medications were defined using the anticholinergic cognitive burden scale (ACB). Medications with definite anticholinergic activity, classified as an ACB score of 3, were included.⁴¹ PIMs were then grouped into mutually exclusive categories of: (a) antipsychotic, (b) anticholinergic (excluding antipsychotics and antidepressants), (c) tricyclic antidepressants, (d) other antidepressants, (e) BZDs and (f) PPI (see online supplementary appendix 1 containing medication code lists).

Polypharmacy

Total number of prescribed and over-the-counter medications was calculated from medication lists collated during interviews. This number excluded the specific PIM described above, to allow for mutually exclusive exposures comparing PIM to polypharmacy and to understand the effect of polypharmacy on mortality, independent of specific PIM use. Polypharmacy was categorised as the use of between five and nine such medications, hyperpolypharmacy as more than ten in line with previous studies.^{11 42}

Time-varying exposure to PIM

To test the extent to which the exposure varied with time, the use of PIM at baseline and 2-year follow-up was compared, among the subsample for whom medication data were available at the 2-year follow-up interview.

Frailty

The frailty phenotype as first described by Fried *et al*⁵ was used to measure frailty. The frailty phenotype is known to predict adverse outcomes in a general older population.⁴³ This definition of frailty incorporates measures from multiple domains reflecting physiological decline and consists of five components: slowness, weakness, exhaustion, weight loss and low physical activity. Individuals are deemed 'frail' if they are positive on three, four or five components, 'prefrail' if positive on one or two and 'not frail' otherwise. We could not operationalise frailty exactly as originally performed in the Cardiovascular Health Study,⁵ but in common with other epidemiological studies of ageing^{44 45} each component was operationalised as closely as possible using available data, as follows:

Slowness was measured using the average walking speed from two gait speed tests across 2.4 metres. Participants falling within the slowest quartile of the whole CFAS II sample were considered impaired for this component. Participants who did not consent or could not complete the test were also considered impaired.

Weakness was assessed using the timed sit-to-stand test.⁴⁶ Participants were asked to stand from sitting five times, without using their arms. Participants who did not consent, could not complete the test and those within the slowest quartile of time among completers were considered impaired.

Exhaustion was self-reported in answer to the question 'Do you get worn out/exhausted towards the evening?' If there was no response, interviewer rating of observed slow movements not due to physical illness was used. Both questions were measured with three response categories (no/mild/severe). Participants with mild or severe exhaustion, not explained by strenuous activities, were coded as frail on this criterion.

Weight loss was assessed by self-report. Participants reporting losing 10 lbs (4.5 kg) or more in ≤ 6 months prior to the interview were classified as positive on this criterion.

Low physical activity was assessed through self-reported time spent doing vigorous, moderate or mildly energetic activities. This was scored based on responses to a series of questions about time spent in specific activities, including, for example, swimming, jogging, walking, gardening and housework (see online supplementary appendix 2 for a full list). A score of 1 was allocated for each activity if a participant reported doing an activity hardly ever or never, less than three times a month or not engaging in the activity at all, and 0 if more frequently. The scores across activities were summed to create a continuous variable, where higher scores indicated less activity. Participants in the least active quartile were coded positive on this criterion.

Other covariates

Multivariate analyses were adjusted for age, sex, living situation (care home, residential homes, nursing homes and long-stay hospitals, or own home), cognitive impairment (MMSE score) and number of self-reported comorbidities (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 and stroke).

Outcomes

CFAS II participants were flagged on the UK Office for National Statistics National Health Service Central Register for notification of date of death, and so survival status is known for all participants. The current analysis includes all deaths up to 31 October 2016, providing up to 8 years follow-up.

Statistical analysis

Univariate analysis

Kaplan-Meier curves estimated survival probabilities from baseline until censoring or death. Logrank tests were used to test survival differences between users and non-users of each PIM. Participants reporting polypharmacy and

hyperpolypharmacy were compared with those reporting zero to four medications.

Cox regression models estimated univariate HRs (95% CIs) for each exposure. Participants entered the analysis at the time of baseline interview, and were followed until death or censoring on 31st October 2016. Time since the interview was the time scale for all analyses.

