Maturitas 185 (2024) 107998

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Original article

# Longitudinal associations of polypharmacy and frailty with major cardiovascular events and mortality among more than half a million middle-aged participants of the UK Biobank

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ARTICLE INFO

*Keywords:*
Polypharmacy
Frailty
Mortality
MACE
Cardiovascular disease mortality

ABSTRACT

*Background:* Studies of the associations of polypharmacy and frailty with adverse health outcomes in middle-aged adults are limited. Furthermore, a potentially stronger association of polypharmacy with adverse health outcomes in frail than in non-frail adults is of interest.
*Objective:* To evaluate associations of frailty (assessed using a frailty index) and polypharmacy (defined as taking five or more drugs) with major cardiovascular events, cancer incidence, all-cause, cardiovascular disease-specific, and cancer-specific mortality.
*Methods:* Cox proportional hazards regression models were used to analyze 501,548 participants of the UK Biobank cohort study aged 40–69 years who were followed up for an average of 12 years.
*Results:* The prevalence of pre-frailty and frailty were 43.2 % and 2.3 %, respectively, and that of polypharmacy was 18.3 %. Although strongly associated with each other, frailty and polypharmacy were independently, statistically significantly associated with major cardiovascular events, cardiovascular disease-specific, and all-cause mortality. In addition, the hazard ratios of polypharmacy were stronger among (pre-)frail than non-frail study participants. No profound associations with cancer incidence and cancer mortality were observed. No sex and age differences were observed.
*Conclusions:* This large cohort study showed that polypharmacy and frailty are independent risk factors for major cardiovascular events, cardiovascular disease-specific and all-cause mortality in both middle-aged (40–64 years) and older people (≥ 65 years). In addition, the hazard ratios of polypharmacy were stronger among (pre-)frail than non-frail study participants. This underlines the need to avoid polypharmacy as far as possible not only in older but also in middle-aged subjects (40–64 years), especially if they are pre-frail or frail.

## 1. Introduction

Polypharmacy, which is most commonly defined as concomitant use of 5 or more medications [1], is common in the older population due to increasing prevalence of multimorbidity with increasing age [2–4]. Previous studies have shown significant associations of polypharmacy with falls, adverse drug reactions/events, hospitalization, and mortality [5]. As co-morbidity and age-related changes in medication pharmacokinetics and pharmacodynamics are more profound, polypharmacy is particularly problematic in frail patients [6].

Frailty describes a state of increased vulnerability secondary to impaired resolution of homoeostasis following a stressor event and has been found to be linked to falls, delirium, disability, hospitalization, and mortality [7,8]. The relationship between polypharmacy and frailty has also been studied showing that polypharmacy is both associated with prevalent frailty and a predictor for incident frailty through an increased risk for adverse drug reactions or functional impairments [9–12]. Previous studies also investigated how frailty and polypharmacy interacted

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https://doi.org/10.1016/j.maturitas.2024.107998
Received 25 September 2023; Received in revised form 4 March 2024; Accepted 11 April 2024
Available online 20 April 2024

with each other with respect to adverse health outcomes [13–17]. However, the study populations were mainly restricted to those aged ≥65 years and the results were inconclusive.

Despite the importance of polypharmacy and frailty in the older population, their relevance is not limited to older adults. Middle-aged individuals can also be affected by polypharmacy and frailty but this received less attention so far [18,19]. Therefore, we aimed to evaluate the individual and joint associations of polypharmacy and frailty state with all-cause mortality, major cardiovascular events (MACE), and cardiovascular disease (CVD) specific mortality using data from UK Biobank, which is a large community cohort of over half a million participants aged 40–69 years. Additionally, we included the outcomes of cancer incidence and cancer specific mortality. While some studies have identified associations between extensive polypharmacy and frailty with cancer and cancer-specific mortality, the direct association or predictive value of these factors for cancer and cancer-specific mortality is not strongly supported [20,21]. These variables serve as negative control outcomes, which, if our regression model is sufficiently adjusted, should not show an association [22].

## 2. Materials and methods

### 2.1. Study design and population

In this study, we used data from a prospective cohort: the UK Biobank from the United Kingdom. For introduction of the UK Biobank, see Appendix Text A1. From 502,411 participants recruited to the UK Biobank between 2006 and 2010, we excluded those with missing information on baseline medication assessment and mortality follow-up (Appendix Fig. A1). Overall, 501,548 participants were included in this study for analyses of mortality outcomes. For analyses of MACE and cancer incidence, we additionally excluded those with history of stroke or myocardial infarction before baseline and those with history of cancer before baseline, leaving 466,173 and 444,349 participants included, respectively.

### 2.2. Definition of polypharmacy

Baseline prescription medication information in the UK Biobank was obtained by nurse-led verbal interview. Participants brought their medications to the assessment centers and only regularly used prescription medications, which were taken weekly, monthly, or three-monthly were recorded through the list of codes used by clinic nurses to code drugs [23,24]. Additionally, over-the-counter medications, vitamins, and supplements were collected in the touch-screen questionnaire [25]. Considering the significant role of herbal medications and dietary supplements in contributing to high rates of polypharmacy, particularly among older individuals with multimorbidity, we included these in our medication count. Herbal medications and dietary supplements are known to interact with conventional medications and are associated with a range of adverse events [26]. Consequently, we retrieved the sum of recorded medications and supplements and defined it as the number of medications the participants were currently taking. Thereafter, we applied the most common polypharmacy definition, which counts all concurrently used drugs and defines use of ≥5 drugs as polypharmacy [1], and further defined concurrently using ≥10 drugs as excessive polypharmacy (EPP).

