Polypharmacy in the Elderly: A Marker of Increased Risk of Mortality in a Population-Based Prospective Study (NEDICES)

Candelas Gómez^a Saturio Vega-Quiroga^b Félix Bermejo-Pareja^{c, d, e}
María José Medrano^f Elan D. Louis^{g, h, i, j} Julián Benito-León^{c, d, e}

^a'Eras del Bosque' Health Center, Palencia, ^b'Arévalo' Health Center, Arévalo, Ávila, and ^cDepartment of Neurology, University Hospital '12 de Octubre', ^dDepartment of Medicine, Faculty of Medicine, Complutense University, ^eCentro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), and ^fVascular Risk Factors Unit, National Center of Epidemiology, ISCIII, Madrid, Spain; ^gG.H. Sergievsky Center, ^hDepartment of Neurology and ⁱTaub Institute for Research on Alzheimer's Disease and the Aging Brain, College of Physicians and Surgeons, Columbia University, and ^jDepartment of Epidemiology, Mailman School of Public Health, Columbia University, New York, N.Y., USA

Key Words

Elderly people · Epidemiology · Mortality · Polypharmacy

Abstract

Background: Little information is available on the potential association between polypharmacy and risk of mortality. **Objective:** To determine in a population-based study whether polypharmacy is associated with increased risk of mortality in elderly persons. **Methods:** In this population-based, prospective study of 5,052 people aged 65 years and older (Neurological Disorders in Central Spain), current medications were recorded. Cox proportional hazards models, adjusted for sociodemographics and comorbidity factors, were used to assess the risk of death up to 13.3 years later, comparing the polypharmacy group (≥ 6 drugs) to those who were taking 1–5 drugs and those in a nonmedicated group (0 drugs). **Results:** Out of 5,052 participants, 2,550 (50.5%) died over a median follow-up of 6.5 years, including 361 (28.8%) deaths among 931 nonmedicated participants, 1,946 (51.4%) deaths among 3,787 participants taking 1–5 drugs daily, and 243 (72.8%) among 334 participants on

polypharmacy. In an unadjusted Cox model, risk of mortality was increased in participants on polypharmacy [hazard ratio (HR) = 2.78, 95% confidence interval (CI): 2.36–3.27, $p < 0.001$] and in those taking between 1 and 5 drugs (HR = 1.47, 95% CI: 1.31–1.64, $p < 0.001$) versus those who were non-medicated (reference group). In a Cox model that adjusted for a variety of demographic factors and comorbidities, HR remained increased in participants on polypharmacy (HR = 1.83, 95% CI: 1.51–2.21, $p < 0.001$). **Conclusion:** This study provides evidence that polypharmacy is associated with increased risk of mortality in elderly people. The extent to which polypharmacy is the proximate cause rather than a marker of this increase risk remains to be determined.

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Introduction

In developed countries, the number of older people is increasing, as is their proportion in the population; both declining fertility and increasing life expectancy are contributing to this trend [1]. This increase implies the need

to adopt policies and manage services with the purpose of combating the social problems affecting a group of people who on their own would be unable to cope with the demands of their living circumstances [2].

Elderly people have their own health characteristics, with a high prevalence of certain disorders such as cardiovascular disease, diabetes mellitus, arterial hypertension, bone and joint problems, and neurodegenerative conditions. Each of these conditions increases fragility and leads to disability [3]. The presence of multiple disease processes further defines elderly people as a population group with a high consumption of healthcare resources, including drugs [3].

Polypharmacy is variously defined as a high number of drugs (e.g. more than 5–10), use of more drugs than clinically indicated, or use of inappropriate medications [4]. Elderly patients are particularly susceptible to issues that arise as a result of polypharmacy – aging affects how their bodies handle medications and they take more medications than younger patients. In recent years, there has been a considerable increase in geriatric polypharmacy [5–9]. For instance, a population-based study of noninstitutionalized people in the United States found that drug consumption, defined as at least one drug, increased with age, reaching close to 90% in adults aged ≥ 65 years [9]. Data from the Swedish Prescribed Drug Register also showed a prevalence of polypharmacy in $>5\%$ of patients in their 40s, and a prevalence of approximately 12% among those in their 50s [10].

