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Quality use of medicines and health outcomes among a cohort of community dwelling older men: an observational study

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Adverse drug reactions and polypharmacy are common, particularly later in life. Suboptimal use of medicines may be associated with adverse health outcomes.

WHAT THIS STUDY ADDS

- Markers of potentially suboptimal medication use (both medication over-use and under-use) were observed frequently among a cohort of community dwelling older men. Potentially suboptimal medication appeared to be independently associated with important adverse health outcomes.

AIM

To determine the prevalence of potentially suboptimal medication use and association with adverse outcomes.

METHODS

A prospective, observational cohort study of 4260 community-dwelling older men from Perth, Western Australia (mean age of 77 ± 3.6 years) was conducted. Follow-up was for 4.5 years (or until death, if sooner). Cox proportional hazard models were used to explore associations between suboptimal medication use and prospective clinical outcomes. Logistic regression analyses were used to explore predictors of a fall in the previous 12 months.

RESULTS

Use of potentially inappropriate medicines (48.7%), polypharmacy (≥5 medications, 35.8%) and potential under-utilization (56.7%) were highly prevalent, and overall 82.3% of participants reported some form of potentially suboptimal medication use. A self-reported history of falls in the previous 12 months was independently associated with the number of medicines taken (odds ratio [OR] = 1.06, 95% confidence interval [CI] 1.02, 1.09) and use of one or more potentially inappropriate medicines (OR = 1.23, 95% CI 1.04, 1.45). After adjusting for age, co-morbidity, smoking status, body mass index, hypertension and educational attainment, the number of medicines reported was associated with admission to hospital (hazard ratio [HR] = 1.04, 95% CI 1.03, 1.06), cardiovascular events (HR = 1.09, 95% CI 1.06, 1.12) and all cause mortality (HR = 1.04, 95% CI 1.00, 1.07). Use of one or more potentially inappropriate medicines was associated with admission to hospital (HR = 1.16, 95% CI 1.08, 1.24). Potential under-utilization was associated with cardiovascular events (HR = 1.20, 95% CI 1.03, 1.40).

CONCLUSIONS

These data suggest that both medication over-use and under-use occur frequently among older men and may be harmful.

Introduction

Adverse drug reactions and polypharmacy are common, particularly later in life [1]. Medication-related symptoms often underlie presentations to primary care services and emergency departments [2] and are a common cause of hospital admission, morbidity and mortality [3]. Among frail older people, non-specific presentations of ill health ('geriatric syndromes' such as falls and confusion, and associated morbidity such hip fracture) are often thought to be drug-related [4]. Despite this, potentially hazardous patterns of prescribing remain highly prevalent [5].

Several approaches to identifying potentially hazardous prescribing of inappropriate drug therapies have been proposed. The Beers criteria [6] define inappropriate therapy for elderly patients including inappropriate drug choices, excess dosages and diseases which contra-indicate some therapies. Polypharmacy *per se* also appears to be a risk factor for adverse outcomes [7]. However this apparent relationship may be confounded by the burden of multiple chronic diseases [8]. Paradoxically, there is also evidence that under-treatment of chronic diseases in older patients is common [9]. Suboptimal medication use among older people is thus a complex problem comprising: (i) use of potentially inappropriate medicines (such as inappropriate drug combinations and use of relatively contra-indicated medicines), (ii) over-utilization (polypharmacy and excessive dose and treatment duration) and (iii) under-utilization of indicated medicines [10].

We hypothesized that suboptimal medication use would be associated with adverse clinical outcomes (falls, other geriatric syndromes, cardiovascular events and mortality) in a population-based cohort of older men.

Methods

Design

This was a prospective cohort study, also comprising collection of self-reported retrospective data.

Setting

The study cohort was derived from the Health In Men Study (HIMS). Between April 1996 and January 1999, men residing in Perth, Western Australia aged 65–83 years were identified using the electoral roll and randomized to either receive an invitation to ultrasound screening or be a control in a randomized controlled trial of screening for abdominal aortic aneurysms [11]. Between 2001 and 2004, surviving men were invited to participate in a follow-up study (HIMS) comprising additional cardiovascular risk factor surveys and clinic attendance [12].