### 2.3. Definition of frailty

A continuous frailty index (FI) was established for all study participants by adopting the method proposed by Mitnitski and Rockwood [27,28], which defines frailty as an accumulation of deficits. These deficits could be diseases, symptoms, medications, disabilities, and biomarkers. However, we did not include medications to avoid an overlap with polypharmacy. We included 30 deficits in the FI (Appendix Table A1). Detailed definition, criteria, and cutoffs for the FI are further described in Appendix Text A2.

### 2.4. Assessment of covariates

Socio-demographics (e.g., years of education, Townsend deprivation index, and average household income), lifestyle (e.g., smoking status, alcohol consumption, and physical activities), and medical history were obtained through a touch-screen questionnaire completed by participants [25]. Participants had a verbal interview with a trained nurse afterwards to provide further information on major illnesses, disabilities, and regularly used prescription medications. To achieve as complete baseline comorbidity information as possible, we further added diagnoses from hospital records, cancer registration, and primary care data. Physical measurements, including blood pressure and anthropometry, and biological samples, including blood, urine, and saliva were also collected [29]. Laboratory methods applied to measure biomarkers in serum and urine samples are described elsewhere [30].

### 2.5. Ascertainment of all-cause, cardiovascular disease specific, and cancer specific mortality, as well as MACE, and cancer incidence

Information about the vital status, date, and cause of death (identified by the ICD-10 codes) of study participants in the UK Biobank was obtained through linkage to national death registries. MACE is a composite outcome and is includes incident stroke, incident myocardial infarction, and CVD specific mortality. Information about incident stroke and incident myocardial infarction was collected from hospital records and primary care data. Information about incident cancer (non-fatal and fatal) was ascertained through linkage to national cancer registries, hospital records and primary care data. The follow-up time covered by all data sources for all study participants was set to the time from UK Biobank's baseline (date of entering the assessment center) to 12 November 2021.

### 2.6. Statistical analyses

Cross-sectional association of polypharmacy and frailty was assessed in logistic regression using categorical variables and linear regression models using continuous variables and restricted cubic splines. Associations of frailty state, polypharmacy with five outcomes were assessed with Cox proportional hazards models. To assess whether analyses on polypharmacy are sufficiently adjusted to prevent confounding by indication, the outcomes cancer incidence and cancer mortality serve as negative control outcomes. Multiple imputation was performed to impute missing covariate data using the Markov Chain Monte Carlo (MCMC) [31] technique with 200 burn-in iterations and 5 datasets were generated. For more detail on statistical analyses, see Appendix Text A3.

## 3. Results

### 3.1. Characteristics of the study population

We included 501,548 participants for analyses on mortality outcomes (Appendix Fig. A1) and baseline characteristics of the study population are presented in Table 1. The mean age of the included study participants was 56.5 years (standard deviation (SD), 8.1 years) at baseline, and 272,931 (54.4 %) were female. The median number of comorbidities in the study population was 2. For more detail on characteristics of the study population, see Appendix Text A4.

### 3.2. Association of frailty and polypharmacy

Dose-response analyses of the association between FI and the number of drugs is shown in Fig. 1. The restricted cubic spline curve for the full model demonstrates a flatter trajectory compared to the curve for the

**Table 1**
Baseline characteristics of the study population (N = 501,548).

| Baseline characteristics | $N_{total}$ (%)[a] | Mean (SD)[a] |
|---|---|---|
| Sex | | |
| Female | 272,931 (54.4) | – |
| Male | 228,617 (45.6) | – |
| Age (years) | – | 56.5 (8.1) |
| Years of education | | |
| ≤9 | 103,413 (21.1) | – |
| 10–11 | 144,046 (29.3) | – |
| ≥12 | 243,780 (49.6) | – |
| Townsend deprivation index | – | −1.30 (3.09) |
| Average household income | | |
| <18,000 | 97,024 (22.8) | – |
| 18,000–30,999 | 108,078 (25.4) | – |
| 31,000–51,999 | 110,681 (26.1) | – |
| 52,000–100,000 | 86,195 (20.3) | – |
| >100,000 | 22,913 (5.4) | – |
| Disability[b] | 29,947 (6.0) | – |
| BMI (kg/m$^2$) | | |
| <18.5 | 2626 (0.5) | – |
| 18.5 – < 20 | 9109 (1.8) | – |
| 20 – < 25 | 153,250 (30.7) | – |
| 25 – < 30 | 212,072 (42.5) | – |
| 30 – < 35 | 87,537 (17.5) | – |
| 30 – < 40 | 24,990 (5.0) | – |
| ≥40 | 9699 (1.9) | – |
| Waist circumference (cm) | – | 90.3 (13.5) |
| IPAQ activity group | | |
| Low | 76,102 (18.9) | – |
| Moderate | 163,865 (40.8) | – |
| High | 161,976 (40.3) | – |
| Smoking status | | |
| Never smoker | 274,885 (54.9) | – |
| Former smoker, occasionally | 57,153 (11.4) | – |
| Former smoker, regularly | 115,834 (23.1) | – |
| Current smoker, occasionally | 13,710 (2.7) | – |
| Current smoker, regularly | 39,150 (7.8) | – |
| Alcohol consumption | | |
| Abstainer | 157,369 (31.4) | – |
| W 0–19.99 g/d or M 0–39.99 g/d | 198,425 (39.6) | – |
| W 20–39.99 g/d or M 40–59.99 g/d | 85,017 (16.9) | – |
| W ≥ 40 g/d or M ≥ 60 g/d | 60,737 (12.1) | – |
| eGFR (mL/min/1.73 m$^2$) | | |
| ≥90 | 279,420 (59.6) | – |
| 60 – < 90 | 179,054 (38.2) | – |
| <60 | 10,668 (2.3) | – |
| Systolic blood pressure (mmHg) | | |
| <140 | 263,882 (52.7) | – |
| 140 – < 160 | 158,852 (31.7) | – |
| 160 – < 180 | 61,757 (12.3) | – |
| ≥180 | 16,582 (3.3) | – |
| Diastolic blood pressure (mmHg) | | |
| <90 | 380,131 (75.9) | – |
| 90 – < 100 | 91,609 (18.3) | – |
| ≥100 | 29,346 (5.9) | – |
| LDL cholesterol (mg/dL) | | |
| <100 | 60,811 (13.0) | – |
| 100 – < 130 | 140,379 (30.0) | – |
| 130 – < 160 | 153,588 (32.8) | – |
| 160 – < 190 | 83,065 (17.7) | – |
| ≥190 | 30,648 (6.5) | – |
| HDL cholesterol (mg/dL) | | |
| <30 | 4308 (1.0) | – |
| 30 – < 35 | 14,856 (3.5) | – |
| 35 – < 40 | 33,799 (7.9) | – |
| ≥40 | 376,710 (87.7) | – |
| HbA1c (%) | | |
| <6.0 | 428,412 (91.9) | – |
| 6.0 – < 6.5 | 19,542 (4.2) | – |
| 6.5 – < 7.0 | 6850 (1.5) | – |
| 7.0 – < 8.0 | 6530 (1.4) | – |
| ≥8.0 | 4959 (1.1) | – |
| C-reactive protein (mg/dL) | | |
| <1 | 183,744 (39.2) | – |
| ≥1 | 284,609 (60.8) | – |
| Frailty-index | | |
| Non-frail | 273,542 (54.5)[c] | – |
| Pre-frail | 216,563 (43.2)[c] | – |
| Frail | 11,443 (2.3)[c] | – |
| No. of comorbidities | – | 2 (1–3)[d] |
| Hypertension | 139,497 (27.8) | – |
| Cardiac insufficiency | 18,254 (3.6) | – |
| Coronary heart disease | 40,323 (8.0) | – |
| History of stroke | 17,948 (3.6) | – |
| Atrial fibrillation | 8253 (1.7) | – |
| COPD | 56,797 (11.3) | – |
| Type 2 diabetes mellitus | 24,748 (4.9) | – |
| Depression | 44,616 (8.9) | – |
| Chronic pain | 78,021 (15.6) | – |
| Gastrointestinal illness | 79,403 (15.8) | – |
| Chronic kidney disease | 36,083 (7.2) | – |
| Cancer | 43,934 (8.8) | – |
| Anemia | 16,201 (3.2) | – |
| Hypothyroidism | 31,112 (6.2) | – |