Multivariate analysis

Two Cox proportional hazards regression models estimated independent effects of each PIM and polypharmacy, controlling for covariates. Model 1 adjusted for age, sex, cognitive impairment, living situation and comorbidities. Model 2 included a categorical frailty variable (non-frail, prefrail and frail). Sensitivity analyses included adding individual frailty components in Cox multivariate regressions to assess their association with mortality, and adjusting for each comorbid condition individually rather than as a single cumulative variable. The proportional hazards assumption was tested by inspection of Schoenfeld residuals.⁴⁷

Frailty as a moderator

First, multivariate analyses as described above were stratified by baseline frailty status. Interaction terms were then added to the full model to test the moderating effect of frailty on the link between each PIM, polypharmacy and mortality. Likelihood-ratio tests assessed the statistical significance of PIM by frailty and polypharmacy by frailty interactions.

The data set analysed during the current study was provided by the CFAS. Details of how to request CFAS data are available (<http://www.cfas.ac.uk/cfas-ii/cfasii-data/>). All analyses were performed using Stata V.14.

RESULTS

Of the 7762 CFAS II participants, 1154 met inclusion criteria (see figure 1). Within the final sample, 62% were female, mean age was 79 years (SD=7.4) and 154 (13%) had a study diagnosis of dementia (see table 1). Participants reported a mean average of 2.4 (SD=1.6) comorbidities, 5.5 (SD=3.6) regular medications and 44% reported taking at least one PIM. PPIs were most frequent (n=331, 28.7%), followed by 'other antidepressants' (n=119, 10.3%), 'tricyclic antidepressants' (n=76, 6.6%), anticholinergics (n=71, 6.2%), BZDs (n=46, 4.0%) and antipsychotics (n=21, 1.8%). There were 493 (42.7%) participants taking 5–9 medications (polypharmacy) and 110 (9.5%) taking ≥10 medications, excluding PIMs.

Survival analyses

Univariate analyses

Up to 31 October 2016, 489 (42.4%) participants had died; the median follow-up time was 5.6 years. Among participants reporting PIM, 73% (n=11) of antipsychotic users, 52% (n=37) of users of other anticholinergics, 43% (n=33) of users of tricyclic antidepressants, 46% (n=21)

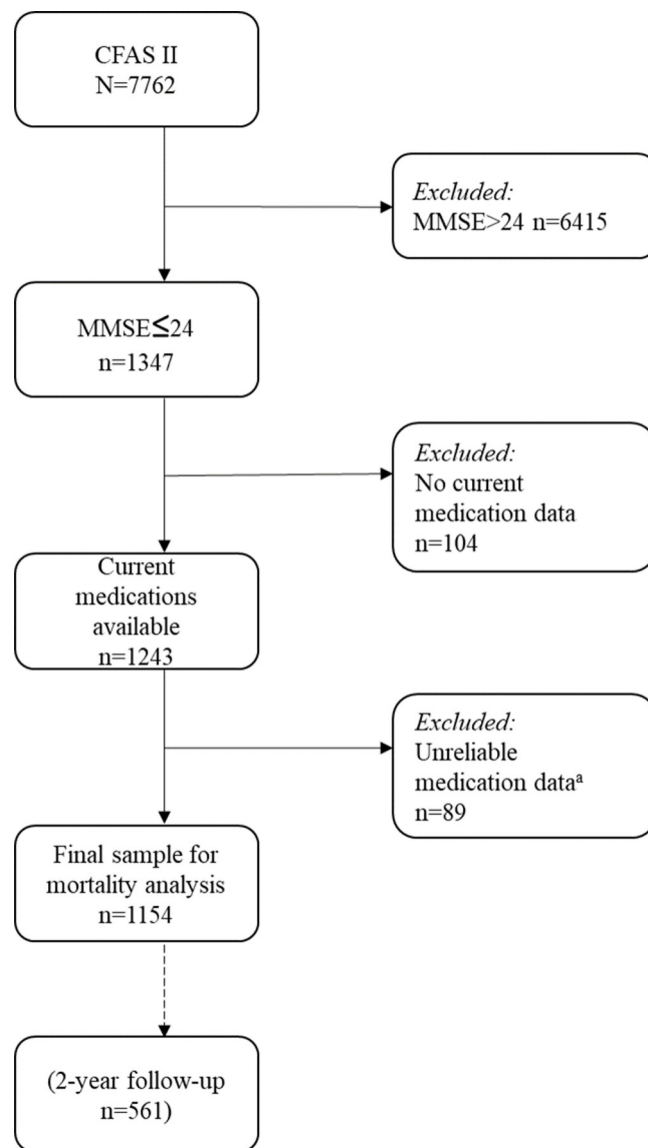


Figure 1 Participant inclusion from CFAS II for analysis. ^aUnreliable medication data includes MMSE score ≤ 18 or missing and no proxy to answer medications question. CFAS II, Cognitive Function and Ageing Study II; MMSE, Mini-Mental State Examination.

