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# Low health literacy and multiple medications in community-dwelling older adults: a population-based cohort study

Jacques Shebehe[1], Scott Montgomery[1,2,3], Anders Hansson[4], Ayako Hiyoshi[1,2,5,6]

1. Clinical Epidemiology and Biostatistics, School of Medical Sciences, Örebro University, Örebro, Sweden
2. Department of Epidemiology and Public Health, University College London, UK
3. Clinical Epidemiology Division, Department of Medicine, Solna, Karolinska Institutet, Stockholm
4. University Health Care Research Centre, Faculty of Medicine and Health, Örebro University, Örebro, Sweden
5. Department of Public Health Sciences, Stockholm University, Stockholm, Sweden
6. Public Health, Department of Social Medicine, Osaka University Graduate School of Medicine, Osaka, Japan

**Correspondence:** [1] Clinical Epidemiology and Biostatistics, Faculty of Medicine and Health, Örebro University, SE 70182 Örebro, Sweden. Jacques.Shebehe@oru.se



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## Abstract

### Objectives

Adequate health literacy is important for patients to manage chronic diseases and medications. This study examined the association between health literacy and multiple medications.

### Design, settings and participants

We included 6368 community-dwelling people of median age 66 years from the English Longitudinal Study of Ageing. Health literacy was assessed at wave 5 (2010/11) with 4 questions concerning a medication label. Four correct answers were categorised as adequate health literacy, otherwise low. Data on medications were collected at wave 6 (2012/13). We used negative binomial regression, estimating incidence rate ratios (IRR), to examine the difference in the number of medications between low and adequate health literacy while adjusting for demographic, socioeconomic and health characteristics, smoking, and cognition. We also stratified the analysis by sex, and age (52-64 and ≥65 years). To be comparable with preceding studies, multinomial regression was fitted using commonly used thresholds of polypharmacy (0-1 vs. 2-4, 5-9, ≥10 medications).

### Results

Compared with participants with adequate health literacy, the number of medications did not differ from those with low health literacy (IRR=1.04, 95% CI:0.99 to 1.10), and this finding did not differ among younger and older age groups or women. However, among men, low health literacy was associated with an IRR=1.10 (95% CI:1.01 to 1.20). Multinomial regression models showed graded but non-significant risks of polypharmacy for low health literacy.

### Conclusions

Health literacy was weakly associated with the number of medications only among men. Therefore, men may gain from increasing health literacy to improve health and reduce the risk of polypharmacy.

**Strengths and limitations of this study**

- Strengths of this study include the use of longitudinal study design based on a large representative sample of older adults in England.
- Qualified nurses checked self-reported medication use; thus, medication misreporting was reduced.
- To minimise the impact of confounding, statistical adjustment included a wide range of potential confounders such as age, sex, income, education, cognitive function, and pre-existing and concurrent morbidity and self-rated health.
- Health literacy in ELSA was measured with a validated instrument and focused on basic document literacy skills, which has been used widely, had good face validity, and has been shown to associate with mortality. However, it does not account for other skills such as prose and health navigation literacy.
- As residual and unmeasured confounding cannot be ruled out and the effect size of the association was small, the results need to be interpreted with caution.

## Introduction

Most developed countries are experiencing an ever-growing ageing population. In Europe, the proportion of people aged ≥65 years is expected to increase and reach 27% by 2050.[1] Although there are older people who remains healthy, a considerable share of older adults has multiple chronic diseases and uses multiple medications, polypharmacy. There is no consensus on the definition of polypharmacy, but the most commonly used cut-offs are ≥5 or ≥10 medications.[2]

Relationships between polypharmacy and health in the ageing process are complex and multidirectional. Polypharmacy may be due to multimorbidity; however, polypharmacy can cause negative consequences, such as poor medication adherence, declines in cognition and quality of life, and increased risk of side-effects such as fall injuries, frailty, hospitalisations, and even death.[3] Therefore, reducing the risk of inappropriate polypharmacy has been a priority among clinicians, public health scientists, and policymakers.[4]

Health literacy has recently gained much attention as a factor that can reduce the risk of polypharmacy.[5] Health literacy is an individual's ability to access, understand, appraise and apply health information to make decisions that prevent disease and excessive medications, promote good health, and improve quality of life throughout the life-course.[6] An estimated 60% of the European older population has low health literacy.[6] Patient-centred interventions have suggested that improving health literacy can reduce polypharmacy risk, medication non-adherence, and healthcare costs. [5 7 8] However, despite that low health literacy was associated with incorrect medication use[9 10] and lesser willingness to reduce the number of medications,[11] low health literacy has not been shown to associate with polypharmacy.[12 13] The lack of association may be because the majority of these studies were cross-sectional with relatively small sample size[14-16] and low statistical power.

Therefore, using a large sample of longitudinal data, we aimed to examine the association between health literacy and multiple medications in community-dwelling older adults. We further examined whether this association differed by sex, age, and morbidity because health behaviour, and disease panorama and its consequences differ between males and females, different age groups, and people with different morbidity burden.[17 18]

## Methods

### Study design and sample

This population-based cohort study used data from the English Longitudinal Study of Ageing (ELSA), an ongoing study of a large representative cohort of people living in England aged ≥50 years. The first cohort of ELSA (wave 1) was collected in 2002 from participants of the Health Survey of England (HSE), an annual cross-sectional household survey of a randomly selected sample representative of the English population living in private homes.[19] ELSA participants have been followed up biannually. New participants have been recruited from HSE to maintain the representativeness of the general English older adult population. At each wave, trained interviewers visit participants at their homes to carry out a survey comprising personal face-to-face computer-assisted interviews and a paper-and-pen self-completion questionnaire. At every other wave, a qualified nurse visits a subset of participants assessed in the survey (nurse visit), carries out interviews, performs a physical examination and collects blood samples.[19]

In this study, we included participants who had completed the health literacy assessment in wave 5 (2010/11) and had data on medication use recorded at nurse visit in wave 6 (2012/13). Of all 6837 participants assessed at wave 5 and with nurse visit at wave 6, we excluded 7% (n=469) who had incomplete data, leaving a total sample of 6368 participants included in our analyses. Participants' partners younger than 50 years and those who moved to institutions were not included in our analysis.

### Patient and public involvement

There was no patient or public involvement in this study. ELSA participants were given a newsletter with recent findings from previous surveys. All ELSA participants provided informed consent and the London Multicentre Research Ethics Committee (MREC/01/2/91) provided ethical approval for all ELSA waves.[19]

### Variables

***Exposure: health literacy***

In wave 5, trained interviewers assessed participants' health literacy using a realistic but fictitious medicine label, the method that is used in the International Adult Literacy Survey.[20] Participants were asked four questions to examine how well they understood the instructions on the label. Response to each of the four questions was scored 1 if correct and otherwise 0.

Using the sum of correct responses (range 0-4), we categorized health literacy as adequate if participants scored 4/4, otherwise as low. This cut-off has been previously used.[20]

***Outcome: number of medications***

In wave 6 nurse visit, participants were asked to name the medications they were taking in the last 7 days. The nurses checked medication containers to ascertain self-reported medication use. Devices that do not deliver drugs, such as stoma or urinary catheters and vaccines, were excluded.[19]

***Adjustment variables: sociodemographic, cognitive function and health-related characteristics.***

Factors that have been reported in the literature to be associated with health literacy[21] and polypharmacy[2 22] have been considered for adjustment. These factors include *age* (≥90 years collapsed in ELSA dataset), *sex* (male/female), *highest education qualification* (no qualification/up to secondary education/degree or higher education), *wealth* (quintiles of household-level net total non-pension wealth), *smoking status* (never smoked/ex-smoker/current smoker), *self-rated health* (excellent/very good/good/fair/poor), *Charlson Comorbidity Index* (CCI), *depression*, and *cognitive function*.

*Charlson Comorbidity Index (CCI)* was derived using the weights of self-reported conditions based on the New Jersey Medicare weights.[23] Identified self-reported conditions were myocardial infarction, heart failure, stroke or cerebrovascular disease, dementia, chronic lung disease including asthma , diabetes mellitus or high blood sugar , diabetes mellitus with end-organ damage defined as diabetes with eye disease, diabetes with protein in urine or kidney trouble told by a doctor, any cancer including any solid cancer, leukaemia, lymphoma, and some other blood disorder. The sum of CCI weights (range 0–8) was categorised into 3 levels: 0, 1–2, and 3–8.

*Depression* was assessed using the dichotomous 8-item Centre for Epidemiologic Studies Depression Scale. Of a score ranging 0–8, a score ≥3 was defined as depression, otherwise no depression.[24]

*Cognitive memory function* was assessed by testing verbal learning, immediate and delayed recall of 10 words, and a score (range 0–20) was provided. *Cognitive executive function* was assessed by testing verbal fluency based on the total number of animals named in one minute, and a score (range 0–51) was provided. A binary variable for any observed or reported *factor* *that could impair cognitive test* was created based on at least one positive answer to the following being one otherwise zero: poor sight, poor hearing, tiredness, illness or physical impairment, impaired concentration, nervousness, external interaction or distraction (e.g. phone call or visit), noisy environment, distressed (e.g. from bereavement), memory problems, the influence of alcohol, or difficulty in understanding English.

**Statistical analyses**

We summarized participants' characteristics using means, standard deviation, median, interquartile range (lower quartile to upper quartile) (IQR), and proportions. To test differences between groups, we used Chi-squared, Student's T or Mann-Whitney U test. To examine the association between health literacy and the number of medications, we estimated incidence rate ratios (IRR) and 95% confidence intervals (CI) using negative binomial regression. Adjustments were made in two steps: first, we adjusted for factors assessed at wave 5, including age, sex, education qualification, wealth, smoking, CCI, self-rate health, depression, and cognition (model 1). Second, we added CCI, self-rated health, and depression assessed at wave 6 to adjust for the influence of health status on concurrent medications (model 2). We used model 2 for all stratified, sensitivity and secondary analyses. We also stratified analyses by sex and age (52-64 and ≥65 years) and assessed interactions with likelihood ratio tests.

To reduce the possible influence of morbidity to conceal the association between health literacy and the number of medications, we conducted a sensitivity analysis restricted to participants with the lowest morbidity (CCI=0), no depression, and 'good' or higher self-rated health at both waves 5 and 6.

To be comparable with preceding studies that used a certain number of medications to define polypharmacy, we conducted secondary analyses using multinomial regression models. The association between health literacy and polypharmacy was estimated with relative risk ratios (RRR) and 95% CI. In these analyses, polypharmacy was classified into four levels: no polypharmacy (0–1) as referent, minor polypharmacy (2–4), major polypharmacy (5–9) and excessive polypharmacy (≥10 medications). [2]

In all regression models, complex survey design and household clustering were accounted for by estimating robust standard errors, and estimates were weighted to adjust for non-response. All analyses were conducted in Stata V.16 SE.

