Osteoporosis and its association with cardiovascular disease, respiratory diseases and cancer – Findings from the UK Biobank prospective cohort study

Irene Rodríguez-Gómez PhD [1,2,3], Stuart R Gray PhD [3], Frederick K. Ho PhD [4], Fanny Petermann-Rocha MSc [3,4], Paul Welsh PhD [3], John Cleland MD, PhD [5], Stamatina Iliodromiti MD, PhD [6], Ignacio Ara PhD [1,2], Jill Pell MD, PhD [3], Naveed Sattar MD, PhD [4], Lyn D. Ferguson MD, PhD [4]*, Carlos Celis-Morales PhD [3,7,8]*

1. GENUD Toledo Research Group, Universidad de Castilla-La Mancha, Toledo, Spain
2. CIBER of Frailty and Healthy Aging (CIBERFES), Madrid, Spain
3. Institute of Cardiovascular and Medical Scienses, BHF Glasgow Cardiovascular Research Centre, Glasgow, G12 8TA
4. Institute of Health and Wellbeing, University of Glasgow, Glasgow, G12 8RZ
5. Robertson Centre for Biostatistics, Institute of Health and Wellbeing, University of Glasgow, Glasgow Royal Infirmary, Glasgow, United Kingdom.
6. Centre for Women's Health, Institute of Population Health Sciences, Queen Mary University London, London, United Kingdom
7. Centro de Investigación en Fisiología del Ejercicio (CIFE), Universidad Mayor, Santiago 7510041, Chile.
8. Grupo de Estudio en Educación, Actividad Física y Salud (GEEAFyS), Universidad Católica del Maule, Talca 3480112, Chile.

*LDF and CCM contributed equaly and are consider joint-senior authors

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Corresponding author:

Dr. Carlos Celis-Morales
BHF Glasgow Cardiovascular Research Centre.
Institute of Cardiovascular and Medical Sciences
University of Glasgow
Glasgow, G12 8TA
United Kingdom
Tel: + 44 141 3304201
Email: Carlos.Celis@glasgow.ac.uk

Disclosures

The authors report no conflict of interest.

Author Contributions

IRG, LDF and CCM postulated the research question and study design. SRG, FKH, FPR, PW, JC, SI, IA, JP and NS helped with implementation. CCM, FH provided statistical expertise and IRG conducted the primary statistical analysis. IRG, LDF and CCM wrote the manuscript. All authors interpreted the results and contributed to refinement of the study protocol and approved the final manuscript. LDF and CCM contributed equaly and are consider joint-senior authors.

Data availability statements

Data from the UK Biobank are available on application. Researchers can apply to use the UK Biobank resource and access the data used. No additional data are available.

Abstract

This study aimed to investigate sex-specific associations of osteoporosis with incidence and mortality from cardiovascular disease (CVD), respiratory diseases, and cancer, as well as with all-cause mortality. In total, 305,072 participants (53% women) of UK Biobank were included in this study. Self-reported diagnosis of osteoporosis at baseline was the exposure of interest. CVD, respiratory disease, including chronic obstructive pulmonary disease (COPD), all cancer, prostate and breast cancer incidence and mortality, as well as all-cause mortality, were the outcomes. Associations between osteoporosis and health outcomes were investigated using Cox-proportional models. In men, osteoporosis was associated with a higher incident risk of all respiratory diseases (HR: 1.26 [95% CI: 1.06 to 1.50] including COPD (HR: 1.82 [1.38 to 2.40]). Men with osteoporosis also had a higher mortality risk from all-causes (HR: 1.71 [1.38 to 2.11]), CVD (HR: 1.68 [1.19 to 2.37]), respiratory disease (HR: 2.35 [1.70 to 3.24]) and COPD (HR 3.64 [2.24 to 5.91]). These associations persisted after adjustment for age, body mass index (BMI), and comorbidities. Women with osteoporosis had a higher risk of incident CVD (HR: 1.24 [1.97 to 1.44], respiratory diseases (HR 1.23 [1.13 to 1.33]) and COPD (HR 1.29 [1.10 to 1.52]). Women with osteoporosis also had a higher mortality risk from respiratory disease (HR: 1.31 [1.00 to 1.72]) and breat cancer (HR 1.60 [1.14 to 2.26]). Compared to women, men with osteoporosis had a higher risk of all-cause mortality, mortality from respiratory diseases including COPD, and cancer incidence. Osteoporosis was strongly associated with respiratory disease, including COPD, in both men and women, even after full adjustment for covariates; although, men with osteoporosis experienced a higher risk of adverse outcomes than women.