of BZD users, 46% (n=55) of other antidepressant users and 44% (n=145) of PPI users had died. Of participants taking 5–9 and ≥10 medications, 47% (n=233) and 55% (n=60) had died.

Kaplan-Meier survival curves suggested a difference in survival in participants with polypharmacy and hyperpolypharmacy and users of antipsychotics, but not in users of the others PIMs compared to non-users (figure 2). A statistically significant difference in survival was seen in users of antipsychotics compared to non-users, in logrank test ($\chi^2=8.21$, $df=1$, $p \leq 0.01$) and unadjusted Cox regression models (HR=2.19, 95% CI 1.26 to 3.81). No significant effect on survival was seen for any other central nervous system acting PIM (table 2) and there was no significant effect on survival associated with PPI use (HR=1.16, 95% CI 0.95 to 1.42). Statistically significant

Table 1 Sample characteristics by frailty classification. Cognitive Function and Ageing Study II

Characteristics	Total sample n=1154	Characteristics within frailty classifications		
		Non-frail n=204	Prefrail 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)
Frailty individual components (count, %)				
Low physical activity	313 (27.1)	–	58 (10.9)	255 (60.7)
Weight loss	122 (10.6)	–	29 (5.5)	93 (22.1)
Weakness*	802 (69.5)	–	388 (73.2)	414 (98.6)
Slowness†	702 (60.8)	–	313 (59.1)	389 (92.6)
Exhaustion	334 (28.9)	–	74 (14.0)	260 (61.9)
Death before 31 October 2016 (count, %)	489 (42.4)	45 (22.1)	226 (42.6)	218 (51.9)

*Missing n=603: categorised as frail if missing due to inability to complete the test.

†Missing n=244: categorised as frail if missing due to inability to complete the test.

MMSE, Mini-Mental State Examination score; PIMs, potentially inappropriate medications.

difference in survival was seen across polypharmacy categories ($\chi^2=23.15$, $df=2$, $p<0.01$). Polypharmacy and hyperpolypharmacy were both significantly associated with mortality, HR=1.39 (95% CI 1.14 to 1.70) and HR=1.95 (95% CI 1.45 to 2.61), respectively (see [table 2](#)).

Multivariable analyses

The association between antipsychotics and mortality remained after adjusting for demographic variables, comorbidities and cognitive impairment (HR=3.24, 95% CI 1.83 to 5.73) and after adjusting for frailty. After adjusting for confounders, no significant association with mortality was evident in the other central nervous system acting PIM or PPIs (see [table 2](#)). Adjustment for confounders explained about half of the univariable

effect of polypharmacy such that it was no longer statistically significant (multivariate model HR=1.21, 95% CI 0.97 to 1.50); however, hyperpolypharmacy remained significantly associated with mortality in both adjusted models (frailty model: HR=1.60, 95% CI 1.16 to 2.22) (see [table 2](#)). The proportional hazards assumption, assessed using Schoenfeld residuals, was not violated in this model ($\chi^2=16.91$, $df=15$, $p=0.324$). There was no substantial change in estimates when comorbid conditions were included individually in the main multivariate model (see online supplementary file appendix 3).

Continuation of medication use

At the 2-year follow-up, 561 (48.6%) had survived and provided medication data. Among these, 69% (n=29) of