The impact of polypharmacy on the elderly population is significant. It is associated with poor adherence, drug-drug interactions, medication errors, and adverse drug reactions (including falls, hip fractures, confusion, and delirium), accounting for a significant percentage of potentially preventable emergency room visits and hospitalization [4, 11, 12]. Although polypharmacy is a major and growing public health issue [13, 14], only a handful of population-based studies have specifically been performed to assess the association of polypharmacy with risk of mortality [15–17]. This motivated us to assess whether polypharmacy is associated with risk of mortality in a prospective population-based study involving more than 5,000 elderly people in central Spain.

Material and Methods

Study Population

Data for these analyses were derived from the Neurological Disorders in Central Spain (NEDICES) study, a longitudinal population-based survey of the prevalence, incidence, and determi-

nants of major age-associated conditions of the elderly, including Parkinson's disease (PD), essential tremor, stroke, and dementia [18–31].

Detailed accounts of the study population and sampling methods have been published [18–27]. The survey area consisted of three communities: (1) Margaritas (approx. 14,800 inhabitants), which is a working-class neighborhood in Getafe (Greater Madrid), (2) Lista (approx. 150,000 inhabitants), a professional-class neighborhood in Salamanca district (central Madrid), and (3) Arévalo (approx. 9,000 inhabitants), the agricultural zone of Arévalo County (125 km northwest of Madrid). Up-to-date lists of residents were generated from population registers. In each community, survey eligibility was restricted to residents aged 65 years or older who were present on December 31, 1993, or during 6 or more months of 1993. Eligible persons who had moved away from the survey area were not traced. In Margaritas and Arévalo, every eligible subject was screened. However, because of the large number of elderly residents in Lista, proportionate stratified random sampling was used to select subjects for screening. All procedures were approved by the ethical standards committees on human experimentation at the university hospitals '12 de Octubre' (Madrid) and 'La Princesa' (Madrid). Written (signed) informed consent was obtained from all enrollees.

Exclusions and Final Sample for Analyses

Beginning in January 1994, letters explaining the survey and inviting participation were mailed to 6,395 subjects. Of these, 5,914 subjects were deemed eligible for screening and 5,278 subjects (89.2%) were screened. The remaining 636 subjects either declined (292, 45.9%), could not be located due to an address change (292, 45.9%), or had died (52, 8.2%). Of the 5,278 participants screened at the baseline evaluation, 217 were excluded because they had no data on daily number of drugs. We further excluded 9 participants due to missing data on death status. Therefore, the final cohort consisted of 5,052 subjects (fig. 1).

The final sample of 5,052 was similar to the base sample of 5,278 participants in terms of gender [2,918 (57.8%) vs. 3,040 (57.6%) women, $\chi^2 = 0.03$, $p = 0.87$], education [669 (13.3%) vs. 711 (13.6%) illiterate, $\chi^2 = 0.96$, $p = 0.812$], and age [74.1 ± 6.9 (median = 73) vs. 74.3 ± 7.0 (median = 73) years, Mann-Whitney U test, $p = 0.306$].

Study Evaluation

Briefly, at the time of their baseline assessment (1994–1995), 5,278 elderly subjects were interviewed using a 500-item screening questionnaire that assessed demographic factors and medical conditions. The face-to-face interview included data collection on demographics, current medications (including drugs that affect the central nervous system), and medical conditions. Subjects were asked to bring all medications taken in the past week to the clinic, where the interviewer recorded the name and the dose of each one. Baseline medication use in the current analyses was therefore based on medications taken in the past week.

A short form of the questionnaire was mailed to subjects who refused or were unavailable for face-to-face or telephone screening. This form assessed demographic characteristics, several neurological disorders (PD, essential tremor, stroke, and dementia), current medications, and the name of their family doctor.

Fig. 1. Flow chart of the study.

Participants who screened positive for any neurological disease (i.e. PD, essential tremor, stroke, and dementia) were examined by 1 of 8 senior neurologists who met at the inception of the study to establish standardized methods to perform and interpret the examination (F.B.-P., J.B.-L.; see <http://www.ciberned.es/estudio-nedices>). For participants who could not be examined, medical records were obtained from their general practitioners, from inpatient hospitalizations, and from neurological specialists (if they had visited one).

The diagnoses of dementia, parkinsonism, and stroke were based on clinical data and medical record review [19, 20, 23–26]. The World Health Organization clinical definition of a stroke was applied [24, 26]. For the diagnosis of dementia, we applied Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria [32] and required evidence of cognitive deficit (neu-

ropsychological test battery, clinical mental status examination) as well as evidence of impairment in social or occupational function. Parkinsonism was diagnosed when at least two cardinal signs (resting tremor, rigidity, bradykinesia, or impaired gait/postural reflexes) were present, and PD was diagnosed in these patients when there were no secondary causes or atypical features [19, 20].