## Results

A total of 6368 participants of median age 66 years (IQR=60–73 years) were included in our analyses. The median reported number of medications was 3 (IQR=1–5) with a range 0–27, and the number of medications was higher among those with low health literacy (median 4), than those with adequate health literacy (median 2) (Table 1). Approximately three-quarters of participants had adequate health literacy, but 25% showed low health literacy. Among men and women, the proportion of low health literacy was similar whereas low health literacy was more prevalent among those aged ≥65 years, with lower education qualification, lower wealth, current smoking, depression, higher morbidity and poorer self-rated health, and lower cognitive performance.

### Health literacy and number of medications

Compared with participants with adequate health literacy, the unadjusted rate of the number of medications was 33% higher for participants with low health literacy (IRR=1.33, 95% CI: 1.26 to 1.44) (Table 2). Unadjusted IRRs of the number of medications showed a stepwise increase by wealth decline up to 1.87 times higher number of medications for the lowest wealth quintile. The highest morbidity score and the poorest self-rated health were associated 3 and 6 times higher number of medications, respectively.

After adjusting for covariates assessed at wave 5 (model 1, table 2), compared with adequate health literacy, the rate of the number of medications among those with low health literacy diminished to IRR=1.06 (95% CI: 1.00 to 1.12). IRRs for the number of medications associated with low socioeconomic characteristics, morbidity and self-rated health also diminished but remained statistically significant.

After further adjustment for health-related variables assessed at wave 6 (model 2, table 2), the difference in the number of medications between those with low and those with adequate health literacy became no longer statistically significant (IRR=1.04, 95% CI: 0.99 to 1.10). Likewise, IRRs associated with low socioeconomic characteristics were no longer statistically significant. However, IRRs for age, morbidity and self-rated health assessed at waves 5 and 6 remained statistically significantly associated with an increased number of medications and were most influential to account for diminishing the association between health literacy and the number of medications.

When the analysis was stratified by sex, low health literacy was associated with a 10% (equivalent to 0.3 of a medication) increased number of medications among men (IRR=1.10, 95% CI: 1.01 to 1.20). However, health literacy was not associated with the number of medications among women (Table 3). The likelihood ratio test for the effect modification by sex was statistically non-significant (*p*-value=0.276). There was no statistically significant association between health literacy and the number of medications in either age group, but the likelihood ratio test was statistically significant (*p*-value=0.003), and among those aged 52-64 years low health literacy was associated with 11% increased risk and significant at the 10% level (*p*-value=0.066).

When we restricted the analysis on 898 individuals who reported the lowest morbidity (CCI=0), good or higher self-rated health, and no depression at both waves 5 and 6, the finding was largely similar to that observed above, and IRR for low health literacy was 1.04 (95% CI: 0.91 to 1.19) (data not shown).

**Secondary analysis: health literacy and polypharmacy**

Among the participants, 35% of individuals used ≤1 (no polypharmacy), 33% used 2-4 (minor), 25% used 5-9 (major) and 6% used ≥10 medications (excessive polypharmacy). Multinomial regression of polypharmacy showed that, compared to adequate health literacy, unadjusted RRR for low health literacy showed a gradient increased risk of up to 2.6 times for excessive polypharmacy (Table 4). However, after full adjustment, low health literacy was no longer associated with polypharmacy. Similar to the results from the main analysis, age, morbidity and self-rated health diminished most of the association between low health literacy and polypharmacy (data not shown).

**Discussion**

This cohort study aimed to examine the association between health literacy and the number of medications and polypharmacy in community-dwelling older people. Although health literacy was associated with polypharmacy in unadjusted estimates, increased morbidity and poorer self-rated health diminished the association in most of the analyses. In men, however, low health literacy remained associated with a 10% higher number of medications, equivalent to 0.3 excess medication, even after adjustment.

In line with previous studies that found no association between health literacy and polypharmacy among community-dwelling older people,[18] older primary care patients,[12 25] as well as in younger population,[13] this study found no association between health literacy and polypharmacy when both sexes were combined. The unadjusted positive associations between low health literacy and polypharmacy diminished when socioeconomic characteristics, morbidity, and self-rated health were accounted for. Health literacy is a construct that formulates from early adolescence and develops across the life-course.[21] It relates to poor health-related behaviour,[26] inappropriate health-information seeking behaviour,[27] delayed healthcare visit, and forgone treatment.[28] Therefore, by the late middle age, as is our participants, low health literacy may have already resulted in poorer health in some individuals. Furthermore, socioeconomic disadvantages across the life-course are associated with both low health literacy and accumulated poor health.[15] Therefore, adjustment for health and socioeconomic characteristics explained away the association, and there was no medication beyond what these factors accounted for.

However, our results indicated low health literacy may be associated with polypharmacy in men. Given the lack of effect modification and the weak effect size, this finding may be a chance. Furthermore, they can also be explained away even by a weak bias, although we adjusted for known confounding factors within the data available to us. For example, the reason the association remained in men may be because men tend to underreport morbidity and poor health to a greater extent,[29] and this may have been even more pronounced among low health literate men. Such differential underreporting may have resulted in incomplete adjustment for the effect of morbidity among men. Therefore, these results should be interpreted with caution.

Nevertheless, the association in men can in part relate to gendered behaviours and attitudes to health. Research suggests men are more reluctant to seek healthcare and receive advice from peers, less likely to read healthcare instructions, and more likely to miss opportunities for medication reviews[30-32] and stay longer on medications.[33] These characteristics may even be more so among low health literate men. Therefore, although in our cohort the difference in health literacy between men and women was small, men's overall health knowledge tends to be poorer;[34] and this may explain why the association remained in men.

Identifying the magnitude of health risk associated with polypharmacy and its clinical implications is beyond the scope of our study, but an increased number of medications was associated with increased risk of fall, hospitalisation, and mortality.[3 35] A recent nation-wide cohort study and a meta-analysis found that one additional medication has been associated with a 3–8% increased risk of death in people aged ≥65 years.[36 37] Although these results do not necessarily imply causality,[36] our finding of a 0.3 excess medication associated with low health literacy in men may thus relate to 1–3% increased risk of adverse health outcomes such as death. Therefore, men may benefit from improving health literacy to prevent poor health and possibly excessive medication. However, as our study focused on those aged over 50 years, and also prescribing and medication review practices may vary with health care system and country, our results may not be generalisable to younger people or other societal contexts.

**Strengths and limitations**

Our study has some potential limitations. First, we could not know whether the reported medications were complete. For example, if individuals with poorer health literacy or cognition have failed to present all medications, this would have resulted in underestimation of association. Furthermore, we were not able to distinguish necessary or inappropriate medications or account for preventive medications such as statins that may have been used more frequently among those with higher health literacy. Nevertheless, a higher number of medications has been associated with inappropriate prescribing and proposed as a marker of inappropriate medications.[38] Second, even though the method used in ELSA to measure health literacy only assesses basic document literacy skills and does not account for other skills such as prose and health navigation literacy,[20] it has been widely used, had good face validity, and has been shown to associate with mortality.[20] Third, although we have dichotomised health literacy by 4/4 correct answers or else[20] other studies have used different cut-offs.[39] To examine whether different classification may change the conclusion, we conducted all main and stratified analyses using health literacy with 3 categories (0–2, 3, or 4 correct answers), and we observed that the conclusion remained the same (data not shown). Fourth, the UK National Service Framework for Older People has recommended regular medication reviews for people with polypharmacy since 2001.[40] Thus, it may be possible that medication reviews reduced likelihood of polypharmacy including among those with low health literacy. Fifth, we adjusted for morbidity assessed in wave 6 even though it is an intermediate factor linking health literacy and polypharmacy and may be in part a consequence of polypharmacy. We did so because multiple medications may be due to concurrent ill health. Also, if low health literate participants have rated their health poorer because of the fact that they received medications, adjustment for self-rated health have weakened the association. However, when we conducted sensitivity analyses restricted to participants with the lowest morbidity, the conclusion remained unchanged.

Our study has several strengths. We used a longitudinal design, included a large representative sample of an older population, and adjusted for a wide range of potential confounding factors. Also, although some participants may miss presenting some medications, as nurses checked medication containers, the risk of medication underreporting was reduced.

## Conclusions

Although there was no overall association between health literacy and the number of medications, low health literacy seems to be associated with a small but increased number of medications in men. While the magnitude of gain and its clinical implications remain to be determined, men may benefit from increasing health literacy to improve health and thus possibly reduce excessive medications.

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**Data sharing statement**

The datasets analysed in the current study are available in the UK Data Service repository for the English Longitudinal Study of Ageing (ELSA), https://beta.ukdataservice.ac.uk/datacatalogue/series/series?id=200011.

**Ethics statement**

All ELSA participants provided informed consent and the London Multicentre Research Ethics Committee (MREC/01/2/91) provided ethical approval for all ELSA waves.

**Competing interests statement**

Following ICJME form and BMJ competing interests policy, all authors have no conflict of interest or financial disclosures for this manuscript.

**Authors' contributions**

**JS**: Conceptualisation, Methodology, Data Curation, Formal analysis, Validation, Writing- Original draft preparation, Writing- Reviewing and Editing, Funding acquisition. **SM**: Conceptualisation, Methodology, Validation, Writing- Reviewing and Editing. **AHa**: Conceptualisation, Methodology, Writing- Reviewing and Editing. **AHi**: Conceptualisation, Methodology, Validation, Writing- Reviewing and Editing, Supervision, Funding acquisition.

All the authors read and approved the final manuscript.