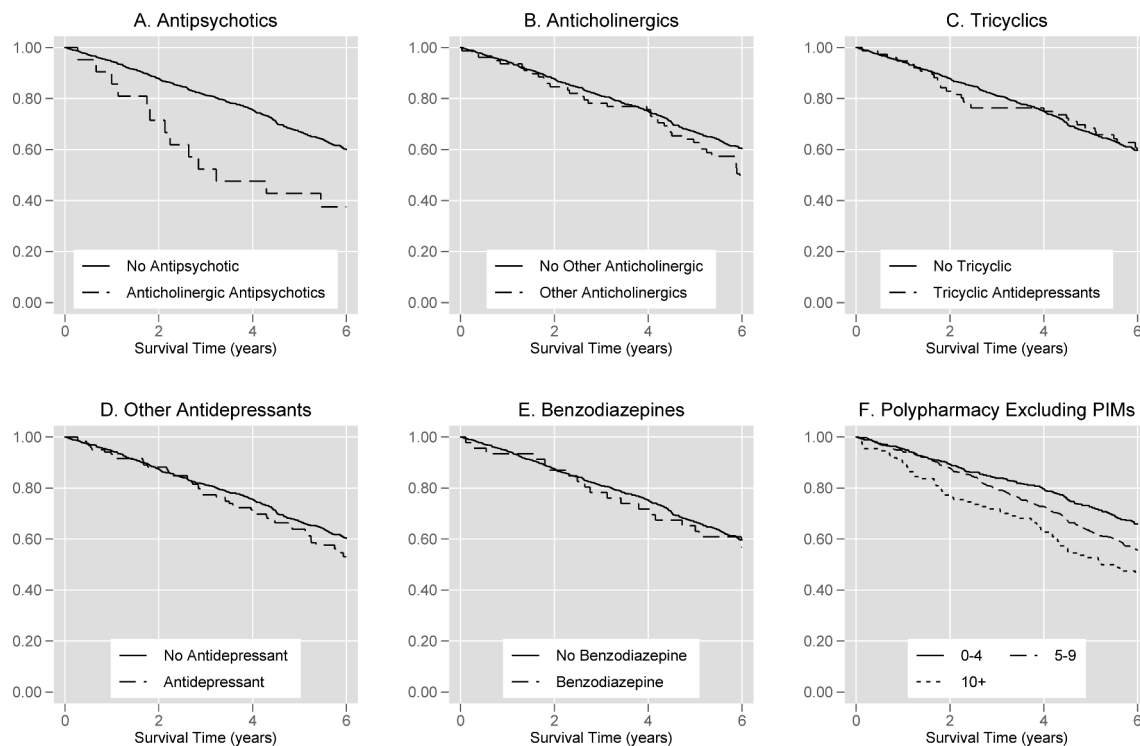


Figure 2 Kaplan-Meier survival curves showing the proportion of patients surviving with time, stratified by baseline use of PIM. (A) Shows the effect of antipsychotics, (B) the effect of anticholinergics apart from antipsychotics and antidepressants, (C) the effect of tricyclics, (D) other antidepressants, (E) benzodiazepines and (F) the total number of other drugs coded as polypharmacy (5–9 drugs) or hyperpolypharmacy (10 or more) excluding any of the categories previously described. PIM, potentially inappropriate medication.

those reporting anticholinergics at baseline also reported antidepressants at 2 years, 60% (n=3) continued antipsychotics, 59% (n=13) continued BZDs, 77% (n=31) continued tricyclics and 85% (n=136) of those using PPI at baseline were also using PPI at follow-up. This suggests that the majority of medication use reported at baseline reflected relatively long-term use.

Frailty

At baseline, 36.4% of the sample were classified as frail (n=420), while 45.9% were prefrail (n=530). PIM use was less frequently reported among the non-frail (17.7%) group compared with prefrail (27.7%) and frail (32.1%) participants. At the point of censoring, 22.1% (n=45) of non-frail, 42.6% (n=226) prefrail and 51.9% (n=218) of frail participants had died.

In univariate analyses, prefrail or frail participants were at a significantly increased risk of mortality compared with non-frail (prefrail: HR=2.22, 95% CI 1.59 to 3.09; frail: HR=2.92, 95% CI 2.09 to 4.07). Being frail and prefrail remained significantly associated with mortality in the fully adjusted model (frail: HR=1.90, 95% CI 1.32 to 2.71; prefrail: HR=1.56, 95% CI 1.11 to 2.20) (see table 2).

Frailty as moderator of the effect of PIM and polypharmacy

Stratifying multivariate models by frailty status suggested similar relative risk of mortality among antipsychotic users at all levels of frailty. The HR associated with antipsychotic use among non-frail users was 3.60 (95% CI 0.40

to 31.99), was 2.89 (95% CI 1.26 to 6.66) in prefrail and was 3.34 (95% CI 1.37 to 8.12) in frail antipsychotic users (table 3).