Participants

Of 19 352 eligible men randomized to screening for abdominal aortic aneurysm, 12 203 (~70%) completed the study assessments [11]. Of 10 940 surviving men invited to participate in HIMS, 4263 men aged between 70 and 88 years were recruited to HIMS and provided both blood samples and medication data. Three men subsequently withdrew from the study. The present cohort comprises these 4260 men.

Outcomes of interest

Prevalent falls, incident hospital admissions (all-cause, and due to falls, incontinence and delirium), cardiovascular events and mortality were the outcomes of interest for this study. These outcomes were selected *a priori* to reflect the major general health problems of older people that may be influenced by prescribing quality, and for which there were available data. An affirmative answer to the question 'In the LAST 12 MONTHS, have you had a fall to the ground? (excluding stumbles and trips)' was considered indicative of prevalent falls. Information about incident falls, incontinence, delirium, cardiovascular events (myocardial infarction or stroke) and all cause mortality was retrieved from the Western Australian Data Linkage System (WADLS), which is a comprehensive, population-based linkage system that connects up to 40 years of data for over 30 collections for residents of Western Australia [13]. The WADLS includes records of all public and private hospital discharges coded using the International Classification of Diseases diagnostic classification (versions 8, 9 and 10) and the Western Australia death register. Deaths and discharges in the 4.5 years after baseline (total admissions and admissions for falls, geriatric syndromes and cardiovascular events) were extracted from the WADLS. Admissions for geriatric syndromes were defined as those due to delirium, injurious falls (i.e. falls requiring hospital contact) and incontinence. Admissions with an ICD-10 diagnosis code in the range W00-19, accompanied by one or more codes in the range S00-99 or T00-14 were identified as an admission related to an injurious fall. ICD-10 code F05 was used to identify admission for delirium. Diagnosis codes of R32, N39.3 or N39.4 were used to identify admissions for incontinence.

Exposures: markers of potentially suboptimal medication use

Participating men provided a list of all medicines they were currently taking during the baseline assessment. These medicines were coded according to the WHO Anatomical, Therapeutic, Chemical Classification [14]. The published criteria for assessment of prescribing quality [6], particularly those relevant to Australia [6, 15–17], were used to compile a list of potentially inappropriate medicines and define markers of suboptimal medication use, including potential over-utilization and potential under-utilization. These definitions and the corresponding data sources are summarized in Table 1. Dosage data were not available. Thus we included some medicines (such as ferrous sulphate, which is included in Beer's Criteria when the dose exceeds

Table 1
Markers of suboptimal medication use

Variable	Definition and data
Potential over utilization	Number of (self-reported) medicines
Potential under-utilization	History of atrial fibrillation or flutter in WADLS (at least two events, without ablation)* and did not report antiplatelet agent or anticoagulant therapy; OR History (WADLS or self-reported) of cerebrovascular† disease and did not report taking ACE inhibitor (or angiotensin II antagonist) and statin; OR History of peripheral arterial disease‡ (WADLS) or CHD§ (WADLS or self-reported) and did not report taking antiplatelet agent, ACE inhibitor (or angiotensin II antagonist), β-adrenoceptor blocker and statin therapy; OR Self reported history of hypertension, or recorded blood pressure ≥ 140/90 mmHg, and did not report taking antihypertensive, diuretic, β-adrenoceptor blocker, calcium channel blocker, ACE inhibitor or angiotensin II receptor antagonist therapy.
Potentially inappropriate medicines use	Self-reported use of a medicine commonly contra-indicated in older people (benzodiazepines, barbiturates, mianserin, tricyclic antidepressants, phenothiazines, NSAIDs, dextropropoxyphene, cyproheptadine, propantheline, amantadine, benzhexol/benztropine, methyldopa, cimetidine, sulfonamide-trimethoprim combinations, disopyramide, hydrochlorothiazide-potassium sparing diuretic combinations, glibenclamide, theophylline, fluoxetine, antihistamines, oxybutynin, ergot alkaloids, nitrofurantoin, amiodarone, nifedipine, clonidine/apraclonidine, promethazine, dicyclomine, hyoscyamine, ticlopidine, dexamphetamine); OR Self-reported use of a medicine which is commonly toxic in among older people (digoxin, ferrous sulphate), antipsychotics, allopurinol, metformin when eGFR < 60 ml min^{-1}, prazosin, warfarin when combined with a NSAID); OR reports use of medicines suggesting prescribing cascade (cholinesterase inhibitors with systemic anticholinergics, anti-Parkinson's medicines with dopamine antagonists, diuretics with NSAIDs, thiazides with anti-gout therapy, β-adrenoceptor blockers with self reported history of asthma).