**Licence statement**

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## Tables

**Table 1. The characteristics of ELSA participants by health literacy.**

| | Total* n (%) | Health literacy: Low N=1581 (24.8%)* | Health literacy: Adequate N=4787 (75.2%)* | P § |
|---|---|---|---|---|
| **Number of medications, median (IQR)** | 3 (1–5) | 4 (1–6) | 2 (1–5) | <0.001 |
| **Sex, *n* (%)** | | | | 0.084 |
| *Male* | 2837 (44.6) | 734 (25.9) | 2103 (74.1) | |
| *Female* | 3531 (55.4) | 847 (24.0) | 2684 (76.0) | |
| **Age group, *n* (%)** | | | | <0.001 |
| *52-64 years* | 2929 (46.0) | 577 (19.7) | 2352 (80.3) | |
| *65 years and older* | 3439 (54.0) | 1004 (29.2) | 2435 (70.8) | |
| **Highest education qualification, *n* (%)** | | | | <0.001 |
| *No qualification or equivalent* | 2553 (40.1) | 933 (36.6) | 1620 (63.5) | |
| *Up to secondary education* | 1723 (27.1) | 330 (19.2) | 1393 (80.9) | |
| *Degree or higher education* | 2092 (32.9) | 318 (15.2) | 1774 (84.8) | |
| **Wealth quintiles, *n* (%)** | | | | <0.001 |
| *1(least wealthy)* | 960 (15.1) | 361 (37.6) | 599 (62.4) | |
| *2* | 1266 (19.9) | 364 (28.8) | 902 (71.3) | |
| *3* | 1254 (19.7) | 343 (27.4) | 911 (72.7) | |
| *4* | 1410 (22.1) | 284 (20.1) | 1126 (79.9) | |
| *5(most wealthy)* | 1478 (23.2) | 229 (15.5) | 1249 (84.5) | |
| **Smoking status, *n* (%)** | | | | <0.001 |
| *Never smoked* | 2440 (38.3) | 558 (22.9) | 1882 (77.1) | |
| *Ex-smoker* | 3188 (50.1) | 777 (24.4) | 2411 (75.6) | |
| *Current smoker* | 740 (11.6) | 246 (33.2) | 494 (66.8) | |
| **Charlson Comorbidity Index (CCI), *n* (%)** | | | | <0.001 |
| *CCI 0* | 4338 (68.1) | 978 (22.5) | 3360 (77.5) | |
| *CCI 1-2* | 1676 (26.3) | 474 (28.3) | 1202 (71.7) | |
| *CCI 3-8* | 354 (5.6) | 129 (36.4) | 225 (63.6) | |
| **Self-rated health, *n* (%)** | | | | <0.001 |
| *Excellent* | 819 (12.9) | 136 (16.6) | 683 (83.4) | |
| *Very good* | 1998 (31.4) | 387 (19.4) | 1611 (80.6) | |
| *Good* | 2095 (32.9) | 540 (25.8) | 1555 (74.2) | |
| *Fair* | 1099 (17.3) | 372 (33.9) | 727 (66.2) | |
| *Poor* | 357 (5.6) | 146 (40.9) | 211 (59.1) | |
| **Depression, *n* (%)** | | | | <0.001 |
| *No* | 5102 (80.1) | 1172 (23.0) | 3930 (77.0) | |

| | | | | |
|---|---|---|---|---|
| *Yes* | 1266 (19.9) | 409 (32.3) | 857 (67.7) | |
| **Cognitive function** | | | | |
| *Memory score, mean (SD)* | 10.8 (3.4) | 9.16(3.3) | 11.3(3.2) | <0.001 |
| *Executive score, mean (SD)* | 21.4 (6.5) | 18.8 (6.1) | 22.3 (6.4) | <0.001 |
| **Factor could impair cognitive test, *n* (%)** | | | | <0.001 |
| *No* | 5962 (93.6) | 1408 (23.6) | 4554 (76.4) | |
| *Yes* | 406 (6.4) | 173 (42.6) | 233 (57.4) | |
| **Charlson Comorbidity Index (CCI), wave 6‡, *n* (%)** | | | | <0.001 |
| *CCI 0* | 4222 (66.3) | 930 (22.0) | 3292 (78.0) | |
| *CCI 1-2* | 1763 (27.7) | 514 (29.2) | 1249 (70.9) | |
| *CCI 3-8* | 383 (6.0) | 137 (35.8) | 246 (64.2) | |
| **Self-rated health at Wave 6‡, *n* (%)** | | | | <0.001 |
| *Excellent* | 709 (11.1) | 120 (16.9) | 589 (83.1) | |
| *Very good* | 1902 (29.9) | 361 (19.0) | 1541 (81.0) | |
| *Good* | 2055 (32.3) | 491 (23.9) | 1564 (76.1) | |
| *Fair* | 1264 (19.8) | 450 (35.6) | 814 (64.4) | |
| *Poor* | 438 (6.9) | 159 (36.3) | 279 (63.7) | |
| **Depression at wave 6‡, *n* (%)** | | | | <0.001 |
| *No* | 5190 (81.5) | 1206 (23.2) | 3984 (76.8) | |
| *Yes* | 100 (1.6) | 375 (31.8) | 803 (68.2) | |

*: Percent of total population size N=6368.
Mean (standard deviation) is displayed for cognitive function scores, median (interquartile range) for number of medications and sample size *n* and (% of sample size *N*) for all other variables.
§: *P* value by Chi-squared test for categorical variables, Student's T-test for cognitive function and Mann-Whitney U-test for number of medications.
‡: Charlson Comorbidity Index (CCI) score, Self-rated health reported and Depression at wave 6 (2012/13). All other factors analysed are baseline factors reported at wave 5 (2010/11).

**Table 2. Incidence rate ratios (IRR) for the association between health literacy at wave 5 and the number of medications at wave 6.**

| | Unadjusted | Multivariable | |
|---|---|---|---|
| | | Model 1 | Model 2 |
| | IRR (95% CI) | IRR (95% CI) | IRR (95% CI) |
| **Health literacy, wave 5** | | | |
| *Low (score<4)* | 1.33 (1.26 to 1.41) | 1.06 (1.00 to 1.12) | 1.04 (0.99 to 1.10) |
| *Adequate (score=4)* | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) |
| **Sex** | | | |
| *Male* | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) |
| *Female* | 1.04 (0.99 to 1.09) | 1.02 (0.97 to 1.07) | 1.03 (0.99 to 1.08) |
| **Age†, wave 5** | 1.04 (1.03 to 1.04) | 1.17 (1.12 to 1.23) | 1.17 (1.12 to 1.22) |
| **Highest education qualification** | | | |
| *No qualification or equivalent* | 1.42 (1.33 to 1.51) | 0.99 (0.93 to 1.05) | 0.98 (0.92 to 1.04) |
| *Up to secondary education* | 1.07 (0.99 to 1.15) | 0.98 (0.92 to 1.04) | 0.98 (0.92 to 1.04) |
| *Degree or higher education* | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) |
| **Wealth quintiles** | | | |
| *1(least wealthy)* | 1.87 (1.72 to 2.04) | 1.15 (1.06 to 1.25) | 1.08 (0.99 to 1.17) |
| *2* | 1.49 (1.37 to 1.63) | 1.09 (1.01 to 1.18) | 1.04 (0.97 to 1.12) |
| *3* | 1.42 (1.30 to 1.55) | 1.09 (1.01 to 1.18) | 1.06 (0.99 to 1.14) |
| *4* | 1.27 (1.15 to 1.39) | 1.11 (1.02 to 1.20) | 1.08 (1.00 to 1.17) |
| *5(most wealthy)* | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) |
| **Smoking status, wave 5** | | | |
| *Never smoked* | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) |
| *Ex-smoker* | 1.27 (1.20 to 1.34) | 1.08 (1.03 to 1.14) | 1.07 (1.02 to 1.13) |
| *Current smoker* | 1.23 (1.12 to 1.34) | 1.01 (0.93 to 1.10) | 0.97 (0.90 to 1.06) |
| **Charlson Comorbidity Index (CCI), wave 5** | | | |
| *CCI 0* | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) |
| *CCI 1-2* | 2.18 (2.08 to 2.29) | 1.68 (1.60 to 1.76) | 1.22 (1.13 to 1.32) |
| *CCI 3-8* | 3.26 (3.05 to 3.48) | 1.97 (1.84 to 2.12) | 1.34 (1.18 to 1.52) |
| **Self-rated health, wave 5** | | | |
| *Excellent* | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) |
| *Very good* | 1.90 (1.68 to 2.15) | 1.65 (1.47 to 1.84) | 1.38 (1.24 to 1.55) |
| *Good* | 2.92 (2.60 to 3.28) | 2.23 (2.01 to 2.48) | 1.64 (1.47 to 1.83) |
| *Fair* | 4.58 (4.07 to 5.16) | 2.98 (2.66 to 3.33) | 1.90 (1.68 to 2.14) |
| *Poor* | 6.67 (5.86 to 7.58) | 3.90 (3.40 to 4.48) | 2.25 (1.95 to 2.58) |
| **Depression, wave 5** | | | |
| *No* | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) |
| *Yes* | 1.68 (1.58 to 1.77) | 1.12 (1.06 to 1.19) | 1.05 (0.99 to 1.12) |
| **Cognitive function** | | | |
| *Memory function* | 0.93 (0.93 to 0.94) | 0.99 (0.99 to 1.00) | 1.00 (0.99 to 1.00) |

| | | | |
|---|---|---|---|
| *Executive function* | 0.97 (0.97 to 0.98) | 1.00 (0.99 to 1.00) | 1.00 (1.00 to 1.00) |
| **Factor that could influence cognitive test, wave 5** | | | |
| *No* | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) |
| *Yes* | 1.23 (1.12 to 1.35) | 0.97 (0.89 to 1.06) | 0.95 (0.87 to 1.04) |
| **Charlson Comorbidity Index (CCI), wave 6** | | | |
| *CCI 0* | 1.00 (ref) | | 1.00 (ref) |
| *CCI 1-2* | 2.26 (2.15 to 2.38) | | 1.42 (1.31 to 1.53) |
| *CCI 3-8* | 3.30 (3.08 to 3.54) | | 1.45 (1.28 to 1.64) |
| **Self-rated health, wave 6** | | | |
| *Excellent* | 1.00 (ref) | | 1.00 (ref) |
| *Very good* | 1.94 (1.70 to 2.21) | | 1.42 (1.26 to 1.59) |
| *Good* | 3.09 (2.73 to 3.50) | | 1.81 (1.60 to 2.05) |
| *Fair* | 4.86 (4.29 to 5.50) | | 2.19 (1.93 to 2.48) |
| *Poor* | 7.35 (6.45 to 8.38) | | 2.52 (2.19 to 2.90) |
| **Depression, wave 6** | | | |
| *No* | 1.00 (ref) | | 1.00 (ref) |
| *Yes* | 1.65 (1.56 to 1.75) | | 1.08 (1.01 to 1.16) |

95% CI: 95% confidence interval with robust standard errors.

† Given that the relationship between age and number of medications was nonlinear, linear term and quadratic term of age (not shown, IRR=1.00 (1.00–1.00), $p<0.001$ for male and female) were adjusted for.

Model 1: Adjustment for baseline factors at wave 5 (N=6368).

Model 2: full adjustment for baseline factors at wave 5 (2010/11) and Charlson Comorbidity Index, Self-rated health, and Depression at wave 6 (2012/13) (N=6368).

**Table 3. Adjusted incidence rate ratios (IRR) for the association between literacy at wave 5 and the number of medications at wave 6, stratified by sex and age group.**

| | Male†<br>IRR (95% CI) | Female†<br>IRR (95% CI) | Age 52-64 years‡<br>IRR (95% CI) | Age ≥ 65 years‡<br>IRR (95% CI) |
|---|---|---|---|---|
| **Health literacy, wave 5** | | | | |
| *Low (score<4)* | 1.10 (1.01 to 1.20) | 1.00 (0.94 to 1.07) | 1.11 (0.99 to 1.24) | 1.00 (0.95 to 1.05) |
| *Adequate (score=4)* | 1.00 (ref.) | 1.00 (ref.) | 1.00 (ref.) | 1.00 (ref.) |

†: The likelihood ratio test for the interaction by sex was $\chi^2(1) = 1.09$, $p$=0.276.
‡: The likelihood ratio test for the interaction by age was $\chi^2(1) = -2.92$, $p$=0.003.
95% CI: 95% confidence interval with robust standard errors.
All estimates are adjusted for baseline factors at wave 5 (2010/11) and Charlson Comorbidity Index, Self-rated health, and Depression at wave 6 (2012/13) (N=6368), equivalent to model 2 in Table 2.