Abbreviations: /d, per day; BMI, body mass index; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; $HbA_{1c}$, hemoglobin $A_{1c}$; HDL, high-density lipoprotein; IPAQ, International Physical Activity Questionnaire; IQR, interquartile range; LDL, low density lipoprotein; M, men; SD, standard deviation; W, women.

[a] Number and frequency are calculated based on unimputed dataset unless otherwise specified.

[b] Disability is defined as having attendance allowance, disability living allowance, or blue badge.

[c] Number and frequency are calculated based on imputed dataset 1.

[d] Median (interquartile range).

model adjusted for age and sex. Interestingly, the slope of the age and sex-adjusted curve becomes noticeably steeper at an FI of ≥0.30, which is the threshold we used to differentiate between non-frail and pre-frail participants. Further detailed descriptions are provided in Appendix Text A5.

### 3.3. Association of frailty and mortality

During mean follow-up of 12.4 years for mortality, 37,812 participants died, among whom 7774 died of CVD as the primary cause of death (20.6 %) and 19,006 (50.3 %) died of cancer (27.7 %). During mean follow-up of 11.8 years for MACE, 63,279 participants developed MACE, and during mean follow-up of 11.6 years for cancer incidence, 70,883 participants were diagnosed with cancer or died of cancer.

The associations of pre-frailty and frailty with all-cause mortality, MACE, and CVD specific mortality were strong and statistically significant in models 1 and 2, whereas much weaker associations were observed with cancer incidence and cancer specific mortality (Table 2). With additional adjustment for disease-related factors in model 3, the hazard ratios (HRs) [95 % confidence interval (CI)] for all-cause mortality (1.12 [1.05–1.20] for frailty vs. non-frailty), MACE (1.16 [1.09–1.23] for frailty vs. non-frailty), and CVD specific mortality (1.20 [1.05–1.37] for frailty vs. non-frailty) remained statistically significant but were attenuated. The associations with cancer incidence (0.98 [0.92–1.03] for frailty vs. non-frailty) and cancer-specific mortality (1.00 [0.91–1.11] for frailty vs. non-frailty) essentially disappeared. The restricted cubic spline curves for model 2 show statistically significantly, monotonically increased all-cause mortality, MACE, CVD specific mortality, and cancer specific mortality with increasing FI (Appendix Fig. A4). In model 3, the curves become flatter and show a plateauing at high FI levels but remain statistically significant for all-cause mortality, MACE, and CVD specific mortality (Appendix Fig. A5). In contrast, the cancer specific mortality and cancer incidence do not show statistically significant, monotonic increases of the HR with increasing FI after adjustment for diseases in model 3, speaking against an association of the FI with the cancer outcomes.