Frailty and polypharmacy interaction terms suggested worse mortality associated with polypharmacy and hyperpolypharmacy in people who were not frail compared with those who were prefrail or frail (table 3). However, this interaction was not statistically significant (likelihood-ratio test for interaction: $\chi^2=7.73$, df=4, p=0.102).

The association between BZDs and mortality significantly varied across frailty groups, (likelihood-ratio test for interaction: $\chi^2=6.05$, df=2, p=0.049) and suggested an inverse relationship between BZD use and mortality among the frail (HR=0.43), but no effect among the prefrail or not frail participants (table 3).

Estimating the effect of individual frailty components

Including frailty components individually in adjusted analysis instead of the composite measure made little difference to HRs estimated from previous models. As individual markers of frailty, low physical activity, weakness (measured by chair-rise test) and slowness (measured by the gait-speed test) were individually associated with mortality (low physical activity: HR=1.41, 95% CI 1.15 to 1.71; weakness: HR=2.23, 95% CI 1.77 to 2.83 and slowness: HR=1.99, 95% CI 1.62 to 2.45). However, slow gait was the only component independently associated with mortality in the multivariate model (HR=1.42, 95% CI 1.12 to 1.81) (table 4).

Table 2 Unadjusted and adjusted potentially inappropriate medication (PIM) use HRs for survival, univariate and multivariate models. Cognitive Function and Ageing Study II n=1154

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

HR (95% CI).

*P<0.05.

†Multivariate model adjusted for frailty.

MMSE, Mini-Mental State Examination score (0–30 with higher scores indicating better cognition).

DISCUSSION

This study estimated the association between PIMs, polypharmacy and risk of mortality among cognitively impaired older adults and the moderating role of frailty in this relationship. We found that, as expected, use of antipsychotic medications, polypharmacy and hyperpolypharmacy were associated with an increased risk of mortality, but no other specific PIM we tested was linked to the risk of death. The excess risk associated with hyperpolypharmacy and with antipsychotics remained after adjustment for frailty status. Polypharmacy was more common among frailer participants. Contrary to expectation, the HR for death associated with polypharmacy appeared higher among the non-frail population than among the prefrail or frail, with excess risk of death associated with using five to nine medications seeming almost exclusively restricted to the least physically frail. The frailty phenotype did independently predict mortality, but when analysed individually slow gait speed was the only component of the frailty measure that independently predicted mortality in this cohort.

The link between antipsychotic medication and mortality in people with dementia is well known⁴⁸ and our result extends this finding to a broader group with

cognitive impairment. Previous studies have also found an increased risk of death associated with increased anticholinergic burden.³³ Since anticholinergic medications encompasses a wide variety of medications, including many antidepressants and antipsychotics, in this analysis, anticholinergics were subclassified into mutually exclusive categories to understand the contribution of specific medication classes. Our finding that only antipsychotic medications were associated with increased mortality, compared with tricyclic antidepressants or other anticholinergic medications, indicates a potential class-specific effect, such that antipsychotic use may be the driver of previously observed associations between anticholinergics and mortality when anticholinergics are considered together.⁴⁹ Hence, as previously suggested elsewhere,⁵⁰ considering ‘anticholinergics’ as a class with respect to adverse outcomes might not be meaningful.

We found no evidence for an association between PPI use and mortality in this cognitively impaired population. PPIs are highly prevalent and are often overused without appropriate indication.^{27 51 52} For people with comorbidities and polypharmacy, who are taking PPIs on a long-term and potentially inappropriate basis, there may also be a risk of drug–drug interactions, which can lead to

Table 3 HRs estimated by Cox regression models for association between potentially inappropriate medication (PIM) use and mortality, adjusted for age, gender, MMSE score, care home residence and comorbidities and stratified by frailty. Data from the Cognitive Function and Ageing Study II