Keywords: mortality, COPD, CVD, bone, risk

Introduction

Osteoporosis affects over 200 million people worldwide [1], and is around 6-fold more common in women than men [2]. Osteoporosis is a systemic skeletal disorder characterized by low bone mineral density and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility [3]. The condition is consdered a public health problem by healthcare authorities because it is associated with an increased risk of fractures [4], which are associated with poorer quality of life, higher disability, institutionalization, and excess mortality [5].

Although previous studies have investigated the association of osteoporosis with chronic diseases including cardiovascular diseases (CVD), respiratory diseases, and cancer [6,7], most of these studies have focused on women with an existing history of osteoporotic fractures, post-menopausal women or older populations [8-17]. With limited evidence available in healthy middle-age individuals and in men, large cohort studies including these populations and a more in-depth analysis of cause-specific incidence and mortality beyond all-cause mortality is required [6,7,18]. Therefore, the present study aimed to investigate the sex-specific associations of osteoporosis with incidence and mortality from CVD, respiratory diseases, and cancer as well as all-cause mortality using data from the UK Biobank prospective cohort study.

Methods

Study design and Participants

The UK Biobank is a prospective, population-based cohort study conducted in 22 assessment centres across England, Wales, and Scotland. A total of 502,536 participants (37-73 years) were recruited from the general population between 2007 and 2010 (5.5%

response rate). Participants completed a touch screen questionnaire, had physical measurements taken, and provided biological samples at their baseline assessment visit, as described in detail elsewhere [19,20]. The outcomes in the current study were all-cause mortality, and incidence of and mortality from cancer, CVD, and respiratory diseases, with the exposure variable being self-reported physician-diagnosis of osteoporosis. Socio-demographic factors (age, sex, ethnicity and area-based socioeconomic status), smoking status, body mass index, systolic blood pressure, medications for CVD, self-reported physical activity time and dietary intake were treated as potential confounders.

Outcomes

Death certificates held within the National Health Service Information Centre (England and Wales) and the National Health Service Central Register Scotland (Scotland) provided dates of deaths. Date and cause of hospital admissions were obtained via record linkage to Health Episode Statistics (England and Wales) and Scottish Morbidity Records (Scotland). Further information about data linkage can be found at http://content.digital.nhs.uk/services. Hospital admissions follow-up was available until June 2020 in England and March 2017 in Wales and Scotland. Mortality was available until June 2020 for the whole cohort. Therefore, incident disease and mortality follow-up were censored at these dates respectively, or on the date of death, if earlier. ~~Follow-up was censored at the latest date for which linked data were available - 31st January 2018 for participants from England and Wales and 30th November 2016 for participants from Scotland - or date of death if this occurred earlier, or the first date of hospitalisation for the outcome of interest (for incident outcomes only).~~ We defined incident events as a hospital admission or death with a relevant ICD-10 (international classification of diseases, 10th revision) code defined as: CVD (I05-I89), respiratory diseases (J09-J98

and I26-I27), chronic obstructive pulmonary disease (COPD) (J44), breast cancer (C50), prostate cancer (C61) and all-cause cancer (C0.0-C9.9, D3.7-9, D4.0-8).

Covariates

Age, ethnicity and education were self-reported and collected through touch-screen questionnaires. Socioeconomic status was measured using the Townsend deprivation score, an area-based index of material deprivation derived from Census information on housing, employment, social class and car availability [17]. Anthropometric measurements were obtained by trained personnel following standard operating procedures and using calibrated equipment. Weight was measured, without shoes and outdoor clothing, using the Tanita BC 418 body composition analyser. Height was measured, without shoes, using the wall-mounted SECA 240 height measure. Body mass index (BMI) was calculated from weight (in kilograms) divided by square of height (in meters). The World Health Organization's criteria were used to classify BMI into categories of underweight (<18.5 kg/m^2), normal weight (18.5 to 24.9 kg/m^2), overweight (25 to 29.9 kg/m^2) and obese (≥30 kg/m^2). Waist circumference was measured midway between lowest rib margin and iliac crest, in a horizontal plane, using a non-elastic SECA 200 tape measure. Further details can be found in the UK Biobank protocol (https://www.ukbiobank.ac.uk/key-documents/).