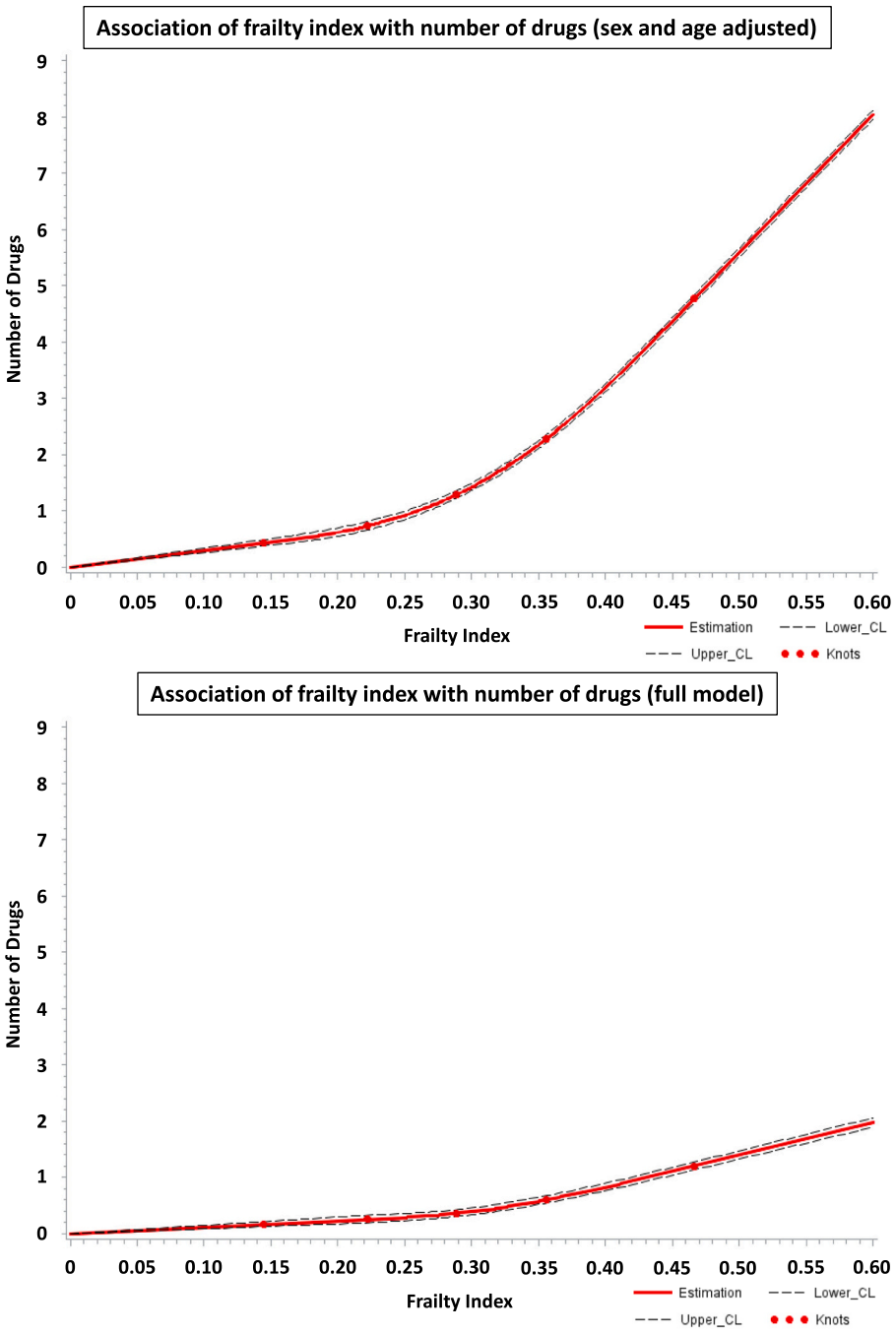


**Fig. 1.** Dose-response curves for the association of continuous frailty index (x-axis) with the number of drugs (y-axis) in sex and age adjusted model and model 3 (full model)
Notes: The dose-response curves were obtained from the imputation dataset 1. The full model is adjusted for all baseline characteristics shown in Table 1.

Subgroup analyses by age and sex did not show pronounced age or sex differences in the associations of pre-frail and frail status with the adverse health outcomes and all confidence intervals overlapped (Appendix Tables A5 and A6). Interestingly, although frailty is often considered most relevant for adults aged 65 years and older, the pre-frail and frail study participants of the UK Biobank aged 40–64 years had comparable relative risks of all-cause mortality, MACE, and CVD specific mortality to adults aged 65 years and older.

### 3.4. Association of polypharmacy and mortality

Likewise for frailty, polypharmacy was profoundly, statistically significant associated with all-cause mortality, MACE, and CVD specific mortality in models 1 and 2, whereas the associations with the negative control outcomes cancer incidence and cancer specific mortality were much weaker (Table 3). With additional adjustment for disease-related factors in model 3, the HRs [95 % CI] for all-cause mortality (1.47 [1.40–1.54] for ≥10 vs. 0–4 medications), MACE (1.32 [1.26–1.38] for ≥10 vs. 0–4 medications), and CVD specific mortality (1.67 [1.51–1.84] for ≥10 vs. 0–4 medications) were attenuated but still statistically significant. Those for the negative control outcomes cancer incidence (1.13 [1.07–1.18] for ≥10 vs. 0–4 medications) and cancer specific mortality (1.07 [0.98–1.16] for ≥10 vs. 0–4 medications) stayed rather stable or became statistically insignificant. The described changes in the results

**Table 2**
The associations of frailty state with all-cause mortality, major adverse cardiovascular event, cardiovascular disease specific mortality, cancer incidence, and cancer specific mortality.