*427.4x (ICD-8), 427.3x (ICD-9), or I48.x (ICD-10); without 37.3[3/4] (ICD-9) or 38512–00, 38515–00, 38287–00 or 38290–00 (ICD-10-AM). †362.3x, 433.x1, 434.x1, 430.x, 431.x, 436.x (ICD-9) or H34.1x, I60.x, I61.x, I63.x, I64.x (ICD-10). ‡440.0-3x, 440.9x, 442.x, 444.0-4x, 444.9x, 443.1, 443.9, 445.0, 445.9 (ICD-8), 250.7x, 440.0-3x, 440.9x, 442.3, 443.1-2x, 443.81, 443.9x, 444.0-2x, 444.8-9x, 447.1, 785.4, 445.0x, 445.8x (ICD-9) or I70x, I71.0[0–3], I74.0–5, I74.8–9, I79.2x, E10.5x, E11.5x, I72.4, I73.1, I73.9, I77.1 (ICD-10). §410.x-414.x (ICD-8,9) or I20.x-I25.x (ICD-10).

325 mg daily) in the category of 'additional commonly toxic medicines'. Given that categorical definitions of polypharmacy (≥5 medicines) are controversial, we handled the number of medicines both as a dichotomous and continuous variable.

Potential confounders and other variables

WADLS inpatient data were used to assign a baseline co-morbidity profile to each participant. This was based on the Charlson Index [18] which was applied to the 10-year period prior to baseline. The Charlson Index identifies 17 common medical conditions. A weighted Charlson index of 5 or greater is indicative of significant health morbidity and increased risk of death over a 2-year period [18].

As part of the baseline assessment subjects completed the SF-36 Health Survey [19] items and self-reported highest level of education completed (never attended school, primary school, some high school, completed high school [year 12 or equivalent], or completed university or other tertiary degree) and smoking status (current, past smoker or never smoked).

Body mass index (BMI) was calculated from height (measured to 0.5 cm) and weight (measured to 0.2 kg) and categorized as underweight (<18.5 kg m^{-2}), normal (18.5 < 25 kg m^{-2}), overweight (25 < 30 kg m^{-2}) or obese (≥30 kg m^{-2}). Hypertension was defined as a recorded blood pressure ≥140/90 mmHg or having a self-reported history of hypertension.

Blood samples were collected between 08.00 h and 10.30 h. Serum was prepared immediately following phlebotomy and stored at −80°C until assayed. Biochemical and hormone assays were performed in the Biochemistry Department, PathWest, Royal Perth Hospital, Western Australia. Creatinine, age and body weight were used to calculate an estimate of glomerular filtration rate (eGFR) using the Cockcroft-Gault formula.