**Table 4. Results for secondary analysis: Relative risk ratios (RRR) for the association between health literacy at wave 5 and polypharmacy at wave 6.**

| | Unadjusted | Multivariable | |
|---|---|---|---|
| | | Model 1 | Model 2 |
| **0 to 1 medication (reference)** | | | |
| | **RRR (95% CI)** | **RRR (95% CI)** | **RRR (95% CI)** |
| **2 to 4 medications** | | | |
| *Low health literacy* | 1.50 (1.27 to 1.77) | 1.08 (0.90 to 1.30) | 1.08 (0.90 to 1.31) |
| *Adequate health literacy* | 1.00 (ref) | | |
| **5 to 9 medications** | | | |
| *Low health literacy* | 2.09 (1.76 to 2.47) | 1.18 (0.95 to 1.46) | 1.15 (0.92 to 1.44) |
| *Adequate health literacy* | 1.00 (ref) | | |
| **10 or more medications** | | | |
| *Low health literacy* | 2.61 (2.03 to 3.35) | 1.22 (0.89 to 1.68) | 1.21 (0.87 to 1.67) |
| *Adequate health literacy* | 1.00 (ref) | | |

Multinomial logistic regressions were used and 95% confidence interval (CI) estimated with robust standard errors.
Model 1. Adjustment for baseline factors at wave 5 (N=6368).
Model 2: full adjustment for baseline factors at wave 5 (2010/11) and Charlson Comorbidity Index, Self-rated health, and Depression at wave 6 (2012/13) (N=6368).

STROBE Statement—checklist of items that should be included in reports of observational studies

| | Item No | Recommendation | Page No |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | Page 1, 2 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | Page 2 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | Page 4 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | Page 4 Introduction, para 4. |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | Page 5 Methods, para 1 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | Page 5 Methods, para 1-2 |
| Participants | 6 | (*a*) ***Cohort study***—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants | Page 5 Methods, para 2 |
| | | (*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case | |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | Page 5, Methods, para 4 to Page 7 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | Page 5-7 |
| Bias | 9 | Describe any efforts to address potential sources of bias | Page 7, Statistical analyses, para 1-2. |
| Study size | 10 | Explain how the study size was arrived at | Page 5 Methods, para 2 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | Page 4, Introduction, para 4. Page 6, Variables, para 2-7. |

| | | | |
|---|---|---|---|
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | Page 7, Statistical analyses, para 1-2. |
| | | (*b*) Describe any methods used to examine subgroups and interactions | Page 7, Statistical analyses, para 1. |
| | | (*c*) Explain how missing data were addressed | (by adjusting for non-response in weighted analyses)<br>Page 7, Statistical analyses, para 4 |
| | | (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed<br>*Case-control study*—If applicable, explain how matching of cases and controls was addressed<br>*Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy | (by adjusting for non-response in weighted analyses)<br>Page 7, Statistical analyses, para 4. |
| | | (*e*) Describe any sensitivity analyses | |

Continued on next page

| | | | |
|---|---|---|---|
| **Results** | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | Page 8, Results para 1. |
| | | (b) Give reasons for non-participation at each stage | |
| | | (c) Consider use of a flow diagram | |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | Page 8, Results para 1 |
| | | (b) Indicate number of participants with missing data for each variable of interest | Not provided |
| | | (c) *Cohort study*—Summarise follow-up time (eg, average and total amount) | Page 5, Study design, para 2. |
| Outcome data | 15* | *Cohort study*—Report numbers of outcome events or summary measures over time | Page 8, Results, para 2.<br><br>Table 1 |
| | | *Case-control study*—Report numbers in each exposure category, or summary measures of exposure | |
| | | *Cross-sectional study*—Report numbers of outcome events or summary measures | |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | Page 8-9 Tables 2 & 4. |
| | | (*b*) Report category boundaries when continuous variables were categorized | Tables 1, 2 & 4 |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | None |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | Page 9, Results, para 5-6.<br><br>Tables 3 & 4 |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | Page 9, Discussion, para 1. |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | Page 11, Discussion, para 6. |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | Page 10, Discussion, para 3. |

| | | | |
|---|---|---|---|
| | | | Page 12, Conclusions. |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | Page 11, Discussions, para 5. |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | Page 13 (Funding statement). |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

# Low health literacy and multiple medications in community-dwelling older adults: a population-based cohort study.

| | |
|---|---|
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# Low health literacy and multiple medications in community-dwelling older adults: a population-based cohort study

Jacques Shebehe[1], Scott Montgomery[1,2,3], Anders Hansson[4], Ayako Hiyoshi[1,2,5,6]

1. Clinical Epidemiology and Biostatistics, School of Medical Sciences, Örebro University, Örebro, Sweden
2. Department of Epidemiology and Public Health, University College London, UK
3. Clinical Epidemiology Division, Department of Medicine, Solna, Karolinska Institutet, Stockholm
4. University Health Care Research Centre, Faculty of Medicine and Health, Örebro University, Örebro, Sweden
5. Department of Public Health Sciences, Stockholm University, Stockholm, Sweden
6. Public Health, Department of Social Medicine, Osaka University Graduate School of Medicine, Osaka, Japan

**Correspondence:** [1] Clinical Epidemiology and Biostatistics, Faculty of Medicine and Health, Örebro University, SE 70182 Örebro, Sweden. Jacques.Shebehe@oru.se



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## Abstract

### Objectives

Adequate health literacy is important for patients to manage chronic diseases and medications. We examined the association between health literacy and multiple medications in community-dwelling adults aged 50 years and older in England.

### Design, settings and participants

We included 6368 community-dwelling people of median age 66 years from the English Longitudinal Study of Ageing. Health literacy was assessed at wave 5 (2010/11) with 4 questions concerning a medication label. Four correct answers were categorised as adequate health literacy, otherwise low. Data on medications were collected at wave 6 (2012/13). To examine the difference in the number of medications between low and adequate health literacy, we used zero-inflated negative binomial regression, estimating odds ratio for zero medication and incidence rate ratios (IRR) for the number of medications, with 95% confidence intervals (95%CIs). Associations were adjusted for demographic, socioeconomic and health characteristics, smoking, and cognition. We also stratified the analysis by sex, and age (50-64 and ≥65 years). To be comparable with preceding studies, multinomial regression was fitted using commonly used thresholds of polypharmacy (0 vs. 1-4, 5-9, ≥10 medications).

### Results

Although low health literacy was associated with a lower likelihood of being medication-free (OR=0.64, 95% CI:0.45 to 0.91), health literacy was not associated with the number of medications among those at risk for medication (IRR=1.01, 95% CI:0.96 to 1.05), and this finding did not differ among younger and older age groups or women. Among men, low health literacy showed a weak association (IRR=1.06 (95% CI:0.99 to 1.14)). Multinomial regression models showed graded risks of polypharmacy for low health literacy.

### Conclusions

Although there was no overall association between health literacy and the number of medications, this study does not support the assertion that low health literacy is associated with a notably higher number of medications in men.

**Strengths and limitations of this study**

- Strengths of this study include the use of longitudinal study design based on a large representative sample of older adults in England.
- Qualified nurses checked self-reported medication use; thus, medication misreporting was reduced.
- To reduce the impact of confounding, statistical adjustment included a wide range of potential confounders such as age, sex, income, education, cognitive function, and pre-existing and concurrent morbidity and self-rated health.
- Although health literacy in ELSA was measured with a validated instrument with good face validity, it mainly focuses on basic document literacy skills does not account for other skills such as prose and health navigation literacy.
- As residual and unmeasured confounding cannot be ruled out and the effect size of the association was weak, the results need to be interpreted with caution.

## Introduction

Most developed countries are experiencing an ever-growing ageing population. In Europe, the proportion of people aged ≥65 years is expected to increase and reach 27% by 2050.[1] Although there are older people who remains healthy, a considerable share of older adults has multiple chronic diseases and uses multiple medications, polypharmacy. There is no consensus on the definition of polypharmacy, but the most commonly used cut-offs are ≥5 or ≥10 medications.[2]

Relationships between polypharmacy and health in the ageing process are complex and multidirectional. Polypharmacy may be due to multimorbidity; however, polypharmacy can cause negative consequences, such as poor medication adherence, declines in cognition and quality of life, and increased risk of side-effects such as fall injuries, frailty, hospitalisations, and even death.[3] Therefore, reducing the risk of inappropriate polypharmacy has been a priority among clinicians, public health scientists, and policymakers.[4]

Health literacy has recently gained much attention as a factor that can reduce the risk of polypharmacy.[5] Health literacy is an individual's ability to access, understand, appraise and apply health information to make decisions that prevent disease and excessive medications, promote good health, and improve quality of life throughout the life-course.[6] An estimated 60% of the European older population has low health literacy.[6] Patient-centred interventions have suggested that improving health literacy can reduce polypharmacy risk, medication non-adherence, and healthcare costs. [5 7 8] However, despite that low health literacy was associated with incorrect medication use[9 10] and reduced willingness to reduce the number of medications,[11] low health literacy has not been shown to associate with polypharmacy.[12 13] The lack of association may be because the majority of these studies were cross-sectional with relatively small sample size[14-16] and low statistical power.

Therefore, using a large sample of longitudinal data, we aimed to examine the association between health literacy and multiple medications in community-dwelling older adults. We further examined whether this association differed by sex, age, and morbidity because sex may modify the association health literacy and medication given differences in health behaviour between men and women, [17 18] and the risk of low health literacy and use of multiple medications differ in by age, [17 18] and morbidity burden.[18 19]

# Methods

## Study design and sample

This population-based cohort study used data from the English Longitudinal Study of Ageing (ELSA),[20] an ongoing study of a large representative cohort of people living in England aged ≥50 years. The first cohort of ELSA (wave 1) was collected in 2002 from participants of the Health Survey of England (HSE), an annual cross-sectional household survey of a randomly selected sample representative of the English population living in private homes.[20] ELSA participants have been followed up biannually. New participants have been recruited from HSE to maintain the representativeness of the general English older adult population. At each wave, trained interviewers visited participants (including members who were identified from HSE and their cohabiting partners) at their homes to carry out a survey comprising personal face-to-face computer-assisted interviews and a paper-and-pen self-completion questionnaire. At every other wave, a qualified nurse visits a subset of participants assessed in the survey (nurse visit), carries out interviews, performs a physical examination and collects blood samples.[20]

In this study, we included participants who had completed the health literacy assessment in wave 5 (2010/11) and had data on medication use recorded at nurse visit in wave 6 (2012/13). There were partners who were younger than 50 years, and they were excluded. Of all 6837 participants assessed at wave 5 and with nurse visit at wave 6, we excluded 7% (n=469) who had incomplete data in relevant variables, leaving a total sample of 6368 participants included in our analyses.