| | $N_{total}$ | $N_{cases}$ (%)[a] | Model 1[b] | Model 2[c] | Model 3[d] |
|---|---|---|---|---|---|
| | | | HR [95 % CI] | HR [95 % CI] | HR [95 % CI] |
| All-cause mortality | | | | | |
| Non-frail | 273,542 | 10,620 (3.9) | Ref | Ref | Ref |
| Pre-frail | 216,563 | 23,831 (11.0) | **1.57 [1.53–1.60]** | **1.45 [1.41–1.49]** | **1.14 [1.11–1.18]** |
| Frail | 11,443 | 3361 (29.4) | **2.77 [2.65–2.90]** | **2.40 [2.29–2.52]** | **1.12 [1.05–1.20]** |
| Major adverse cardiovascular event | | | | | |
| Non-frail | 269,425 | 22,702 (8.4) | Ref | Ref | Ref |
| Pre-frail | 191,238 | 38,365 (20.1) | **1.69 [1.66–1.72]** | **1.53 [1.50–1.55]** | **1.18 [1.16–1.21]** |
| Frail | 5510 | 2212 (40.2) | **3.12 [2.97–3.28]** | **2.56 [2.43–2.69]** | **1.16 [1.09–1.23]** |
| Cardiovascular disease specific mortality | | | | | |
| Non-frail | 273,542 | 1624 (0.6) | Ref | Ref | Ref |
| Pre-frail | 216,563 | 5106 (2.4) | **2.16 [2.03–2.29]** | **1.87 [1.75–1.99]** | **1.30 [1.21–1.39]** |
| Frail | 11,443 | 1044 (9.1) | **5.41 [4.93–5.93]** | **4.14 [3.75–4.56]** | **1.20 [1.05–1.37]** |
| Cancer incidence | | | | | |
| Non-frail | 254,113 | 33,440 (13.2) | Ref | Ref | Ref |
| Pre-frail | 182,158 | 35,529 (19.5) | **1.04 [1.03–1.06]** | **1.02 [1.00–1.04]** | **0.97 [0.95–0.99]** |
| Frail | 8078 | 1914 (23.7) | **1.15 [1.10–1.21]** | **1.11 [1.06–1.17]** | 0.98 [0.92–1.03] |
| Cancer specific mortality | | | | | |
| Non-frail | 273,542 | 6196 (2.3) | Ref | Ref | Ref |
| Pre-frail | 216,563 | 11,721 (5.4) | **1.41 [1.37–1.46]** | **1.32 [1.27–1.37]** | **1.08 [1.03–1.12]** |
| Frail | 11,443 | 1089 (9.5) | **1.84 [1.71–1.98]** | **1.64 [1.53–1.77]** | 1.00 [0.91–1.11] |

Values in bold are statistically significant ($p < 0.05$).
Abbreviations: CI, confidence interval; HR, hazard ratio.
[a] Number and frequency are calculated based on imputed dataset 1.
[b] Adjusted for age, sex, years of education, income, Townsend deprivation index, and disability allowance.
[c] Adjusted for variables of model 1, physical activity, smoking status, alcohol consumption, BMI, and waist circumference.
[d] Adjusted for variables of model 2, eGFR, systolic blood pressure, diastolic blood pressure, LDL, HDL, $HbA_{1c}$, CRP, number of comorbidities, 14 frequently seen comorbidities (including hypertension, cardiac insufficiency, coronary heart disease, history of stroke (excluded from the major adverse cardiovascular event analyses), atrial fibrillation, chronic obstructive pulmonary disease, type 2 diabetes mellitus, depression, chronic pain, gastrointestinal illness, chronic kidney disease, cancer (excluded from the cancer incidence analyses), anemia, and hypothyroidism), and number of drugs.

**Table 3**
The associations of polypharmacy with all-cause mortality, major adverse cardiovascular event, cardiovascular disease specific, cancer incidence, and cancer specific mortality.

| | $N_{total}$ | $N_{cases}$ (%) | Model 1[a] | Model 2[b] | Model 3[c] |
|---|---|---|---|---|---|
| | | | HR [95 % CI] | HR [95 % CI] | HR [95 % CI] |
| All-cause mortality | | | | | |
| 0–4 medications | 409,991 | 23,531 (5.7) | Ref | Ref | Ref |
| 5–9 medications | 79,616 | 11,138 (14.0) | **1.54 [1.50–1.58]** | **1.47 [1.44–1.51]** | **1.24 [1.21–1.28]** |
| ≥10 medications | 11,941 | 3143 (26.3) | **2.28 [2.19–2.37]** | **2.07 [1.98–2.16]** | **1.47 [1.40–1.54]** |
| Major adverse cardiovascular event | | | | | |
| 0–4 medications | 395,678 | 46,241 (11.7) | Ref | Ref | Ref |
| 5–9 medications | 63,241 | 14,487 (22.9) | **1.58 [1.55–1.61]** | **1.47 [1.44–1.50]** | **1.15 [1.12–1.17]** |
| ≥10 medications | 7254 | 2551 (35.2) | **2.43 [2.34–2.54]** | **2.14 [2.05–2.23]** | **1.32 [1.26–1.38]** |
| Cardiovascular disease specific mortality | | | | | |
| 0–4 medications | 409,991 | 4094 (1.0) | Ref | Ref | Ref |
| 5–9 medications | 79,616 | 2742 (3.4) | **2.15 [2.05–2.27]** | **1.98 [1.88–2.08]** | **1.41 [1.33–1.50]** |
| ≥10 medications | 11,941 | 938 (7.9) | **3.87 [3.58–4.19]** | **3.27 [3.01–3.55]** | **1.67 [1.51–1.84]** |
| Cancer incidence | | | | | |
| 0–4 medications | 367,243 | 55,438 (15.1) | Ref | Ref | Ref |
| 5–9 medications | 67,395 | 13,363 (19.8) | **1.06 [1.05–1.10]** | **1.06 [1.04–1.08]** | **1.04 [1.01–1.06]** |
| ≥10 medications | 9711 | 2082 (21.4) | **1.19 [1.13–1.24]** | **1.17 [1.12–1.23]** | **1.13 [1.07–1.18]** |
| Cancer specific mortality | | | | | |
| 0–4 medications | 409,991 | 13,421 (3.3) | Ref | Ref | Ref |
| 5–9 medications | 79,616 | 4696 (5.9) | **1.21 [1.17–1.25]** | **1.16 [1.12–1.21]** | **1.09 [1.05–1.13]** |
| ≥10 medications | 11,941 | 889 (7.4) | **1.29 [1.20–1.39]** | **1.20 [1.11–1.29]** | 1.07 [0.98–1.16] |