Smoking status was categorized into never, former or current smoker. Physical activity was collected through the International Physical Activity Questionnaire (IPAQ) short form, and total physical activity was computed as the sum of walking, moderate and vigorous activity, measured as metabolic equivalents (MET-min/week) [18]. We derived total time spent in sedentary behaviours from the sum of self-reported time spent driving, using a computer, and watching television. Average sleep duration was self-reported and

156 further classified as short (<7 h/day), normal (7-9 h/day) or long (>9 h/day). Handgrip
157 strength was measured as previously described [21], and the mean of the right and left
158 values was expressed in absolute units (kg) for subsequent analysis. Dietary information
159 was collected via the Oxford WebQ, a web-based 24-hour recall questionnaire that was
160 developed specifically for use in large population studies [22,23]. Medical history of health
161 conditions diagnosed by a physician (menopause, depression, stroke, angina, heart attack,
162 hypertension, cancer, diabetes, hypertension, COPD, hypothyroidism, hyperthyroidism,
163 eating disorders, Cushing's syndrome, rheumatoid arthritis, inflammatory bowel disease,
164 Crohn's disease, ulcerative colitis, liver disease, kidney chronic disease, bone fractures,
165 and femoral fractures and longstanding illness) was collected using the self-completed
166 baseline assessment questionnaire. Medication use was also self-reported and included
167 diuretic medications, vitamin or calcium and micronutrients supplementation,
168 corticosteroid, hormone replacement therapy (HRT). Biochemical assays was measured
169 at the baseline assessment visit, including C-reactive protein and 25(OH)D (a measure of
170 vitamin D status) were performed at a central laboratory on around 480,000 samples.
171 Further details of these measurements can be found in the UK Biobank Data Showcase
172 and Protocol (https://www.ukbiobank.ac.uk/key-documents/). Vitamin D was imputed
173 with the minimum detectable value (10 nmol/L) if it was below the limit of detection, and
174 the maximum detectable value (375 nmol/L) if too high for detection.
175
176 ***Ethics***
177 The UK Biobank study was approved by the North West Multi-Centre Research Ethics
178 Committee; participants provided written informed consent for data collection, analysis,
179 and record linkage. This study is part of UK Biobank project 7155 (NHS National
180 Research Ethics Service 16/NW/0274).

181

182 ***Statistical analyses***

183 Participant characteristics were presented according to presence or absence of
184 osteoporosis using means and standard deviation (SD) for quantitative variables and
185 percentages for categorical variables. The association between osteoporosis and health
186 outcomes, for men and women, were investigated using Cox-proportional hazard models
187 with years of follow up as the time varying co-variate. The results are reported as hazard
188 ratios (HR) and their 95% confidence intervals (95% CI). The proportional hazard
189 assumption was checked using Schoenfeld residuals. Participants who already had the
190 disease outcome of interest at baseline were excluded from the analysis (i.e. participants
191 with prevalent CVD at baseline were excluded from analysis on CVD incidence and
192 mortality). In addition, sensitivity analyses were conducted where participants who had
193 any of the disease outcomes of interest at baseline (CVD, cancer and respioratory
194 diseases) were excluded from all analyses (Supplementary table S1). Furthermore, all
195 analyses were performed using a 2-year landmark analysis to exclude participants who
196 experienced events within the first two years of follow-up. Finally, to assess whether the
197 associations between osteoporosis and health outcomes differed by sex, sex*risk factor
198 interaction terms were included in the Cox models, which can be interpreted as the ratio
199 of HR among men to HR among women.

200

201 For all these analyses, we ran three incremental models that included different covariates.
202 Model 0 included sociodemographic covariates: age, deprivation index, ethnicity and
203 education. Model 1 also included lifestyle factors: BMI categories, smoking, grip
204 strength, total physical activity, sedentary time, sleep duration and dietary intake of dairy
205 products, alcohol, fruit and vegetables, red meat and processed meat. Model 2 was the

same as Model 1 but also included health markers: systolic blood pressure, C-reactive protein, total cholesterol, medication (including diuretic), vitamin D blood concetration, vitamin or calcium and micronutrients supplementation, corticosteroid, hormone replacement therapy (HRT), bone fractures and prevalent comorbidities including hypothyroidism, hyperthyroidism, eating disorders, Cushing's syndrome, diabetes, rheumatoid arthritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, liver disease, kidney chronic disease, and femoral fractures at baseline. In this last model, hypogonadism and menopause were also included as sensitivity analyses for men and women, respectively. Statistical analyses were performed using the statistical software STATA 14 (StataCorp LP). Statistical significance was defined as $p<0.05$.