There is no consensus in defining polypharmacy [4]. However, a systematic review of the literature stated ‘use of six or more concomitant medications’ as one of the most cited definitions of polypharmacy [33]. Accordingly, we classified the variable into three categories: (1) 0 drugs, (2) 1–5 drugs, and (3) polypharmacy (≥6 drugs).

Follow-up data on death were collected until May 1, 2007. The date of death was obtained from the National Population Register

of Spain (Instituto Nacional de Estadística). In Spain, all deceased individuals receive a death certificate, completed by a doctor, at the time of death. The certificate is then sent to the local authorities in the municipality where the person had been living, and the information is added to the National Register. The cause of death [using the International Classification of Diseases (ICD) 9th Revision for deaths occurring prior to 1999 (<http://www.cdc.gov/nchs/icd/icd9.htm>), and the ICD 10th Revision (<http://www.cdc.gov/nchs/icd/icd10.htm>) for deaths occurring thereafter] was classified by NEDICES investigators into 1 of 6 primary categories: dementia, cerebrovascular disorders, cardiovascular disorders (pulmonary embolism, congestive heart failure, myocardial infarction, heart or aortic rupture, and asystole), respiratory diseases, cancer, and other causes (infections, trauma, and genitourinary or gastrointestinal disorders). In accordance with the recommendations of the World Health Organization, the classification of causes of death were tabulated by the doctors who completed the death certificates, depending on the basic cause of death (<http://www.who.int/topics/mortality/en/>). This was defined as the illness or injury that started the chain of pathological events which directly led to death (<http://www.who.int/topics/mortality/en/>).

Statistical Analyses

Data analyses were performed in SPSS Version 21.0 (SPSS Inc., Chicago, Ill., USA). Age and comorbidity index (see below) were not normally distributed (Kolmogorov-Smirnov, $p < 0.001$), even after log transformation. Therefore, it was compared using non-parametric tests (Mann-Whitney and Kruskal-Wallis tests). The χ^2 test was used to analyze categorical variables.

We used Cox proportional hazards models to estimate the relative risk of mortality, which generated hazard ratios (HR) with 95% confidence intervals (CI). The time variable was the years from the date of the baseline evaluation (1994–1995) to either (1) May 1, 2007 in living participants or (2) the date of death in participants who had died prior to May 1, 2007.

Several potential confounding variables (baseline age, gender, educational level, and comorbidity), which were assessed at the baseline study, were included. The comorbidity index was calculated based on the presence of the following conditions (according to a recently published comorbidity score developed in ambulatory care settings) [34]: atrial fibrillation, cancer, chronic obstructive pulmonary disease, depression, dementia, diabetes, epilepsy (treated), heart failure, myocardial infarction, other psychiatric disorders (psychosis, schizophrenia, or bipolar affective disorder), renal disease, and stroke. The presence of some items resulted in the assignment of more points than others. The score ranged from 0–28 (i.e. all conditions present).

In the Cox proportional hazards analyses, we estimated the risks of mortality in participants with polypharmacy (≥ 6 drugs) and in participants taking between 1 and 5 drugs, each compared with the reference group (nonmedicated participants). In adjusted models, we first considered variables that were associated with both daily number of drugs and death [model 1 (more restrictive criteria for confounding)] and then considered baseline variables that were associated with either daily number of drugs or death [model 2 (less restrictive criteria for confounding)]. In additional analyses, we created tertiles of the number of drugs based on our own data (≤ 1 , 2, and ≥ 3) and also treated the number of medications as a continuous variable.

Survival curves for participants with polypharmacy, those taking 1–5 medications, and those who were nonmedicated were calculated using the Kaplan-Meier method. The log-rank test was used to compare the differences between curves.

Results

Of 5,052 participants, 2,550 (50.5%) died over a median follow-up of 6.5 years (range: 0.01–13.3), including 361 (28.8%) deaths among 931 nonmedicated participants, 1,946 (51.4%) deaths among 3,787 participants who were taking between 1 and 5 drugs daily, and 243 (72.8%) deaths among 334 participants on polypharmacy (fig. 1). There were significant differences in age, gender, and medical comorbidities when participants in the three drug-use categories were compared (table 1). As expected, deceased participants were significantly older, predominantly men, and had more medical comorbidity than living participants (table 2).