Statistical analysis

Data were analyzed with the statistical package Stata, version 10.0 (StataCorp, 2007). Pearson's Chi-square test was used to assess relationships between categorical baseline variables, and the Mann-Whitney *U*-test was used to assess continuous baseline variables as these were not normally distributed. Cross-sectional analyses using binary logistic regression were undertaken to determine cross-sectional associations between markers of potentially suboptimal medication use and self-reported history of a fall in the previous 12 months. For the prospective outcomes, each suboptimal medication use variable was entered into a Cox proportional hazard model adjusted for age, Charlson's index, SF-36 physical component score, educational attainment, smoking status, hypertension and body mass index (BMI). Assessment of the Schoenfeld residuals confirmed the proportional hazards assumption. Owing to missing data, 4183 men were included in the cross-sectional analyses and 4188 in the longitudinal models. All tests were two-tailed, and *P* values <0.05 were considered statistically significant.

Ethical approval

The Human Research Ethics Committee of the University of Western Australia approved the study, and all participants provided written informed consent to participate in HIMS and to allow record linkage of health data.

Results

Demographic characteristics and prevalence of potentially suboptimal medication use

The HIMS sample included 4260 men with a mean age of 77 ± 3.6 years. Demographic and clinical characteristics of participants reporting potentially suboptimal medication use compared with men not reporting potentially suboptimal medication use are summarized in Table 2. The majority of participants (82.3%, *n* = 3504) reported some form of potentially suboptimal medication use. We identified polypharmacy (use of five or more medicines) in 1523 men (35.8%). In addition, nearly half (48.7%, *n* = 2074) of the participants reported use of a potentially inappropriate medicine. Twenty-six percent of men were taking non-steroidal anti-inflammatory medicines and 10% were taking allopurinol. Of the 242 men taking metformin, 69 (28.5%) had an eGFR <60 ml min^{-1}. Benzodiazepine and prazosin use were both reported by 5% of men. Four percent reported taking digoxin. Three percent of men reported taking tricyclic antidepressants, nifedipine, amiodarone or antihistamines. No men reported use of promethazine, dicyclomine, hyoscyamine, ticlopidine, dexamphetamine or hydrochlorothiazide-potassium sparing diuretic combinations. Consumption of all other potentially inappropriate medicines, and warfarin in combination with a non-steroidal anti inflammatory drug, was found in less than 2% of men. Figure 1 shows the distribution of participants according to potentially suboptimal use of medicines.

Potential prescribing cascades, as described in Table 1, were observed in 5% of men. Three percent were taking diuretics concurrently with NSAIDs. No men reported use of anticholinergic medicines concurrently with cholinesterase inhibitors. Other potential prescribing cascades were each found in less than 1.5% of men.

Markers of potential under-utilization of medicines (Table 1) were also detected very commonly, with 86% of patients with peripheral arterial disease, 84% of patients with coronary heart disease, 73% of patients with cerebrovascular disease, 39% of patients with hypertension and 14% of patients with AF reporting absence of medication use indicating potential under-utilization.

Suboptimal medication use and prevalent falls

A fall to the ground in the past 12 months was reported by 772 men (18.2%). The self-reported number of medicines taken, use of potentially inappropriate medicines and potential under-utilization were all associated with self reported history of falls in the preceding 12 months in univariate models (Table 3). However, after adjustment for potential confounders, only the number of medicines taken (odds ratio [OR] = 1.06, 95% confidence interval [CI] 1.02, 1.09, *P* = 0.001) and the number of potentially inappropriate medicines (OR = 1.23, 95% CI

Table 2
Characteristics of 4260 participants with and without markers of suboptimal medication use