Values in bold are statistically significant ($p < 0.05$).
Abbreviations: CI, confidence interval; HR, hazard ratio.
[a] Adjusted for age, sex, years of education, income, Townsend deprivation index, and disability allowance.
[b] Adjusted for variables of model 1, physical activity, smoking status, alcohol consumption, BMI, and waist circumference.
[c] Adjusted for variables of model 2, eGFR, systolic blood pressure, diastolic blood pressure, LDL, HDL, $HbA_{1c}$, CRP, number of comorbidities, 14 frequently seen comorbidities (including hypertension, cardiac insufficiency, coronary heart disease, history of stroke (excluded from the major adverse cardiovascular event analyses), atrial fibrillation, chronic obstructive pulmonary disease, type 2 diabetes mellitus, depression, chronic pain, gastrointestinal illness, chronic kidney disease, cancer (excluded from the cancer incidence analyses), anemia, and hypothyroidism), and frailty index.

from model 2 (Appendix Fig. A6) to model 3 (Appendix Fig. A7) were comparably observed in dose-response analyses between the number of drugs and the outcomes. Here, the associations of the number of drugs with the cancer outcomes were very weak and close to the null effect value of HR = 1.0.

Likewise for frailty, subgroup analyses by age and sex did not show pronounced age or sex differences in the associations of polypharmacy with the adverse health outcomes and all confidence intervals overlapped (Appendix Tables A7 and A8).

### 3.5. Joint association of polypharmacy and frailty status with mortality

Like individual analyses of frailty and polypharmacy, the joint score of frailty and polypharmacy was profoundly associated with all-cause mortality, MACE, and CVD specific mortality in models 1 and 2 and the HRs got substantially attenuated in model 3 but remained statistically significant (Table 4). Interestingly, the HRs increased stepwise from 1 to 3 points and then stayed stable at 4 points. This plateauing was comparable to the one observed in the dose-response analyses of the FI and these outcomes in model 3 analyses (Appendix Fig. A5). Nevertheless, the strongest associations were observed for the comparison of 4 and 0 joint score points: the HRs [95 % CI] were 1.73 [1.59–1.89], 1.56 [1.40–1.74], and 2.08 [1.76–2.46] for all-cause mortality, MACE, and CVD specific mortality, respectively. The stronger associations in the joint score compared to the associations of either polypharmacy or frailty alone with all-cause mortality, MACE, and CVD specific mortality speak for independent associations of polypharmacy and frailty with these outcomes. As seen before, the associations with the negative control outcomes, cancer incidence and cancer specific mortality were either not statistically significant in model 3 or much weaker compared to the other outcomes.

### 3.6. Association of polypharmacy and mortality by frailty status

Stronger associations of polypharmacy with all-cause mortality, MACE, and CVD specific mortality were observed among pre-frail and frail participants than among non-frail participants (Appendix Table A9). Notably, the interaction tests revealed these differences to be statistically significant ($p = 0.002$ for all-cause mortality; $p < 0.001$ for all-cause MACE; $p = 0.004$ for CVD specific morality). Associations of EPP with MACE and CVD specific mortality were not statistically significant among non-frail subjects. Furthermore, associations of polypharmacy with the negative control outcomes cancer incidence and cancer specific mortality were generally weak and mostly not statistically significant, regardless of the frailty state. The results were comparable if the study population was restricted to adults aged 65–69 years (Appendix Table A10).

**Table 4**
Associations of joint score of frailty state and polypharmacy with all-cause mortality, major adverse cardiovascular event, cardiovascular disease specific, cancer incidence, and cancer specific mortality.

| Score points[a] | $N_{total}$ | $N_{cases}$ (%) | Model 1[b] | Model 2[c] | Model 3[d] |
|---|---|---|---|---|---|
| | | | HR [95 % CI] | HR [95 % CI] | HR [95 % CI] |
| All-cause mortality | | | | | |
| 0 points | 254,150 | 9366 (3.7) | Ref | Ref | Ref |
| 1 point | 171,958 | 14,908 (8.7) | **1.45 [1.41–1.49]** | **1.37 [1.33–1.41]** | **1.19 [1.15–1.23]** |
| 2 points | 58,518 | 8814 (15.1) | **2.00 [1.94–2.07]** | **1.86 [1.80–1.92]** | **1.45 [1.39–1.51]** |
| 3 points | 13,735 | 3455 (25.2) | **2.81 [2.69–2.94]** | **2.53 [2.42–2.65]** | **1.64 [1.54–1.73]** |
| 4 points | 3187 | 1269 (39.8) | **3.96 [3.71–4.23]** | **3.43 [3.21–3.67]** | **1.73 [1.59–1.89]** |
| Major adverse cardiovascular event | | | | | |
| 0 points | 251,125 | 20,431 (8.1) | Ref | Ref | Ref |
| 1 point | 160,418 | 27,498 (17.1) | **1.57 [1.54–1.60]** | **1.45 [1.42–1.48]** | **1.20 [1.18–1.23]** |
| 2 points | 45,402 | 11,728 (25.8) | **2.22 [2.17–2.28]** | **1.97 [1.92–2.03]** | **1.37 [1.32–1.41]** |
| 3 points | 8127 | 3064 (37.7) | **3.34 [3.21–3.48]** | **2.85 [2.73–2.97]** | **1.55 [1.48–1.63]** |
| 4 points | 1101 | 558 (50.7) | **4.68 [4.25–5.16]** | **3.78 [3.42–4.17]** | **1.56 [1.40–1.74]** |
| Cardiovascular disease specific mortality | | | | | |
| 0 points | 254,150 | 1432 (0.6) | Ref | Ref | Ref |
| 1 point | 171,958 | 2740 (1.6) | **1.76 [1.64–1.88]** | **1.58 [1.47–1.69]** | **1.32 [1.22–1.42]** |
| 2 points | 58,518 | 2153 (3.7) | **3.24 [3.01–3.48]** | **2.81 [2.60–3.03]** | **1.83 [1.67–2.00]** |
| 3 points | 13,735 | 1030 (7.5) | **5.69 [5.20–6.23]** | **4.67 [4.25–5.13]** | **2.17 [1.92–2.45]** |
| 4 points | 3187 | 419 (13.2) | **8.87 [7.84–10.03]** | **6.80 [5.98–7.74]** | **2.08 [1.76–2.46]** |
| Cancer incidence | | | | | |
| 0 points | 236,402 | 30,713 (13.0) | Ref | Ref | Ref |
| 1 point | 146,174 | 26,984 (18.5) | **1.03 [1.02–1.05]** | 1.02 [0.99–1.03] | 0.98 [0.96–1.00] |
| 2 points | 48,696 | 10,192 (20.9) | **1.09 [1.06–1.11]** | **1.07 [1.04–1.09]** | 1.01 [0.98–1.04] |
| 3 points | 10,743 | 2460 (22.9) | **1.19 [1.14–1.25]** | **1.16 [1.11–1.22]** | **1.07 [1.01–1.13]** |
| 4 points | 2334 | 534 (22.9) | **1.25 [1.15–1.37]** | **1.21 [1.11–1.33]** | 1.09 [0.99–1.21] |
| Cancer specific mortality | | | | | |
| 0 points | 254,150 | 5586 (2.2) | Ref | Ref | Ref |
| 1 point | 171,958 | 8211 (4.8) | **1.37 [1.32–1.42]** | **1.29 [1.24–1.34]** | **1.09 [1.05–1.14]** |
| 2 points | 58,518 | 3775 (6.5) | **1.54 [1.48–1.61]** | **1.43 [1.36–1.50]** | **1.17 [1.11–1.24]** |
| 3 points | 13,735 | 1124 (8.2) | **1.72 [1.59–1.85]** | **1.55 [1.43–1.67]** | **1.14 [1.04–1.26]** |
| 4 points | 3187 | 310 (9.7) | **1.91 [1.69–2.16]** | **1.68 [1.48–1.91]** | 1.10 [0.95–1.27] |