All ELSA participants provided informed consent and the London Multicentre Research Ethics Committee (MREC/01/2/91) provided ethical approval for all ELSA waves.[20]

## Variables

### *Exposure: health literacy*

In wave 5, trained interviewers assessed participants' health literacy using a realistic but fictitious medicine label, the method that is used in the International Adult Literacy Survey.[21] Participants were asked four questions to examine how well they understood the instructions on the label. Response to each of the four questions was scored 1 if correct and otherwise 0. Using the sum of correct responses (range 0-4), we categorized health literacy as adequate if participants scored 4/4, otherwise as low. This cut-off has been previously used.[21]

***Outcome: number of medications***

In wave 6 nurse visit, participants were asked to name the medications they were taking in the last 7 days. The nurses checked medication containers to ascertain self-reported medication use. Devices that do not deliver drugs, such as stoma or urinary catheters and vaccines, were excluded.[20]

***Adjustment variables: sociodemographic, cognitive function and health-related characteristics.***

Factors that have been reported in the literature to be associated with health literacy[17] and polypharmacy[2 22] have been considered for adjustment. These factors include *age* (≥90 years collapsed in ELSA dataset), *sex* (male/female), *highest education qualification* (no qualification/up to secondary education/degree or higher education), *wealth* (quintiles of household-level net total non-pension wealth), *smoking status* (never smoked/ex-smoker/current smoker)*, self-rated health* (excellent/very good/good/fair/poor), *Charlson Comorbidity Index* (CCI), *depression*, and *cognitive function*.

*Charlson Comorbidity Index (CCI)* was derived using the weights of self-reported conditions based on the New Jersey Medicare weights.[23] Identified self-reported conditions were myocardial infarction, heart failure, stroke or cerebrovascular disease, dementia, chronic lung disease including asthma , diabetes mellitus or high blood sugar , diabetes mellitus with end-organ damage defined as diabetes with eye disease, diabetes with protein in urine or kidney trouble told by a doctor, any cancer including any solid cancer, leukaemia, lymphoma, and some other blood disorder. The sum of CCI weights (range 0–8) was categorised into 3 levels: 0, 1–2, and 3–8.

*Depression* was assessed using the dichotomous 8-item Centre for Epidemiologic Studies Depression Scale. Of a score ranging 0–8, a score ≥3 was defined as depression, otherwise no depression.[24]

*Cognitive memory function* was assessed by testing verbal learning, immediate and delayed recall of 10 words, and a score (range 0–20) was provided. *Cognitive executive function* was assessed by testing verbal fluency based on the total number of animals named in one minute, and a score (range 0–51) was provided. A binary variable for any observed or reported *factor that could impair cognitive test* was created based on at least one positive answer to the following being one otherwise zero: poor sight, poor hearing, tiredness, illness or physical impairment, impaired concentration, nervousness, external interaction or distraction (e.g. phone call or visit), noisy environment, distressed (e.g. from bereavement), memory problems, the influence of alcohol, or difficulty in understanding English.

**Statistical analyses**

We summarized participants' characteristics using means, standard deviation, median, interquartile range (lower quartile to upper quartile) (IQR), and proportions. To test differences between groups, we used Chi-squared, Student's T or Mann-Whitney U test. To examine the association between health literacy and the number of medications, we used zero-inflated negative binomial models because the proportion of participants with zero medication was 22%, the variability of data on medication was high (range=0-27, mean=3.4, variance=11.7) and Akaike and Bayesian Information Criteria as well as the Vuong statistic favoured zero-inflated negative binomial model over negative binomial model. Zero-inflated negative binomial models account for excess zeros by combining two separate models; a logistic model for estimating likelihood of being certain zeros (not at risk of medication, possibly because of absence of diseases), and a negative binomial model for modelling the number of medications for those who are not certain zeros (at risk of medication).[25] The former computes odds ratio (OR) and 95% confidence intervals (CI), and the latter computes incidence rate ratios (IRR) and 95% CI. Initially, we fitted three models; a model not adjusting for any variable (model 1), a model adjusting for factors assessed at wave 5, including age, sex, education qualification, wealth, smoking, CCI, self-rate health, depression, and cognition (model 2), and finally a model additionally including CCI, self-rated health, and depression assessed at wave 6 to account for the influence of concurrent health status on medications (model 3). Since the models 2 and 3 did not differ notably, we present unadjusted estimates and estimates adjusting for all variables. We included all covariates in both the logistic part and the negative binomial part.

For all following stratified and secondary analyses, we used the full adjusted model. First, we stratified analyses by sex and age (50-64 and ≥65 years). Second, to reduce the possible influence of morbidity to conceal the association between health literacy and the number of medications, we conducted an analysis restricting participants to those with the lowest morbidity (CCI=0), no depression, and 'good' or higher self-rated health at both waves 5 and 6. Third, to be comparable with preceding studies that used a certain number of medications to define polypharmacy, we conducted a secondary analysis using multinomial regression models. The association between health literacy and polypharmacy was estimated with relative risk ratios (RRR) and 95% CI. In these analyses, polypharmacy was classified into four levels: no polypharmacy (0) as referent, minor polypharmacy (1–4), major polypharmacy (5–9) and excessive polypharmacy (≥10 medications).[2]

In all regression models, complex survey design and household clustering were accounted for by estimating robust standard errors, and estimates were weighted to adjust for non-response. All analyses were conducted in Stata V.16 SE.

### Patient and public involvement

There was no patient or public involvement in this study. ELSA participants were given a newsletter with recent findings from previous surveys.

## Results

A total of 6368 participants of median age 66 years (range 52 to 90 years, IQR=60–73 years) were included in our analyses. The number of reported medications was ranged 0–27, with 22% reporting zero medication and a median of 3 medications (IQR=1–5). The number of medications was higher among those with low health literacy (median 4) than those with adequate health literacy (median 2) (Table 1). Approximately three-quarters of participants had adequate health literacy, but 25% showed low health literacy. Both in men and women, the proportion of low health literacy was similar whereas low health literacy was more prevalent among those aged ≥65 years, with lower education qualification, lower wealth, current smoking, depression, higher morbidity and poorer self-rated health, and lower cognitive performance.

### Health literacy and number of medications

Compared with participants with adequate health literacy, the unadjusted odds of reporting zero medication were 61% lower for those with low health literacy (OR=0.39, 95% CI: 0.27 to 0.57). Among those at-risk of medications, the unadjusted rate of the number of medications was 20% higher for participants with low health literacy compared to those with adequate health literacy (IRR=1.20, 95% CI: 1.13 to 1.27) (Table 2, online supplementary appendix 1). Furthermore, the probability of reporting zero medication was low for females than males, but there was no difference between men and women in the number of medications among those who are at risk of medications (online supplemental appendix 1). Higher age and current or past smoking was associated with higher number of medications but not consistently with likelihood of zero medication. Disadvantageous socioeconomic position, indicated by lower education and wealth, was linked to a lower probability of zero medication as well as to a higher number of medications among those at risk of medications. On the other hand, odds ratios for zero medication declined as health status, indicated by self-rated health and morbidity, declined while the rate of medications among those at risk increased, and the highest morbidity score and the poorest self-rated health were associated with up to a 2 and 4 times higher number of medications compared with the lowest morbidity score and excellent self-rated health, respectively.

When the model was adjusted for covariates measured at waves 5 and 6, participants with low health literacy had still a lower probability of zero medication compared to those with adequate health literacy (OR=0.64, 95% CI: 0.45 to 0.91) (Table 2, online supplementary appendix 1). However, among those at risk of medications, there was no evidence of a difference in the number of medications between those with low and those with adequate health literacy (IRR=1.01, 95% CI: 0.96 to 1.05). Among covariates, IRRs associated with more disadvantaged socioeconomic characteristics were no longer consistently statistically significant (online supplementary appendix 1). However, IRRs for age, morbidity and self-rated health assessed at waves 5 and 6 remained statistically significantly associated with a higher number of medications and notably accounted for diminishing the association between health literacy and the number of medications among those at risk of medications.

There was little evidence that associations were different by age and sex, with Wald test for the interaction terms for sex ($p$=0.096) and age ($p$=0.106). Nevertheless, when the analysis was stratified by sex, in men, health literacy was not associated the likelihood of zero medication; but among those at risk of medications there was an indication of a weak association between low health literacy and number of medications (IRR=1.06, 95% CI: 0.99 to 1.14, $p$=0.095) (table 3). In women, low health literacy was associated with a lower likelihood of no medication (OR=0.59, 95% CI: 0.35 to 0.98), but not with the number of medications. While low health literacy was associated with a lower probability of reporting no medication among those aged 50-64 years (OR=0.45, 95% CI 0.24 to 0.83), there was no statistically significant association between health literacy and the number of medications in those at risk of medications in either age group.

When we restricted the analysis on 898 individuals who reported the lowest morbidity (CCI=0), good or higher self-rated health, and no depression at both waves 5 and 6, the finding was largely similar to that observed above; low health literacy was not associated with either the probability of zero medication or the number of medications. (online supplementary appendix 2 ).

**Secondary analysis: health literacy and polypharmacy**

Among the participants, 22% of individuals used no medication (no polypharmacy), 47% used 1-4 (minor), 25% used 5-9 (major) and 6% used ≥10 medications (excessive polypharmacy). Multinomial regression of polypharmacy showed that, compared to adequate health literacy, unadjusted RRR for low health literacy showed a gradient increased risk of up to 2.6 times for excessive polypharmacy (Table 4). This association diminished after full adjustment but an adjusted risk of up to 1.44 times for excessive polypharmacy compared to no polypharmacy remained after full adjustment.

## Discussion

This cohort study aimed to examine the association between health literacy and the number of medications and polypharmacy in community-dwelling older people. There was no evidence of an association between health literacy and the number of medications among those at risk of medications, although low health literacy was associated with a low likelihood of being medication-free. In unadjusted estimates, low health literacy was associated with increased number of medications among those at risk of medications, but adjustment for morbidity and poorer self-rated health diminished the association. In men, however, there was weak indication that low health literacy was associated with a 6% higher number of medications, equivalent to 0.3 excess medication, after adjustment.

In line with previous studies that found no association between health literacy and the number of medication among community-dwelling older people,[19] older primary care patients,[12 26] as well as in younger population,[13] this study found no association between health literacy and polypharmacy when both sexes were combined. The unadjusted positive associations between low health literacy and polypharmacy diminished when socioeconomic characteristics, morbidity, and self-rated health were accounted for. The association was observed when polypharmacy was analysed using multinomial regression models; however, this is considered to be because the model does not differentiate certain zeros (those not at risk of medication, possibly because of absence of diseases) and those at risk of medication. Given that health literacy was strongly associated with at risk of medication or not (logistic part), but not with the number of medication (negative binomial part), the results from multinomial regression would be much driven by association observed in logistic part. Health literacy is a construct that formulates from early adolescence and develops across the life-course.[17] It relates to poor health-related behaviour,[27] inappropriate health-information seeking behaviour,[28] delayed healthcare visit, and forgone treatment.[29] Therefore, by the late middle age, as is our participants, low health literacy may have already resulted in poorer health in some individuals. Furthermore, socioeconomic disadvantages across the life-course are associated with both low health literacy and accumulated poor health.[15] Therefore, logistic part focusing on at risk of medication showed strong association, and adjustment for health and socioeconomic characteristics diminished effect size for logistic part and explained away the association for negative binomial part.