The cause of death noted on the death certificates differed significantly by number of drugs consumed (table 3). Cancer and dementia were reported significantly less often in participants on polypharmacy than in those who were taking between 1 and 5 drugs or in those who were nonmedicated. In contrast, cerebrovascular diseases and respiratory diseases were reported significantly more often in participants on polypharmacy than in those taking between 1 and 5 drugs or in those who were nonmedicated (table 3).

In an unadjusted Cox model, risk of mortality was increased in participants on polypharmacy (HR = 2.78, 95% CI: 2.36–3.27, $p < 0.001$) and in those taking between 1 and 5 drugs (HR = 1.47, 95% CI: 1.31–1.64, $p < 0.001$) versus those who were nonmedicated (reference group). In a Cox model that adjusted for baseline age, gender, comorbidity index (13 conditions), PD, current smoker, and current drinker (i.e. variables that were associated with both daily number of drugs and death), the risk of mortality remained increased in participants on polypharmacy (HR = 1.83, 95% CI: 1.51–2.21, $p < 0.001$; model 1 in table 4).

The results did not change in a Cox model that adjusted for variables that were associated with either number of drugs or death [baseline age, gender, educational level, geographical area, comorbidity index (13 conditions), PD, current smoker, and current drinker; model 2 in table 4]. We also considered a number of different forms of the age variable; thus, when we added quadratic and cubic forms of age to model 2, along with age itself, the

Table 1. Baseline (1994–1995) characteristics of the study participants (n = 5,052), according to number of drugs consumed

	Number of drugs consumed			p
	0 (n = 931)	1–5 (n = 3,787)	≥6 (n = 334)	
Age, years	72.7±6.7 (71)	74.4±6.9 (73)	75.4±6.7 (74)	<0.001 ^c
Gender, women	421 (45.2%)	2,320 (61.3%)	177 (53.0%)	<0.001 ^d
Educational level ^a				
Illiterate	107 (11.6%)	510 (13.6%)	52 (15.6%)	0.187 ^d
Can read and write	372 (40.2%)	1,538 (40.9%)	136 (40.7%)	
Primary studies	327 (35.3%)	1,194 (31.7%)	96 (28.7%)	
Secondary and higher studies	120 (13.0%)	521 (13.8%)	50 (15.0%)	
Geographical area				
Lista	207 (22.2%)	1,185 (31.3%)	130 (38.9%)	<0.001 ^d
Arévalo	356 (38.2%)	1,340 (35.4%)	84 (25.1%)	
Margaritas	368 (39.5%)	1,262 (33.3%)	120 (35.9%)	
Comorbidity index ^b	0.6±1.2 (0)	1.2±1.5 (1)	2.4±1.9 (2)	<0.001 ^c
PD	4 (0.4%)	69 (1.8%)	7 (2.1%)	0.007 ^d
Current smoker ^a	139 (19.6%)	324 (10.4%)	21 (7.1%)	<0.001 ^d
Current drinker ^a	329 (46.3%)	971 (31.3%)	66 (22.4%)	<0.001 ^d

Means ± SD (median) and n (%) are reported. ^a Data on some participants were missing. ^b Comorbidity included the following conditions: atrial fibrillation, cancer, chronic obstructive pulmonary disease, depression, dementia, diabetes, epilepsy (treated), heart failure, myocardial infarction, other psychiatric disorders (psychosis, schizophrenia, or bipolar affective disorder), renal disease, and stroke. ^c A Kruskal-Wallis test was used for age and comorbidity index. ^d A χ^2 test for categorical variables.

Table 2. Demographic and clinical characteristics of cohort stratified by mortality

	Alive (n = 2,502)	Died (n = 2,550)	p
Age in years	71.2±5.1 (70)	77.0±7.2 (76)	<0.001 ^c
Gender, women	1,636 (65.4%)	1,282 (50.3%)	<0.001 ^d
Educational level ^a			
Illiterate	299 (12.0%)	370 (14.6%)	0.028 ^d
Can read and write	1,015 (40.7%)	1,031 (40.7%)	
Primary studies	835 (33.5%)	782 (30.9%)	
Secondary and higher studies	343 (13.8%)	348 (13.7%)	
Geographical area			
Lista	715 (28.6%)	807 (31.6%)	0.010 ^d
Arévalo	873 (34.9%)	907 (35.6%)	
Margaritas	914 (36.5%)	836 (32.8%)	
Comorbidity index ^b	0.8±1.2 (0)	1.5±1.7 (1)	<0.001 ^c
PD	15 (0.6%)	65 (2.5%)	<0.001 ^d
Current smoker ^a	221 (10.7%)	263 (12.9%)	0.027 ^d
Current drinker ^a	720 (34.7%)	646 (31.7%)	0.040 ^d