	No marker (*n* = 756)		Any marker of potentially suboptimal medicine use (*n* = 3500)			Potential over-utilization (≥5 meds) (*n* = 1523)			Potential under-utilization (*n* = 2416)			Potentially inappropriate medication use (*n* = 2074)		
	Median or n	IQR or %	Median or *n*	IQR or %	*P*	Median or *n*	IQR or %	*P*	Median or *n*	IQR or %	*P*	Median or *n*	IQR or %	*P*
Age (years)	75.7	73.9–78.5	76.9	74.4–79.6	<0.001				76.8	74.4–79.7	<0.001	76.6	74.3–79.4	<0.001
Number of medicines	2	1–3	6	5–8	<0.001				3	2–5	<0.001	5	3–7	<0.001
Charlson's index														
0	574	75.5	509	33.4	<0.001				1171	48.5	<0.001	1017	49.0	<0.001
1–2	159	20.9	595	39.1					790	32.7		661	31.9	
3–4	19	2.5	273	17.9					303	12.5		263	12.7	
5 +	8	1.1	146	9.6					152	6.3		133	6.4	
SF-36 PCS	46.5	41.1–52.2	36.4	28.6–44.7	<0.001				42.0	32.7–49.2	<0.001	39.1	30.6–46.3	<0.001
Educational attainment														
Tertiary	166	21.8	328	21.6	0.611				516	21.4	0.151	452	21.8	0.362
Completed Secondary	188	24.7	408	26.8					664	27.5		551	26.6	
Some Secondary	304	40.0	571	37.5					869	36.0		761	36.8	
Primary school	102	13.4	214	14.1					364	15.1		307	14.8	
eGFR (ml min^{-1})	69.3	59.0–80.4	64.9	52.6–77.1	<0.001				67.1	56.2–79.1	0.004	66.9	55.8–78.9	0.002

eGFR estimate of glomerular filtration rate; IQR interquartile range; PCS physical component score. *P* values: comparison between group with each marker of suboptimal medication use, and the 'no marker' group.

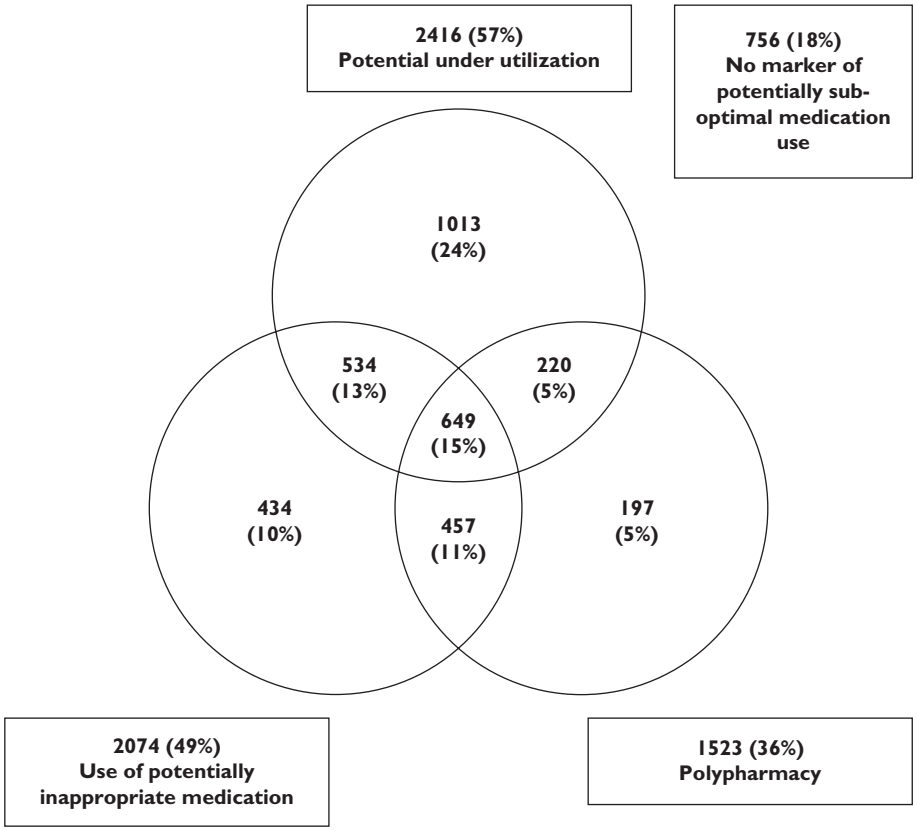

Figure 1
Prevalence of potentially suboptimal medication use

Table 3
Logistic regression of factors associated with self-reported history of falls in previous 12 months