Values in bold are statistically significant ($p < 0.05$).
Abbreviations: CI, confidence interval; HR, hazard ratio.
[a] The score is the sum of the following points: 0–4 drugs (0 points), 5–9 drugs (1 point), ≥10 drugs (2 points), non-frail (0 points), pre-frail (1 point), and frail (2 points).
[b] Adjusted for age, sex, years of education, income, Townsend deprivation index, and disability allowance.
[c] Adjusted for variables of model 1, physical activity, smoking status, alcohol consumption, BMI, and waist circumference.
[d] Adjusted for variables of model 2, eGFR, systolic blood pressure, diastolic blood pressure, LDL, HDL, $HbA_{1c}$, CRP, number of comorbidities, and 14 frequently seen comorbidities (including hypertension, cardiac insufficiency, coronary heart disease, history of stroke (excluded from the major adverse cardiovascular event analyses), atrial fibrillation, chronic obstructive pulmonary disease, type 2 diabetes mellitus, depression, chronic pain, gastrointestinal illness, chronic kidney disease, cancer (excluded from the cancer incidence analyses), anemia, and hypothyroidism).

## 4. Discussion

In this large-scale cohort study in more than half-million participants of the UK Biobank, an increasing FI and number of medications at baseline were significantly and independently associated with increased risks for all-cause mortality, MACE, and CVD specific mortality. As expected, frailty and polypharmacy were not or only weakly associated with cancer incidence and cancer mortality. Furthermore, associations of polypharmacy with MACE, cardiovascular mortality, and all-cause mortality were stronger among frail and pre-frail participants than among non-frail participants. No prominent age and sex differences were observed speaking for robust results for males, females, and the total age range of the UK Biobank, which was with few exceptions 40–69 years.

Previous studies aiming to construct frailty in the UK Biobank adopted different methods. For more detailed discussion, see Appendix Text A6.

The associations of polypharmacy and frailty with MACE as well as all-cause and CVD-specific mortality have been extensively studied previously and their results agree with ours regarding statistically significant associations with these outcomes [32–37]. Further detailed discussion is described in Appendix Text A7.

Observational studies on polypharmacy and frailty are highly prone to residual confounding [35,38], which why we took utmost care to address this risk of bias. We adjusted for many potential confounders in model 3 and checked the effectiveness of the control for confounding with the negative control outcomes cancer incidence and cancer specific mortality, which are likely not causally related to polypharmacy and frailty [39]. Since no or only weak associations of polypharmacy and frailty with cancer incidence and cancer specific mortality were observed in model 3, we are confident that the associations obtained for MACE, CVD specific mortality and all-cause mortality are not biased by residual confounding to any relevant extent.

An important aspect of causality assessment is a dose-response relationship. In accordance with previous studies [20,40,41], we also observed such a dose-response relationship between the number of drugs used as well as the FI with all-cause mortality, MACE, and CVD specific mortality. For the analysis of the FI, the dose-response relationship with these outcomes was clearer in model 2 (adjusted for age, sex, socioeconomic and lifestyle factors) than in model 3 (adjusted for disease-related factors). In model 3, a ceiling effect was observed near the FI cut-off from pre-frailty to frailty, implying that the risks for adverse outcomes were similar in pre-frail and frail participants. Although previous relevant studies reported rather linear dose-response relationships between the continuous FI and all-cause mortality [40,41], they mainly recruited older study participants and adjusted for a covariate set similar to the one of our model 2. Therefore, future studies including a middle-aged population and adjusting for more disease-related factors are needed to corroborate findings for the dose-response relationship between FI, MACE, and mortality outcomes.