Our results showed weak indication that low health literacy may be associated with polypharmacy in men. Given the lack of effect modification and the weak effect size, this finding may be a chance finding. Furthermore, they can also be explained away even by a weak bias, although we adjusted for known confounding factors within the data available to us. For example, the reason the association remained in men may be because men tend to underreport morbidity and poor health to a greater extent,[30] and this may have been even more pronounced among low health literate men. Such differential underreporting may have resulted in incomplete adjustment for the effect of morbidity among men. Therefore, these results should be interpreted with caution.

Nevertheless, the weak possible association in men can in part relate to gendered behaviours and attitudes to health. Research suggests men are more reluctant to seek healthcare and receive advice from peers, less likely to read healthcare instructions, and more likely to miss opportunities for medication reviews[31-33] and stay longer on medications.[34] These characteristics may even be more so among low health literate men. Therefore, although in our cohort the difference in health literacy between men and women was small, men's overall health knowledge tends to be poorer;[35] and this may relate to why there was some indication of association in men.

Identifying the magnitude of health risk associated with polypharmacy and its clinical implications is beyond the scope of our study, but an increased number of medications was associated with increased risk of fall, hospitalisation, and mortality.[3 36] A recent nation-wide cohort study and a meta-analysis found that one additional medication has been associated with a 3–8% increased risk of death in people aged ≥65 years.[37 38] Although these results do not necessarily imply causality,[37] they underline the need to identify risk groups and modifiable factors associated with polypharmacy. In this study, only in men there was a weak indication of association between low health literacy and higher number of medications. Therefore, men may benefit from improving health literacy to prevent poor health and possibly excessive medication. As our study focused on those aged over 50 years, and also prescribing and medication review practices may vary with health care system and country, our results may not be generalizable to younger people or other societal contexts.

**Strengths and limitations**

Our study has some potential limitations. First, we could not know whether the reported medications were complete. For example, if individuals with poorer health literacy or cognitive function have failed to present all medications, this would have resulted in underestimation of association. Furthermore, we were not able to distinguish necessary or inappropriate medications or account for preventive medications such as statins that may have been used more frequently among those with higher health literacy. Nevertheless, a higher number of medications has been associated with inappropriate prescribing and proposed as a marker of inappropriate medications.[39] Second, even though the method used in ELSA to measure health literacy only assesses basic document literacy skills and does not account for other skills such as prose and health navigation literacy,[21] it has been widely used, had good face validity, and has been shown to associate with mortality.[21] Third, although we have dichotomised health literacy by 4/4 correct answers or else[21] other studies have used different cut-offs.[40] To examine whether different classification may change the conclusion, we conducted all main and stratified analyses using health literacy with 3 categories, low (score 0–2), intermediate (score 3), or adequate (score 4 correct answers); and we observed that the conclusion remained the same (online supplementary appendix 3). Fourth, the UK National Service Framework for Older People has recommended regular medication reviews for people with polypharmacy since 2001.[41] Thus, it may be possible that medication reviews reduced likelihood of polypharmacy including among those with low health literacy. Fifth, we adjusted for morbidity assessed in wave 6 even though it is an intermediate factor linking health literacy and polypharmacy and may be in part a consequence of polypharmacy. We did so because multiple medications may be due to concurrent ill health. Also, if low health literate participants have rated their health poorer because of the fact that they received medications, adjustment for self-rated health may have weakened the association. However, when we restricted analyses to participants with the lowest morbidity, the conclusion remained unchanged. Sixth, the lack of significant association between health literacy and the number of medications in most of the stratified analyses, as well as interaction tests, should be interpreted with caution because these analyses may have lacked statistical power. Lastly, 7% of participants were excluded from analysis due to incomplete data, and this can lower precision of our estimates. It is also possible that this missingness introduced bias. However, to address non-response, we used survey weights in all analyses.

Our study has several strengths. We used a longitudinal design, included a large representative sample of an older population, and adjusted for a wide range of potential confounding factors. Also, although some participants may miss presenting some medications, as nurses checked medication containers, the risk of medication underreporting was reduced.

## Conclusions

Although there was no overall association between health literacy and the number of medications, this study does not support the assertion that low health literacy is associated with a notably higher number of medications in men.

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## Data sharing statement

The datasets analysed in the current study are available in the UK Data Service repository for the English Longitudinal Study of Ageing (ELSA), https://beta.ukdataservice.ac.uk/datacatalogue/series/series?id=200011.

## Ethics statement

All ELSA participants provided informed consent and the London Multicentre Research Ethics Committee (MREC/01/2/91) provided ethical approval for all ELSA waves.

## Competing interests statement

Following ICJME form and BMJ competing interests policy, all authors have no conflict of interest or financial disclosures for this manuscript.

## Authors' contributions

**JS**: Conceptualisation, Methodology, Data Curation, Formal analysis, Validation, Writing- Original draft preparation, Writing- Reviewing and Editing, Funding acquisition. **SM**: Conceptualisation, Methodology, Validation, Writing- Reviewing and Editing. **AHa**: Conceptualisation, Methodology, Writing- Reviewing and Editing. **AHi**: Conceptualisation, Methodology, Validation, Writing- Reviewing and Editing, Supervision, Funding acquisition.

All the authors read and approved the final manuscript.

## Licence statement

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# Tables

**Table 1. The characteristics of ELSA participants by health literacy.**

| | Total* n (%) | Health literacy Low N=1581 (24.8%)* | Adequate N=4787 (75.2%)* | P § |
|---|---|---|---|---|
| **Number of medications, median (IQR)** | 3 (1–5) | 4 (1–6) | 2 (1–5) | <0.001 |
| **Sex, n (%)** | | | | 0.084 |
| *Male* | 2837 (44.6) | 734 (25.9) | 2103 (74.1) | |
| *Female* | 3531 (55.4) | 847 (24.0) | 2684 (76.0) | |
| **Age group, n (%)** | | | | <0.001 |
| *50-64 years* | 2929 (46.0) | 577 (19.7) | 2352 (80.3) | |
| *65 years and older* | 3439 (54.0) | 1004 (29.2) | 2435 (70.8) | |
| **Highest education qualification, n (%)** | | | | <0.001 |
| *No qualification or equivalent* | 2553 (40.1) | 933 (36.6) | 1620 (63.5) | |
| *Up to secondary education* | 1723 (27.1) | 330 (19.2) | 1393 (80.9) | |
| *Degree or higher education* | 2092 (32.9) | 318 (15.2) | 1774 (84.8) | |
| **Wealth quintiles, n (%)** | | | | <0.001 |
| *1(least wealthy)* | 960 (15.1) | 361 (37.6) | 599 (62.4) | |
| *2* | 1266 (19.9) | 364 (28.8) | 902 (71.3) | |
| *3* | 1254 (19.7) | 343 (27.4) | 911 (72.7) | |
| *4* | 1410 (22.1) | 284 (20.1) | 1126 (79.9) | |
| *5(most wealthy)* | 1478 (23.2) | 229 (15.5) | 1249 (84.5) | |
| **Smoking status, n (%)** | | | | <0.001 |
| *Never smoked* | 2440 (38.3) | 558 (22.9) | 1882 (77.1) | |
| *Ex-smoker* | 3188 (50.1) | 777 (24.4) | 2411 (75.6) | |
| *Current smoker* | 740 (11.6) | 246 (33.2) | 494 (66.8) | |
| **Charlson Comorbidity Index (CCI), n (%)** | | | | <0.001 |
| *CCI 0* | 4338 (68.1) | 978 (22.5) | 3360 (77.5) | |
| *CCI 1-2* | 1676 (26.3) | 474 (28.3) | 1202 (71.7) | |
| *CCI 3-8* | 354 (5.6) | 129 (36.4) | 225 (63.6) | |
| **Self-rated health, n (%)** | | | | <0.001 |
| *Excellent* | 819 (12.9) | 136 (16.6) | 683 (83.4) | |
| *Very good* | 1998 (31.4) | 387 (19.4) | 1611 (80.6) | |
| *Good* | 2095 (32.9) | 540 (25.8) | 1555 (74.2) | |
| *Fair* | 1099 (17.3) | 372 (33.9) | 727 (66.2) | |
| *Poor* | 357 (5.6) | 146 (40.9) | 211 (59.1) | |
| **Depression, n (%)** | | | | <0.001 |
| *No* | 5102 (80.1) | 1172 (23.0) | 3930 (77.0) | |

| | | | | |
|---|---|---|---|---|
| *Yes* | 1266 (19.9) | 409 (32.3) | 857 (67.7) | |
| **Cognitive function** | | | | |
| *Memory score, mean (SD)* | 10.8 (3.4) | 9.16(3.3) | 11.3(3.2) | <0.001 |
| *Executive score, mean (SD)* | 21.4 (6.5) | 18.8 (6.1) | 22.3 (6.4) | <0.001 |
| **Factor could impair cognitive test, *n* (%)** | | | | <0.001 |
| *No* | 5962 (93.6) | 1408 (23.6) | 4554 (76.4) | |
| *Yes* | 406 (6.4) | 173 (42.6) | 233 (57.4) | |
| **Charlson Comorbidity Index (CCI), wave 6‡, *n* (%)** | | | | <0.001 |
| *CCI 0* | 4222 (66.3) | 930 (22.0) | 3292 (78.0) | |
| *CCI 1-2* | 1763 (27.7) | 514 (29.2) | 1249 (70.9) | |
| *CCI 3-8* | 383 (6.0) | 137 (35.8) | 246 (64.2) | |
| **Self-rated health at Wave 6‡, *n* (%)** | | | | <0.001 |
| *Excellent* | 709 (11.1) | 120 (16.9) | 589 (83.1) | |
| *Very good* | 1902 (29.9) | 361 (19.0) | 1541 (81.0) | |
| *Good* | 2055 (32.3) | 491 (23.9) | 1564 (76.1) | |
| *Fair* | 1264 (19.8) | 450 (35.6) | 814 (64.4) | |
| *Poor* | 438 (6.9) | 159 (36.3) | 279 (63.7) | |
| **Depression at wave 6‡, *n* (%)** | | | | <0.001 |
| *No* | 5190 (81.5) | 1206 (23.2) | 3984 (76.8) | |
| *Yes* | 100 (1.6) | 375 (31.8) | 803 (68.2) | |

*: Percent of total population size N=6368.
Mean (standard deviation) is displayed for cognitive function scores, median (interquartile range) for number of medications and sample size *n* and (% of sample size *N*) for all other variables.
§: *P* value by Chi-squared test for categorical variables, Student's T-test for cognitive function and Mann-Whitney U-test for number of medications.
‡: Charlson Comorbidity Index (CCI) score, Self-rated health reported and Depression at wave 6 (2012/13). All other factors analysed are baseline factors reported at wave 5 (2010/11).