	Univariate OR	95% CI	*P* value	Adjusted OR	95% CI	*P* value
Number of medicines reported	1.14	1.11,1.17	<0.001	1.06	1.02,1.09	0.001
Potentially inappropriate medication use	1.66	1.42,1.94	<0.001	1.23	1.04,1.45	0.018
Potential under-utilization	1.24	1.06,1.45	0.008	1.10	0.93,1.31	0.278
Any marker of potentially suboptimal medicine use	1.63	1.29,2.04	<0.001	1.17	0.91,1.49	0.227

Models adjusted for age, Charlson's index, SF-36 physical component score, educational attainment, smoking status, hypertension and BMI. CI confidence interval; OR odds ratio.

1.04, 1.45, $P = 0.018$) were associated with self-reported history of a fall.

Suboptimal medication use, incident geriatric syndromes, cardiovascular events and death

We followed HIMS men for 4.5 years (or until death, if sooner; range 0.6–4.5 years) to investigate the longitudinal association between medication use, hospital admissions due to geriatric syndromes, cardiovascular events and death.

The number of medicines used was independently associated with all cause admission to hospital (hazard ratio [HR] = 1.04, 95% CI 1.03, 1.06, $P < 0.001$), cardiovascular events (HR = 1.09, 95% CI 1.06, 1.12, $P < 0.001$), and all cause mortality (HR = 1.04, 95% CI 1.00, 1.07, $P = 0.046$) over 4.5 years of follow-up (Table 4). The presence of potential medication under-utilization was also independently associated with subsequent cardiovascular events (HR = 1.20, 95% CI 1.03, 1.40, $P = 0.020$). Reported use of one or more potentially inappropriate medicines was associated with greater hazard of admission to hospital (HR = 1.16, 95% CI 1.08, 1.24, $P < 0.001$). Admissions for falls were not independently associated with any of the markers of suboptimal prescribing. None of the markers of potentially

Table 4
Cox proportional hazards models to determine association of potentially suboptimal prescribing with health outcomes

Marker of potentially suboptimal prescribing	Death			Any admission			Admission for falls			Admission for geriatric syndrome			Cardiovascular event		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Any marker	1.14	0.86, 1.52	0.366	1.21	1.10, 1.33	<0.001	1.19	0.78, 1.79	0.417	1.28	0.91, 1.80	0.151	1.42	1.12, 1.80	0.004
Number of medicines	1.04	1.00, 1.07	0.046	1.04	1.03, 1.06	<0.001	1.03	0.98, 1.08	0.198	1.03	0.99, 1.07	0.171	1.09	1.06, 1.12	<0.001
Potentially inappropriate medication use	1.01	0.84, 1.21	0.932	1.16	1.08, 1.24	<0.001	0.98	0.77, 1.26	0.896	0.95	0.77, 1.16	0.610	1.01	0.87, 1.17	0.873
Potential under-utilization	1.18	0.98, 1.43	0.081	1.02	0.95, 1.10	0.527	1.15	0.89, 1.49	0.283	1.16	0.94, 1.43	0.169	1.20	1.03, 1.40	0.020

Models adjusted for age, Charlson's index, SF-36 physical component score, educational attainment, smoking status, hypertension and BMI. CI confidence interval; HR hazard ratio.

suboptimal medication use was associated with overall admissions for geriatric syndromes (Table 4).

Discussion

This study confirms that potentially suboptimal medication use is very common in later life. Self reported use of potentially inappropriate medicines, over- and under-treatment are all highly prevalent, with substantial overlap between these markers of suboptimal medication use. Our results also show that potentially suboptimal medication use is associated with important adverse health outcomes. Polypharmacy appears to be independently associated with prevalent falls, and incident cardiovascular events, all cause admissions and all cause mortality among community dwelling older men. Use of potentially inappropriate medicines is associated with falls and all cause admission to hospital. The magnitude of the associations observed, when extrapolated to the total number of older men living in the community, suggests that substantial numbers of admissions, cardiovascular events and deaths may be associated with suboptimal medication use.