Results

Of the 502,536 participants recruited to UK Biobank, 305,072 (52.9% women) were eligible for inclusion in the 2-year landmark analyses and had full data available. The mean follow-up period was 9.2 (range 7.9-11.0) years for mortality and 8.9 (range 4.6-11.0) years for disease-specific incidence. Over the follow-up period, 28,411 (5.7%) participants developed CVD, 89,174 (17.8%) respiratory disease [16,832 (3.4%) COPD], and 69,675 (13.9%) cancer [10,586 (2,1%) breast cancer and 9,944 (2,0%) prostate cancer]. In addition, 31,073 (6.2%) participants died: 10,774 (2.1%) from CVD, 7,422 (1,5%) from respiratory disease [1,985 (0.4%) from COPD], and 17,154 (3.4%) from cancer [1,422 (0.3%) from breast cancer and 1,127 (0.2%) from prostate cancer].

Table 1 summarises the main characteristics of the participants by presence of osteoporosis and sex. In summary, people with osteoporosis were older, more likely to be

underweight, report short sleep duration, and were more likely to use corticosteroids and vitamin or mineral supplement use. Individuals with osteoporosis also had a higher prevalence of comorbidities including hypothyroidism, hyperthyroidism, Cushing's syndrome, rheumatoid arthritis, Crohn's disease, ulcerative colitis, liver disease, chronic kidney disease, CVD, COPD and cancer. In addition, men with osteoporosis had a higher prevalence of current smoking, were more likely to report long sleep duration and hypogonadism, and spent less time physically active than participants without osteoporosis. A greater proportion of women with osteoporosis had a history of eating disorders and were post-menopausal compared to women without osteoporosis.

The associations of osteoporosis with incidence and mortality outcomes in men are reported in **Figure 1.** After full adjustment for age, BMI, and multiple covariates, osteoporosis in men was associated with an 71% higher risk of all-cause mortality. Risk of CVD mortality was 68% higher in men with osteoporosis compared to those without the condition. The incidence and mortality risk for all respiratory diseases was 1.26 and 2.35 fold higher in men with osteoporosis compared to men without osteoporosis and, for COPD specifically, was 1.82- and 3.64–fold higher respectively in men with versus without osteoporosis. Cancer incidence, except to the fully adjusted model, was 1.26–fold higher in men with osteoporosis in comparison to their counterparts without osteoporosis. No associations were observed for cancer mortality or, more especially, for prostate cancer incidence and mortality in men. When these analyses were re-run excluding participants with prevalent diseases at baseline the results held true for all-cause mortality, respiratory incidence and mortality, COPD incidence and mortality and cancer incidence in men, but the association was only significant in the minimally adjusted models for CVD mortality (**Supplementary Table S1**).

Women with osteoporosis showed in the initial analysis with the minimally adjusted model that they had an 15% higher risk of all-cause mortality (**Figure 2**). The incidence of CVD was 24% higher in women with osteoporosis compared to those without the condition after adjustment for confounders. The incidence and mortality risk for all respiratory diseases was 1.23- and 1.31-fold higher in women with osteoporosis compared to men without osteoporosis and, for COPD specifically, was 1.29- and 1.63-fold higher respectively, although for mortality risk only the least adjusted model was significant. Risk of breast cancer mortality was 60% higher in women with osteoporosis. No associations were observed for all cancer mortality or incidence. When these analyses were re-run, excluding participants with prevalent diseases at baseline, the results remained similar for CVD incidence, respiratory mortality and incidence and COPD incidence in women (**Supplementary Table S1**).

The male:female risk ratios are reported in **Figure 3.** Compared to women, men with osteoporosis had a higher risk of all-cause mortality and a higher risk of mortality from respiratory diseases and COPD. Men with osteoporosis also had a higher risk of cancer incidence compared to women.

Discussion

The current study examined the associations between osteoporosis and a range of fatal and non-fatal health outcomes in men and women participating in UK Biobank, a large prospective population-based study. Our findings demonstrated differences by sex. Compared with women, osteoporosis in men was associated with a wider range of adverse

heath outcomes and had stronger associations. These findings suggest that drivers to osteoporosis are more harmful to general health in men than in women.