Means ± SD (median) and n (%) are reported. ^a Data on some participants were missing. ^b Comorbidity included the following conditions: atrial fibrillation, cancer, chronic obstructive pulmonary disease, depression, dementia, diabetes, epilepsy (treated), heart failure, myocardial infarction, other psychiatric disorders (psychosis, schizophrenia, or bipolar affective disorder), renal disease, and stroke. ^c Mann-Whitney U test. ^d χ^2 test.

Table 3. Basic cause of death by number of drugs consumed

	Nonmedicated	1–5	≥6	p ^a
Dementia	38 (10.5%)	127 (6.5%)	5 (2.1%)	<0.001
Cerebrovascular disorders	23 (6.4%)	174 (8.9%)	16 (6.6%)	0.155
Cardiovascular diseases	75 (20.8%)	556 (28.6%)	85 (35.0%)	<0.001
Respiratory diseases	39 (10.8%)	272 (14.0%)	58 (23.9%)	<0.001
Cancer	130 (36.0%)	457 (23.5%)	37 (15.2%)	<0.001
Other causes	56 (15.5%)	360 (18.5%)	42 (17.3%)	0.381
Total	361 (100%)	1,946 (100%)	243 (100%)	–

Values represent n (%). ^a χ^2 test.

Table 4. Predictors of mortality in the NEDICES cohort

	Model 1			Model 2		
	HR	95% CI	p	HR	95% CI	p
Daily number of drugs						
≥6	1.83	1.51–2.21	<0.001	1.82	1.50–2.20	<0.001
1–5	1.32	1.15–1.51	<0.001	1.31	1.15–1.50	<0.001
Nonmedicated (reference)	1.00	–	–	1.00	–	–
Age (years)	1.10	1.09–1.11	<0.001	1.10	1.09–1.11	<0.001
Gender (women)	0.55	0.50–0.61	<0.001	0.55	0.50–0.61	<0.001
Educational level						
Illiterate	not included	–	–	1.03	0.86–1.23	0.757
Can read and write	not included	–	–	0.99	0.86–1.14	0.894
Primary studies	not included	–	–	0.97	0.83–1.12	0.654
≥Secondary studies, reference	not included	–	–	1.00	–	–
Geographical area						
Lista	1.26	1.13–1.40	<0.001	1.27	1.13–1.43	<0.001
Arévalo	0.97	0.87–1.08	0.546	0.98	0.88–1.10	0.760
Margaritas (reference)	1.00	–	–	1.00	–	–
Comorbidity index ^a	1.18	1.15–1.21	<0.001	1.18	1.15–1.21	<0.001
PD	1.66	1.27–2.17	<0.001	1.65	1.26–2.16	<0.001
Current smoker	1.34	1.17–1.54	<0.001	1.34	1.17–1.54	<0.001
Current drinker	0.81	0.73–0.90	<0.001	0.81	0.73–0.90	<0.001

^a Comorbidity included the following conditions: atrial fibrillation, cancer, chronic obstructive pulmonary disease, depression, dementia, diabetes, epilepsy (treated), heart failure, myocardial infarction, other psychiatric disorders (psychosis, schizophrenia, or bipolar affective disorder), renal disease, and stroke.

HR was 1.82 (95% CI: 1.50–2.20, $p < 0.001$) for participants on polypharmacy. In that model, neither the quadratic nor the cubic forms of age were independently associated with outcome (both $p = 1.00$).

In additional analyses, we created tertiles of numbers of medications based on our own data (≤ 1 , 2, and ≥ 3). The results were similar: unadjusted HR for participants within the highest tertile of number of drugs

consumed versus those in the lowest tertile = 1.45 (95% CI: 1.30–1.62, $p < 0.001$), and model 2-adjusted HR = 1.45 (95% CI: 1.30–1.61, $p < 0.001$). We also treated number of drugs as a continuous variable and polypharmacy was associated with higher mortality: unadjusted HR = 1.16 (95% CI: 1.14–1.18, $p < 0.001$) and model 2-adjusted HR = 1.10 (95% CI: 1.08–1.13, $p < 0.001$).