Five previous studies specifically addressed how frailty and polypharmacy interact with each other with respect to adverse health outcomes [13–17]. Bonaga et al. [13] and Midão et al. [15] observed that polypharmacy had a stronger association with mortality in pre-frail and frail participants than in non-frail participants. Poudel et al. [17] pointed out that frailty was associated with adverse health outcomes within each polypharmacy category, and the lowest overall incidence was among robust patients prescribed with 10 or more drugs. In contrast, Porter et al. [16] obtained a lower HR for the association of polypharmacy and mortality among frailer individuals compared to non-frail ones in a specific study population with cognitive impairment. Chen et al. [14] assessed the joint association of polypharmacy and frailty status with all-cause mortality. The adjusted relative risks [95 % CI] were 1.58 [1.52–1.64], 2.70 [2.60–2.80], 4.62 [4.44–4.82], and 6.81 [6.50–7.13] in the fit, mild, moderate, and severe frailty groups with polypharmacy compared to fit patients without polypharmacy, respectively. However, the cited studies mainly included study participants aged ≥65 years. Our study is the first with mainly middle-aged older adults and our results were in line with the results of 4 out of 5 of the previous studies by observing stepwise increasing HRs for the joint association of polypharmacy and frailty status, and observing higher HRs for the associations of polypharmacy with all-cause mortality, MACE, and CVD specific mortality in pre-frail and frail compared to non-frail participants. Thus, our findings indicate that there might be a need to identify polypharmacy and frailty already in middle-aged adults aged 40 years and older and to take appropriate intervention measures to reduce their cardiovascular risk.

Despite its unique strengths, we acknowledge that there are some limitations in our study, thus our findings should be interpreted with caution. As what we stated above, we think residual confounding cannot explain the main findings in our study. However, we had no information on medication adherence and changes of prescriptions over time. Furthermore, frailty and the covariates were only assessed at baseline, which has most likely led to an underestimation of effect estimates. Another aspect that could have led to misclassification of frailty state is that although the same age distribution was obtained, the study population of the UK Biobank is healthier than the one of the ESTHER study due to recruitment differences (low response rate in the UK Biobank) [42]. Therefore, choosing cut-offs for the FI in the UK Biobank by using the ESTHER study as the reference population might not have been optimal. However, the very similar prevalence of pre-frailty and frailty of our approach and the one of Hanlon et al. [19] in the UK Biobank was reassuring that our FI cut-off points worked well. An underestimation of effect estimates could also have been resulted from the healthy-user/sick-stopper bias because a new-user design was not possible to apply in this study [43]. Additionally, we simultaneously adjusted our main model for a high number of covariates, which in part were dependent on each other (e.g., the total number of chronic conditions and individual medical conditions). Being aware that this could cause model instability, we have conducted multicollinearity diagnostics and we can confirm that the fully adjusted model is stable (all correlation coefficients are below 0.8, all variation inflation factors are below 10 and no eigenvalues are near zero). Besides, our study was conducted using data from the UK Biobank and the generalizability of its results to other countries may be limited.

## 5. Conclusions

In this large-scale cohort study in more than half-million participants in the UK Biobank, increasing FI and number of medications were both significantly and independently associated with increased all-cause mortality, MACE, and CVD specific mortality. Furthermore, associations of polypharmacy with MACE, cardiovascular mortality, and all-cause mortality were stronger among frail and pre-frail participants than among non-frail participants. No or modest associations of frailty and polypharmacy were observed with cancer incidence and cancer mortality, which suggests the control for confounding was sufficient because an association would not be biologically plausible. Although some aspects of our results suggest a causal relationship of polypharmacy and frailty with all-cause mortality, MACE, and CVD specific mortality (temporality, low risk of confounding, and dose-response relationship), it needs to be stated causality can generally not be ascertained in observational studies. Further well-designed randomized controlled deprescribing trials are necessary to assess potential positive effects of reducing polypharmacy. While the results of such trials are being awaited, our results highlight the need for careful prescribing practices aiming to avoid polypharmacy not only in older but also middle-aged patients. Furthermore, our study shows that a frailty assessment can identify people with particularly high risks for MACE and all-cause mortality when they are exposed to polypharmacy.

## Contributors

Li-Ju Chen substantially contributed to the conception and design of the study, was primarily responsible for the acquisition and analysis of data, including performing the statistical analyses, and was actively involved in drafting the manuscript and revising it critically for important intellectual content.

Sha Sha provided significant contributions to the interpretation of results and critically reviewed the manuscript for key intellectual content during its advanced stages.

Hermann Brenner provided significant contributions to the interpretation of results and critically reviewed the manuscript for key intellectual content during its advanced stages.

Ben Schöttker substantially contributed to the conception and design of the study, and was actively involved in drafting the manuscript and revising it critically for important intellectual content. All authors have given final approval of the version to be published. L.-J.C. and B.S. take responsibility for the integrity and accuracy of the data analysis.

## Funding

UK Biobank was established by the Wellcome Trust, Medical Research Council, Department of Health, Scottish government, and Northwest Regional Development Agency. It has also had funding from the Welsh assembly government and the British Heart Foundation. The sponsors had no role in data acquisition or the decision to publish the data.

## Ethical approval

UK Biobank received ethical approval from the North West Multicentre Research Ethics Committee (REC reference: 11/NW/03820). UK Biobank is conducted in accordance with the 1964 Helsinki declaration and its later amendments.

## Provenance and peer review

This article was not commissioned and was externally peer reviewed.

## Research data (data sharing and collaboration)

There are no linked research data sets for this paper. Data from the UK Biobank (https://www.ukbiobank.ac.uk/) is available to researchers on application. This research was conducted using the UK Biobank's data under application 89,329. Results from UK Biobank are routinely disseminated to study participants via the study website and Twitter feed.

## Declaration of competing interest

The authors declare that they have no competing interest.

## Acknowledgments

We are thankful to the study participants featured in this manuscript.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.maturitas.2024.107998.

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