Variables	Cox regression analysis stratified by frailty classification†			Likelihood ratio‡ χ^2 (p value)
	Not frail n=204	Prefrail n=530	Frail n=420	
PIM				
Antipsychotic	3.60 (0.40 to 31.99)	2.89* (1.26 to 6.66)	3.34* (1.37 to 8.12)	0.01 (0.995)
Tricyclic antidepressant	0	1.84 (0.98 to 3.44)	0.90 (0.55 to 1.48)	5.63 (0.060)
Anticholinergics	1.29 (0.16 to 10.61)	1.05 (0.61 to 1.79)	1.23 (0.76 to 2.01)	0.32 (0.854)
Other antidepressants	0.86 (0.23 to 3.20)	1.12 (0.67 to 1.89)	0.74 (0.49 to 1.12)	2.93 (0.230)
Benzodiazepines	0.92 (0.11 to 7.78)	1.40 (0.66 to 2.97)	0.43* (0.21 to 0.86)	6.05 (0.049)*
Proton pump inhibitor	1.05 (0.43 to 2.59)	1.04 (0.76 to 1.42)	1.09 (0.80 to 1.49)	0.43 (0.808)
Polypharmacy				
0–4	1	1	1	7.73
5–9	2.34* (1.16 to 4.70)	1.07 (0.78 to 1.45)	1.17 (0.84 to 1.64)	(0.102)
10+	4.22 (0.90 to 19.90)	1.31 (0.75 to 2.29)	1.80* (1.15 to 2.82)	
Covariates				
Age at interview	1.13* (1.07 to 1.19)	1.11* (1.09 to 1.13)	1.08* (1.06 to 1.11)	
Gender (female)	0.71 (0.35 to 1.43)	0.67* (0.50 to 0.89)	0.43* (0.31 to 0.58)	
MMSE score (per point)	0.87* (0.77 to 0.98)	0.92* (0.88 to 0.96)	0.91* (0.87 to 0.96)	
Care home residence	0.00	0.92 (0.50 to 1.71)	1.68 (0.98 to 2.88)	
Comorbidities	1.16 (0.90 to 1.50)	1.03 (0.93 to 1.14)	1.02 (0.92 to 1.12)	

HR (95% CI).

* $P < 0.05$.

†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 prefrail if 1–2 components.

‡Likelihood ratio test comparing exposure–frailty interaction models with multivariate frailty model with prefrail group as baseline.

MMSE, Mini-Mental State Examination score (0–30 with higher scores indicating better cognition).

a range of adverse effects. Deprescribing inappropriate PPIs among older people is considered a priority⁴⁰ and while we did not find PPI use was associated with survival, there is building evidence suggesting PPIs are associated with other clinically important adverse effects including *C. difficile* and increased risk of fractures.^{27 53}

In this novel investigation of the role of frailty on the effect of PIM in older adults with cognitive impairment, we found some evidence of a moderating role in that the HR for polypharmacy was higher among the least physically frail individuals. This may be partly caused by a lower risk of death from other causes among the less frail groups, so that if polypharmacy caused a similar increase in absolute risk of mortality across groups, this would correspond to a lower relative risk among the frailer participants.

BZD use was associated with better survival in frail participants. Long-term use of BZDs is discouraged; however, more than two-thirds of our participants using BZD at baseline were still using BZD 2 years later, suggesting that much of the BZD use recorded in our study is long-term. It is possible that prescribing behaviours around BZDs may differ compared with other PIMs. This could include improved monitoring of efficacy and safety leading to

subsequent apparent protective effects. Alternatively, this finding might represent residual confounding such that BZDs are prescribed to those with a lower risk of death, an effect of BZDs causing otherwise healthy people to be classified as frail, or it is possible that this is a chance association given the large numbers of individual hypotheses being tested and borderline statistical significance of the interaction effect. In any case, there is no evidence from this study that BZDs or other individual PIM apart from antipsychotics are associated with excess mortality among people with cognitive impairment.

Previous studies have described that polypharmacy and hyperpolypharmacy are associated with frailty⁴ and that frailty and polypharmacy are associated with mortality, incident disability and hospitalisation.^{11 42} While including frailty and polypharmacy interactions in our analysis did indicate a significantly increased risk of mortality in frail, hyperpolypharmacy participants, the greatest risk was observed in non-frail participants with polypharmacy. This interaction effect was not statistically significant in our study; however, a cohort study of men aged 70 years and older characterised transitions across frailty states and death and similarly found that additional medications

Table 4 Risk of mortality associated with the use of PIM and individual frailty components in univariate and multivariate models. Cognitive Function and Ageing Study II n=1154

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

*P<0.05.

†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).