The study is novel and important because it examines the association between medication use variables and objective health outcomes in a community dwelling sample of older adults. Most previous studies have used selected populations, such as patients presenting to ambulatory or inpatient care. Use of potentially inappropriate medicines is known to contribute to adverse events among frail people, such as those living in nursing homes [20]. The present data extend those findings to show that use of inappropriate medicines is associated with a history of falling in the last 12 months, and all cause admission to hospital in community dwelling older men.

Key strengths of the study include community based sampling of participants, the large population-based sample size, and use of the WADLS to capture reliably morbidity and mortality endpoints [13]. The population of Western Australia is relatively stable and thus the mortality dataset is likely to be largely complete [21, 22].

The study design has limitations that need to be considered in the interpretation of its results. Although invitations to participate in the study were random, those enrolling were self-selecting, introducing a potential for volunteer bias. In addition, capturing outcome data from the WADLS may lead to underestimation of certain events. This is most notable for falls, which was the rationale for assessing a combination of self-reported falls and falls resulting in admission to hospital. The WADLS only captures falls which lead to hospital admission (about 4% of all cases) whereas another ~40% may sustain an injury [23]. In addition, our definition of a 'fall' (which excluded 'trips and stumbles') was more conservative than that used by many investigators. Thus the lack of association between some markers of potentially suboptimal prescribing and

injurious falls requiring hospitalization may relate to the reduced power associated with the incomplete ascertainment of falls. It is also possible that baseline variables may have changed over the follow-up period. For example, the stability of medication use over time in this population is not known. We utilized self-reported medication histories and did not validate their accuracy, so cannot be certain of their reliability. However, self reported medication histories tend to under-estimate actual medication use. Our definitions of potentially suboptimal medication use attempted to encompass common instances of potentially suboptimal medication use. However, dosage data were not available and this limits the interpretation of the data, given that some medicines may become 'inappropriate' only when prescribed in an excessive dose. Our definition of potential under-utilization focused on cardiovascular therapies (given that vascular outcomes are common, with relatively clear indications for preventive therapies) and may thus not be representative of the broader problem of potential under-utilization of medicines. Finally, our medication use variables did not account for all valid medication indications/contraindications (which would be required to validate whether *potentially* suboptimal use of medicines is *actually* suboptimal).

Interpretation of the study results is further limited by the potential for residual confounding. Although our models attempted to control comprehensively for co-morbidity (by using Charlson's weighted index and the SF-36 physical component score) we did not apply criteria to assess the clinical appropriateness of potential overuse of medicines. It is possible that residual confounding by co-morbidity (given that the Charlson's index does not account for all common morbidities) and severity of disease, a manifestation of indication bias, could partly explain some of the associations between suboptimal medication use and adverse health outcomes. Several of our markers are relatively crude. However, substantial confounding by co-morbidity seems unlikely, given the 'healthy volunteer' nature of the cohort and survivorship bias (which would tend to lead to underestimation of the prevalence of suboptimal medication use and any association with adverse health outcomes). Other factors, such as selection bias due to socio-economic status, are unlikely to produce systematic bias. If they did, this would move the results towards the null, as men who are more likely to be able to afford medicines would have less risk of adverse outcomes. Association of both markers of under- and over-utilization with health outcomes in our study suggests that the results cannot be entirely explained by indication or selection bias.

Polypharmacy or use of inappropriate medicines, and simultaneous under-treatment with other medicines, are common. Our data accord with intervention studies showing that improved adherence to indicated medicines among non-complaint patients is associated with reduced mortality [24]. Future studies should assess interventions to reduce medication under-utilization in broader samples of patients. Although some previous intervention studies to reduce polypharmacy have not been effective [25], alternative approaches which seek to modify polypharmacy and optimize effective medicines may be more effective at reducing the risk of adverse health outcomes. Thus, intervention studies should assess the effect of simultaneously targeting polypharmacy and medication under-utilization amongst community-dwelling older people.

Competing Interests

The authors have no conflicts of interest to declare.

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