**Table 2. Unadjusted and adjusted odds ratios (OR) and incidence rate ratios (IRR) based on zero-inflated negative binomial models for the association between literacy at wave 5 and the number of medications at wave 6.**

| | Unadjusted | | Adjusted‡ | |
|---|---|---|---|---|
| | Logistic part* | Negative binomial part* | Logistic part* | Negative binomial part* |
| | OR (95% CI) | IRR (95% CI) | OR (95% CI) | IRR (95% CI) |
| **Health literacy** | | | | |
| *Low (score<4)* | **0.39 (0.27 to 0.57)** | **1.20 (1.13 to 1.27)** | **0.64 (0.45 to 0.91)** | 1.01 (0.96 to 1.05) |
| *Adequate (score=4)* | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) |

95% CI: 95% confidence interval with robust standard errors.
*: The logistic part estimates the probability (odds ratios) of being certain zero medication whereas the negative binomial part estimates the number of medications (incidence rate ratios) among those at risk of medications.
‡: full adjustment for baseline factors at wave 5 (2010/11) and Charlson Comorbidity Index, Self-rated health, and Depression at wave 6 (2012/13).
Estimates for covariates are reported in online supplementary appendix 1.

**Table 3. Adjusted odds ratios (OR) and incidence rate ratios (IRR) based on zero-inflated negative binomial models for the association between literacy at wave 5 and the number of medications at wave 6, stratified by sex and age group.**

| | | Health literacy | Logistic part* | Negative binomial part* |
|---|---|---|---|---|
| | | | OR (95% CI) | IRR (95% CI) |
| Sex† | Males | *Low (score<4)* | 0.62 (0.37 to 1.04) | 1.06 (0.99 to 1.14) |
| | | *Adequate (score=4)* | 1.00 (ref.) | 1.00 (ref.) |
| | Females | *Low (score<4)* | **0.59 (0.35 to 0.98)** | 0.96 (0.90 to 1.02) |
| | | *Adequate (score=4)* | 1.00 (ref.) | 1.00 (ref.) |
| Age ‡ | Age 50-64 years | *Low (score<4)* | **0.45 (0.24 to 0.83)** | 1.02 (0.92 to 1.12) |
| | | *Adequate (score=4)* | 1.00 (ref.) | 1.00 (ref.) |
| | Age ≥ 65 years | *Low (score<4)* | 1.16 (0.75 to 1.81) | 1.01 (0.96 to 1.06) |
| | | *Adequate (score=4)* | 1.00 (ref.) | 1.00 (ref.) |

95% CI: 95% confidence interval with robust standard errors.
*: The logistic part estimates the probability (odds ratios) of being certain zero medication whereas the negative binomial part estimates the number of medications (incidence rate ratios) among those at risk of medications.
†: Wald test for the interaction term for sex was $p$= 0.096.
‡: Wald test for the interaction term for age was $p$=0.106.
All estimates are full-adjusted for baseline factors at wave 5 (2010/11) and Charlson Comorbidity Index, Self-rated health, and Depression at wave 6 (2012/13), equivalent to adjusted model in Table 2.

**Table 4. Secondary analysis using multinomial regression models: Relative risk ratios (RRR) for the association between health literacy at wave 5 and polypharmacy at wave 6.**

| | Unadjusted | Adjusted* |
|---|---|---|
| **No medication (reference)** | | |
| | **RRR (95% CI)** | **RRR (95% CI)** |
| **1 to 4 medications** | | |
| *Low health literacy* | **1.63 (1.35 to 1.96)** | **1.32 (1.06 to 1.63)** |
| *Adequate health literacy* | 1.00 (ref) | 1.00 (ref) |
| **5 to 9 medications** | | |
| *Low health literacy* | **2.39 (1.96 to 2.91)** | **1.37 (1.07 to 1.77)** |
| *Adequate health literacy* | 1.00 (ref) | 1.00 (ref) |
| **10 or more medications** | | |
| *Low health literacy* | **2.98 (2.28 to 3.90)** | **1.44 (1.02 to 2.04)** |
| *Adequate health literacy* | 1.00 (ref) | 1.00 (ref) |

95% CI: 95% confidence interval with robust standard errors.
*: full adjustment for baseline factors at wave 5 (2010/11) and Charlson Comorbidity Index, Self-rated health, and Depression at wave 6 (2012/13).

# Online supplementary appendices

**Appendix 1. Unadjusted and adjusted odds ratios (OR) and incidence rate ratios (IRR) based on zero-inflated negative binomial models for the association between literacy at wave 5 and the number of medications at wave 6.**

| | Unadjusted | | Adjusted‡ | |
|---|---|---|---|---|
| | Logistic part* | Negative binomial part* | Logistic part* | Negative binomial part* |
| | OR (95% CI) | IRR (95% CI) | OR (95% CI) | IRR (95% CI) |
| **Health literacy** | | | | |
| *Low (score<4)* | **0.39 (0.27 to 0.57)** | **1.20 (1.13 to 1.27)** | **0.64 (0.45 to 0.91)** | 1.01 (0.96 to 1.05) |
| *Adequate (score=4)* | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) |
| **Sex** | | | | |
| *Male* | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) |
| *Female* | **0.73 (0.59 to 0.91)** | 0.99 (0.95 to 1.05) | **0.71 (0.56 to 0.89)** | 1.00 (0.96 to 1.04) |
| **Age†, wave 5** | 1.20 (0.77 to 1.89) | **1.09 (1.04 to 1.15)** | **1.09 (1.05 to 1.13)** | **1.09 (1.05 to 1.13)** |
| **Highest education qualification** | | | | |
| *No qualification or equivalent* | **0.45 (0.34 to 0.59)** | **1.27 (1.20 to 1.35)** | 1.03 (0.77 to 1.38) | 0.97 (0.92 to 1.03) |
| *Up to secondary education* | 0.81 (0.63 to 1.05) | 1.03 (0.96 to 1.11) | 0.85 (0.63 to 1.14) | 0.96 (0.90 to 1.01) |
| *Degree or higher education* | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) |
| **Wealth quintiles** | | | | |
| *1(least wealthy)* | **0.40 (0.26 to 0.62)** | **1.67 (1.53 to 1.82)** | 1.04 (0.66 to 1.64) | 1.07 (0.99 to 1.16) |
| *2* | 0.74 (0.54 to 1.02) | **1.42 (1.31 to 1.55)** | 1.29 (0.88 to 1.89) | 1.06 (0.99 to 1.14) |
| *3* | **0.57 (0.40 to 0.82)** | **1.31 (1.20 to 1.42)** | 0.96 (0.65 to 1.41) | 1.05 (0.98 to 1.13) |
| *4* | 0.91 (0.68 to 1.22) | **1.25 (1.13 to 1.37)** | 1.12 (0.80 to 1.58) | **1.1 (1.02 to 1.19)** |
| *5(most wealthy)* | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) |
| **Smoking status, wave 5** | | | | |
| *Never smoked* | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) |

| | | | | |
|---|---|---|---|---|
| *Ex-smoker* | **0.61 (0.48 to 0.78)** | **1.18 (1.12 to 1.25)** | 0.81 (0.63 to 1.05) | **1.05 (1.00 to 1.10)** |
| *Current smoker* | 0.99 (0.72 to 1.38) | **1.22 (1.12 to 1.34)** | 1.34 (0.94 to 1.92) | 0.99 (0.92 to 1.07) |
| **Charlson Comorbidity Index (CCI), wave 5** | | | | |
| *CCI 0* | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) |
| *CCI 1-2* | **0.13 (0.09 to 0.20)** | **1.76 (1.68 to 1.85)** | 0.91 (0.44 to 1.88) | **1.21 (1.12 to 1.31)** |
| *CCI 3-8* | "not estimated" | **2.54 (2.38 to 2.71)** | 0.27 (0.12 to 42.79) | **1.32 (1.16 to 1.51)** |
| **Self-rated health, wave 5** | | | | |
| *Excellent* | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) |
| *Very good* | **0.56 (0.42 to 0.76)** | **1.62 (1.41 to 1.85)** | 1.04 (0.70 to 1.56) | **1.35 (1.19 to 1.53)** |
| *Good* | **0.24 (0.17 to 0.33)** | **2.15 (1.89 to 2.45)** | 0.75 (0.47 to 1.18) | **1.52 (1.34 to 1.73)** |
| *Fair* | **0.08 (0.05 to 0.13)** | **3.12 (2.74 to 3.56)** | **0.48 (0.24 to 0.95)** | **1.74 (1.52 to 1.98)** |
| *Poor* | **0.03 (0.01 to 0.13)** | **4.43 (3.86 to 5.09)** | **0.25 (0.08 to 0.77)** | **2.03 (1.75 to 2.35)** |
| **Depression, wave 5** | | | | |
| *No* | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) |
| *Yes* | **0.37 (0.26 to 0.53)** | **1.50 (1.42 to 1.59)** | 0.84 (0.57 to 1.23) | 1.04 (0.98 to 1.10) |
| **Cognitive function** | | | | |
| *Memory function* | **1.13 (1.09 to 1.17)** | **0.95 (0.94 to 0.96)** | 0.98 (0.94 to 1.03) | 0.99 (0.99 to 1.00) |
| *Executive function* | **1.06 (1.04 to 1.08)** | **0.98 (0.98 to 0.98)** | 1.01 (0.99 to 1.03) | 1.00 (1.00 to 1.00) |
| **Factor that could influence cognitive test, wave 5** | | | | |
| *No* | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) |
| *Yes* | 0.64 (0.39 to 1.07) | **1.17 (1.06 to 1.28)** | 1.14 (0.66 to 1.97) | 0.95 (0.88 to 1.03) |
| **Charlson Comorbidity Index (CCI), wave 6** | | | | |
| *CCI 0* | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) |
| *CCI 1-2* | **0.07 (0.04 to 0.14)** | **1.78 (1.69 to 1.86)** | **0.14 (0.05 to 0.39)** | **1.23 (1.14 to 1.34)** |
| *CCI 3-8* | **0.02 (0.00 to 0.30)** | **2.56 (2.39 to 2.73)** | 0.3 (0.01 to 16.72) | **1.32 (1.16 to 1.50)** |
| **Self-rated health, wave 6** | | | | |
| *Excellent* | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) |

| | | | | |
|---|---|---|---|---|
| *Very good* | **0.46 (0.35 to 0.62)** | **1.51 (1.31 to 1.74)** | **0.61 (0.42 to 0.87)** | **1.21 (1.07 to 1.37)** |
| *Good* | **0.17 (0.12 to 0.23)** | **2.03 (1.77 to 2.32)** | **0.31 (0.20 to 0.46)** | **1.39 (1.23 to 1.58)** |
| *Fair* | **0.06 (0.04 to 0.10)** | **2.98 (2.61 to 3.41)** | **0.21 (0.11 to 0.39)** | **1.66 (1.46 to 1.89)** |
| *Poor* | **0.04 (0.02 to 0.09)** | **4.43 (3.86 to 5.10)** | **0.29 (0.12 to 0.71)** | **1.94 (1.68 to 2.24)** |
| **Depression, wave 6** | | | | |
| *No* | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) |
| *Yes* | **0.48 (0.35 to 0.66)** | **1.52 (1.43 to 1.60)** | 1.22 (0.82 to 1.81) | **1.08 (1.02 to 1.15)** |

The estimates for health literacy is also reported in Table 2
95% CI: 95% confidence interval with robust standard errors.
*: The logistic part estimates the probability (odds ratios) of reporting zero medication whereas the negative binomial part estimates the number of medications (incidence rate ratios) among those at risk of medications.
† Given that the relationship between age and number of medications was nonlinear, linear term and quadratic term of age (not shown, IRR=1.00 (1.00–1.00), $p<0.001$ for male and female) were adjusted for.
‡: full adjustment for baseline factors at wave 5 (2010/11) and Charlson Comorbidity Index, Self-rated health, and Depression at wave 6 (2012/13). Adjusted estimates for health literacy are identical to those reported in table 2 in the main text.