MMSE, Mini-Mental State Examination; PIM, potentially inappropriate medication; PPI, proton pump inhibitor.

were associated with increased risk of mortality from non-frail state but not from prefrail or frail state.⁵⁴

Strengths and limitations of the study

Our results were drawn from a large, nationally representative, population-based cohort study with data on both prescribed and over-the-counter medications. The strength of this analysis lies in the mutually exclusive categorisation of exposures, including polypharmacy that excluded individual PIM exposure, since the probability of PIM exposure is a function of the total number of medications. However, we did not consider medication dose or duration of use. Although we did not directly incorporate varying medication exposure as only a subset of participants underwent a single second assessment at 2 years, we did find that the exposure was typically long-term as the majority of participants who reported each PIM use at baseline, also reported the same PIM at 2-year follow-up. This suggests that much PIM use recorded in our study was 'prevalent use', reflecting long-term use among a population who are stable on each medication,

and so might not be applicable to those considering a new prescription of a PIM and who may be expected to be at higher initial risk.

We could not operationalise phenotypic frailty measures exactly as per their original definition,⁵ although our frailty measure did independently predict mortality in this sample and our approach to measuring frailty using existing data is similar to that taken by many other epidemiological studies.

Finally, although the analysis adjusted for multiple covariates, the possibility of residual confounding remains. In particular, we could not control for every possible indication for medications contributing to polypharmacy owing to the limitations of the available data. For example, CFAS II did not record data on chronic kidney disease or heart failure that are also linked to medication use and mortality. However, controlling for the frailty variables, which reflect general health status, did not attenuate the associations between polypharmacy and death.

Implications

There are few prescribing guidelines addressing the specific needs of patients living with dementia and multimorbidity, the findings from this study will assist in understanding the safety of medicines in this population. Given these findings, consideration of the number of medications used rather than individual PIM (with the exception of antipsychotics) may be more important among cognitively impaired older adults. With respect to antipsychotics, deprescribing guidelines for behavioural and psychological symptoms of dementia have been developed and could help in reducing the harm associated with inappropriate prescribing.²²

Implications for the measurement and clinical application of frailty measures

This study used a widely applied physical phenotypic definition of frailty.⁵ However, this definition does not account for cognitive, psychological and social frailty components, potentially resulting in underestimation of frailty in a cognitively impaired sample.⁵⁵ There are no single established means of defining frailty but including frailty assessment in clinical practice is increasing.¹⁰ Slow gait speed was the only frailty marker independently associated with mortality in this study, suggesting this alone may provide as useful an assessment of frailty as the full phenotypic measure in this group. A valid, feasible and reliable frailty assessment is needed and important for identifying vulnerable individuals, applying evidence-based interventions and comparing or predicting health outcomes within this growing older population.

Frailty itself has been shown to be a strong predictor of adverse outcomes but this effect may differ with varying levels polypharmacy.⁵⁶ Frailty as applied in our study did not identify those at most risk of the adverse effects of PIM. That the interaction between polypharmacy and frailty was of the opposite direction to that expected, with

the least frail at highest relative risk calls into question the concept of frailty as reflecting susceptibility to other risks; this should be more rigorously tested in future studies.

To conclude, in this analysis of a large, nationally representative cognitively impaired sample, we found that with the exception of antipsychotics, potentially inappropriate central nervous system acting medications were not individually associated with mortality. Polypharmacy and hyperpolypharmacy were associated with an increased risk of mortality indicating that managing the number of medications used remains a priority, particularly in cognitively impaired older adults, irrespective of physical frailty.

Acknowledgements We would like to thank all CFAS II participants for their time and participation, and thank Carlotta Grossi Sampedro and Kathryn Richardson, of the University of East Anglia, for sharing the CFAS II medication codes and other guidance.

Contributors AA, BP and GMS conceived and designed the study. BP conducted the analysis and drafted the manuscript. The Cognitive Function and Ageing Study collaboration devised and conducted the CFAS II study and provided data for the current analysis. All authors were responsible for interpretation of the results, critical revision and approval of the final manuscript.

Funding This work was supported by the Alzheimer's Society (Grant Ref: AS-DTC-2014-027).

Disclaimer The funder had no input into the design, collection of data, analysis or interpretation of data nor the writing of the report or the decision to submit for publication.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Data from CFAS II is available to researchers on the application as per the process described at www.cfas.ac.uk.

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