Fig. 2. Kaplan-Meier curves of percent survival for participants with polypharmacy vs. those taking between 1 and 5 daily medications vs. nonmedicated participants (log-rank $p < 0.001$).

The Kaplan-Meier curves for overall survival (fig. 2) showed the cohort of participants with polypharmacy to be at an increased risk of death (log-rank $p < 0.001$).

Discussion

Using follow-up mortality data collected as part of a prospective population-based study, we demonstrated that polypharmacy was an independent predictor of mortality. We acknowledge that elderly patients are more likely to have multiple diseases and more comorbidity, and are therefore likely to use more medications [35]. However, even after adjusting for a variety of potentially confounding comorbid medical conditions, polypharmacy continued to be associated with increased risk of mortality. Assessing the daily number of drugs consumed might provide useful mortality risk stratification in the community-dwelling elderly. It remains to be determined whether detecting and lowering the extent of polypharmacy could improve the health risks of community-dwelling elderly individuals.

Our results are in agreement with prior surveys that have analyzed the risk of mortality according to the num-

ber of drugs consumed, using a population-based approach [15, 16]. In a population of 3,050 community-based Mexican-American older adults, living in the southwestern United States, use of more than four different medications was associated with mortality, independent of age, socioeconomic status, or chronic disease status and/or severity [15]. In another population-based study involving elderly persons aged ≥ 75 years ($n = 700$) living in the city of Kuopio, Finland, two separate analyses were carried out [16]. In the first phase, participants (aged ≥ 75 years, $n = 601$) were followed from 1998 (baseline) to 2002. In the second phase, survivors (aged ≥ 80 years, $n = 339$) were followed from 2003 to 2007 [16]. In the first phase, the univariate model showed an association between excessive polypharmacy (≥ 10 drugs) and mortality (HR = 2.53, 95% CI: 1.83–3.48) [16]; however, after adjustment for demographics and other variables measuring functional and cognitive status, the association between excessive polypharmacy and mortality did not remain statistically significant [16]. In the second phase, the association between excessive polypharmacy and mortality (HR = 2.23, 95% CI: 1.21–4.12) remained significant after adjustments [16]. In contrast, in the ICARE Dicomano study, involving 1,022 elderly people from a small town in Tuscany, Italy, in univariate analysis, mortality was twice as high in participants with polypharmacy (≥ 6 drugs) [17]; however, in multivariable models, polypharmacy, was no longer associated with an increased risk of death [17].

The extent to which polypharmacy is the proximate cause rather than a marker of increased risk of mortality remains to be determined. Polypharmacy could contribute to increased risk of mortality in the elderly in several ways. First, elderly patients are at risk for severe adverse drug events since the physiologic changes that occur with ageing make the body more sensitive to the effects of drugs [36]. The cumulative effects of multiple medications on the renal or hepatic systems would initiate a cascade of interactions in these older adults, who already suffer from multiple comorbidities [15]. Second, drugs that affect the central nervous system may cause drowsiness, impaired memory, confusion, and prolonged sedation, which increase an elderly patient's risk for falls, fractures, and aspiration pneumonias [37]. Third, drug-disease interactions, in which a medication worsens a disease condition, are also common among elderly patients. Finally, polypharmacy is potentially harmful because it increases the probability of adverse drug-drug interactions [38, 39].

Our study has limitations. First, community-dwelling elders might also take self-prescribed over-the-counter drugs or complementary and alternative medicines,

which they might not tell their doctor about. Although this would imply an underestimation of drug use, it would be compensated in part by the lack of adherence to therapy, very often found among the elderly population [40]. Second, data on drug exposure were available at baseline, but not for any intermediate time intervals between baseline and follow-up. Such data would have been of value in terms of assessing variation in drug exposure over time.

This study also had several strengths. First, the study was population-based, allowing us to assess a group of participants who were unselected for treatment considerations. Second, the assessments were conducted prospectively in a standardized manner. Finally, we were able to adjust for the potential confounding effects of a number of important factors.

Using a prospective, population-based design, we demonstrated that polypharmacy in community-dwelling elders was associated with increased risk of mortality. By asking patients about the usage of drugs, practitioners might be better positioned to identify patients with poorer prognoses.

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