**Appendix 2. Analysis restricted on 898 participants with the lowest morbidity and good health status: Adjusted odds ratios (OR) and incidence rate ratios (IRR) based on zero-inflated negative binomial models for the association between literacy at wave 5 and the number of medications at wave 6.**

| | Logistic part* | Negative binomial part* |
|---|---|---|
| | OR (95% CI) | IRR (94% CI) |
| **Health literacy** | | |
| *Low (score<4)* | 1.19 (0.47 to 3.03) | 1.04 (0.91 to 1.20) |
| *Adequate (score=4)* | 1.00 (ref) | 1.00 (ref) |

95% CI: 95% confidence interval with robust standard errors.
*: The logistic part estimates the probability (odds ratios) of reporting zero medication whereas the negative binomial part estimates the number of medications (incidence rate ratios) among those at risk of medications.
† Given that the relationship between age and number of medications was nonlinear, linear term and quadratic term of age (not shown, IRR=1.00 (1.00–1.00), $p$<0.001) were adjusted for.
Adjustment for sex, age, education qualification, wealth, smoking status, and cognitive function assessed at wave 5.
Analysis restricted on 898 individuals who reported the lowest morbidity (Charlson Comorbidity Index=0), good or higher self-rated health, and no depression at both waves 5 and 6.

**Appendix 3. Analysis with literacy in three levels: Adjusted odds ratios (OR) and incidence rate ratios (IRR) based on zero-inflated negative binomial models for the association between literacy at wave 5 and the number of medications at wave 6.**

| | Logistic part* | Negative binomial part* |
|---|---|---|
| | OR (95% CI) | IRR (95% CI) |
| **Health literacy** | | |
| *Low (score<3)* | 0.53 (0.27 to 1.04) | 1.01 (0.94 to 1.09) |
| *Intermediate (score=3)* | 0.69 (0.47 to 1.03) | 1.00 (0.95 to 1.05) |
| *Adequate (score=4)* | 1.00 (ref) | 1.00 (ref) |
| **Sex** | | |
| *Male* | 1.00 (ref) | 1.00 (ref) |
| *Female* | 0.70 (0.55 to 0.89) | 1.00 (0.96 to 1.04) |
| **Age†, wave 5** | **0.75 (0.57 to 0.99)** | **1.09 (1.05 to 1.13)** |
| **Highest education qualification** | | |
| *No qualification or equivalent* | 1.00 (ref) | 1.00 (ref) |
| *Up to secondary education* | 0.82 (0.60 to 1.11) | 0.98 (0.93 to 1.03) |
| *Degree or higher education* | 0.97 (0.72 to 1.30) | 1.03 (0.97 to 1.08) |
| **Wealth quintiles** | | |
| *1(least wealthy)* | 1.00 (ref) | 1.00 (ref) |
| *2* | 1.25 (0.81 to 1.93) | 0.99 (0.93 to 1.05) |
| *3* | 0.93 (0.58 to 1.47) | 0.98 (0.92 to 1.05) |
| *4* | 1.08 (0.69 to 1.68) | 1.02 (0.95 to 1.10) |
| *5(most wealthy)* | 0.96 (0.60 to 1.52) | 0.93 (0.86 to 1.01) |
| **Smoking status, wave 5** | | |
| *Never smoked* | 1.00 (ref) | 1.00 (ref) |
| *Ex-smoker* | 0.81 (0.63 to 1.05) | **1.05 (1.00 to 1.10)** |
| *Current smoker* | 1.34 (0.94 to 1.92) | 0.99 (0.92 to 1.07) |
| **Charlson Comorbidity Index (CCI), wave 5** | | |
| *CCI 0* | 1.00 (ref) | 1.00 (ref) |
| *CCI 1-2* | 0.92 (0.44 to 1.92) | **1.21 (1.12 to 1.31)** |
| *CCI 3-8* | 0.27 (0.00 to 52.03) | **1.32 (1.16 to 1.51)** |
| **Self-rated health, wave 5** | | |
| *Excellent* | 1.00 (ref) | 1.00 (ref) |
| *Very good* | 1.04 (0.70 to 1.55) | **1.35 (1.19 to 1.53)** |
| *Good* | 0.74 (0.47 to 1.17) | **1.52 (1.34 to 1.73)** |
| *Fair* | **0.46 (0.23 to 0.93)** | **1.73 (1.52 to 1.98)** |
| *Poor* | **0.25 (0.08 to 0.76)** | **2.03 (1.75 to 2.35)** |
| **Depression, wave 5** | | |
| *No* | 1.00 (ref) | 1.00 (ref) |

| | | |
|---|---|---|
| *Yes* | 0.83 (0.56 to 1.23) | 1.04 (0.98 to 1.10) |
| **Cognitive function** | | |
| *Memory function* | 0.98 (0.94 to 1.03) | 0.99 (0.99 to 1.00) |
| *Executive function* | 1.01 (0.99 to 1.03) | 1.00 (1.00 to 1.00) |
| **Factor that could influence cognitive test, wave 5** | | |
| *No* | 1.00 (ref) | 1.00 (ref) |
| *Yes* | 1.13 (0.65 to 1.97) | 0.95 (0.88 to 1.03) |
| **Charlson Comorbidity Index (CCI), wave 6** | | |
| *CCI 0* | 1.00 (ref) | 1.00 (ref) |
| *CCI 1-2* | **0.14 (0.05 to 0.39)** | **1.23 (1.14 to 1.34)** |
| *CCI 3-8* | 0.30 (0.00 to 18.79) | **1.32 (1.16 to 1.50)** |
| **Self-rated health, wave 6** | | |
| *Excellent* | 1.00 (ref) | 1.00 (ref) |
| *Very good* | **0.61 (0.42 to 0.88)** | **1.21 (1.07 to 1.37)** |
| *Good* | **0.31 (0.21 to 0.47)** | **1.40 (1.23 to 1.59)** |
| *Fair* | **0.21 (0.11 to 0.40)** | **1.66 (1.46 to 1.90)** |
| *Poor* | **0.29 (0.12 to 0.73)** | **1.94 (1.68 to 2.24)** |
| **Depression, wave 5** | | |
| *No* | 1.00 (ref) | 1.00 (ref) |
| *Yes* | 1.24 (0.84 to 1.83) | **1.08 (1.02 to 1.15)** |

95% CI: 95% confidence interval with robust standard errors.

*: The logistic part estimates the probability (odds ratios) of reporting zero medication whereas the negative binomial part estimates the number of medications (incidence rate ratios) among those at risk of medications.

† Given that the relationship between age and number of medications was nonlinear, linear term and quadratic term of age (not shown, IRR=1.00 (1.00–1.00), $p$<0.001 for male and female) were adjusted for.

ǂ: full adjustment for baseline factors at wave 5 (2010/11) and Charlson Comorbidity Index, Self-rated health, and Depression at wave 6 (2012/13).

STROBE Statement—checklist of items that should be included in reports of observational studies

| | Item No | Recommendation | Page No |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | Page 1, 2 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | Page 2 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | Page 4 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | Page 4<br>Introduction, para 4. |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | Page 5<br>Methods, para 1 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | Page 5<br>Methods, para 1-2 |
| Participants | 6 | (*a*) ***Cohort study***—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br>*Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls<br>*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants | Page 5<br>Methods, para 2 |
| | | (*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed<br>*Case-control study*—For matched studies, give matching criteria and the number of controls per case | |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | Page 5, Methods, para 4 to Page 7 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | Page 5-7 |
| Bias | 9 | Describe any efforts to address potential sources of bias | Page 7-8, Statistical analyses, para 1-2. |
| Study size | 10 | Explain how the study size was arrived at | Page 5<br>Methods, para 2 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | Page 4, Introduction, para 4.<br><br>Page 6, Variables, para 2-7. |

| | | | |
|---|---|---|---|
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | Page 7-8, Statistical analyses, para 1-2. |
| | | (*b*) Describe any methods used to examine subgroups and interactions | Page 7, Statistical analyses, para 1. |
| | | (*c*) Explain how missing data were addressed | (by adjusting for non-response in weighted analyses)<br>Page 7-8, Statistical analyses, para 2-3 |
| | | (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed<br>*Case-control study*—If applicable, explain how matching of cases and controls was addressed<br>*Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy | (by adjusting for non-response in weighted analyses)<br>Page 7-8, Statistical analyses, para 2-3. |
| | | (*e*) Describe any sensitivity analyses | |

Continued on next page

| | | | |
|---|---|---|---|
| **Results** | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | Page 8, Results para 1. |
| | | (b) Give reasons for non-participation at each stage | |
| | | (c) Consider use of a flow diagram | |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | Page 8, Results para 1 |
| | | (b) Indicate number of participants with missing data for each variable of interest | Not provided |
| | | (c) *Cohort study*—Summarise follow-up time (eg, average and total amount) | Page 5, Study design, para 2. |
| Outcome data | 15* | *Cohort study*—Report numbers of outcome events or summary measures over time | Page 8, Results, para 2.<br><br>Table 1 |
| | | *Case-control study*—Report numbers in each exposure category, or summary measures of exposure | |
| | | *Cross-sectional study*—Report numbers of outcome events or summary measures | |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | Page 8-9 Tables 2 & 4, and online supplemental appendix 1. |
| | | (*b*) Report category boundaries when continuous variables were categorized | Tables 1, 2 & 4 |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | None |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | Page 9, Results, para 5-6.<br><br>Tables 3 & 4 |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | Page 10, Discussion, para 1. |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | Page 12, Discussion, para 6. |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | Page 10, Discussion, para 3. |

| | | | |
|---|---|---|---|
| | | | Page 13, Conclusions. |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | Page 12, Discussions, para 5. |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | Page 14 (Funding statement). |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.