Our findings on all-cause mortality are in agreement with previous studies conducted in patients with osteoporosis, such as the Tromso study, where both men and women with osteoporosis had a higher risk of all-cause mortality [6]. However, no sex differences were observed between osteoporosis and all-cause mortality, probably due to the relatively small sample size of the Tromso study (n=6,565 participants aged 50-79 years). Consistent with our findings, previous systematic reviews have reported a higher risk of mortality for men after suffering from bone fracture compared to women [9,10]. Most of the studies included in these systematic reviews evaluated risk of death associated with osteoporotic fractures. However, one study conducted by Gutzwiller et al. (2018) showed that all-cause mortality was higher in men than women independent of bone fractures [11].

Concerning cause-specific incidence and mortality, previous studies have reported that men and women with osteoporosis have a higher risk of respiratory diseases [24] [25]. Looker et al., using data from 3,275 older, non-Hispanic white adults from the third National Health and Nutrition Examination Survey, reported that participants with osteoporosis had a 38% increased risk of COPD mortality compared to those without osteoporosis; however, this study did not assess men and women separately [24]. Another study conducted in 5,779 men and women participating in the Rotterdam Study reported a strong association between bone mineral density and respiratory disease mortality in men (HR: 2.15 [95% CI: 1.05; 4.42]) and women (HR 1.72 [95% CI: 1.16; 2.57]) [25]. Our data add to these findings by confirming an association when including non-fatal as well as fatal respiratory disease. Also, we were able to show that the associations with

306 respiratory disease were independent of age, BMI, and multiple comorbidities. Moreover,
307 our study provided novel evidence that men with osteoporosis experienced a higher risk
308 than women for respiratory and COPD incidence and mortality.
309
310 Osteoporosis was associated with a higher mortality risk from CVD in men only.
311 However, when the analyses were restricted to participants without any chronic disease
312 at baseline (CVD, respiratory diseases and cancer) the association in men remains
313 significant only in the minimally adjusted model, suggesting they may have been due to
314 confounding and reverse causation. These findings differed from studies which reported
315 an association between osteoporosis and CVD outcomes [26,27]. However, these
316 differences may reflect adjustment for fewer potential confounders, not performing a 2-
317 year landmark analysis, or inclusion of people with existing chronic conditions, in
318 contrast with our study. Our study also demonstrated that CVD incidence was higher only
319 in osteoporotic women, which in this case still remains when excluding participants with
320 prevalent diseases at baseline. Similar results from the Multiple Outcomes of Raloxifene
321 Evaluation (MORE) trial also indicated that osteoporosis was a strong predictor of
322 incident cardiovascular events in postmenopausal women independent of age and other
323 traditional cardiovascular risk factors (adjusted RR = 3.9, 95% CI 2.0-7.7) [26]. Likewise,
324 osteoporosis was also associated with angiographically-determined coronary artery
325 disease in a retrospective study, comprised predominantly of women referred for
326 angiography and bone mineral density assessment [27].
327
328 Previous studies have suggested that cancer, especially breast and prostate cancer, is a
329 risk factor for osteoporosis [28], however, there is limited evidence on whether
330 osteoporosis is a risk factor for cancer [28]. Our findings demonstrated an association

between osteoporosis and increased incidence of cancer in men, although this incidence disappeared when we adjusted for all confounding factors. Similarly, in women the association between osteoporosis and increased risk of breast cancer was also found. In this respect, after excluding participants without any chronic disease at baseline, these associations were no longer significant, but a trend was observed. Considering this and the reported potential risk factor of HRT for breast cancer, especially in older women, which is also commonly prescribed for osteoporosis [29], studies involving a larger sample of participants with both diseases are needed.

Our study show that men with osteoporosis have a higher risk of developing respiratory diseases and COPD and dying from CVD, respiratory diseases and COPD compared with women with osteoporosis. Although the prevalence of osteoporosis is lower in men than in women, diagnosis of osteoposrosis in men should not be overlooked as it is an early indicator of long term morbidity and mortality irrespective of the risk of fractures.

Our study has some limitations. The UK Biobank has been shown to have a "healthy volunteer selection bias" and is not representative of the general population of the UK in several ways; therefore our estimates of prevalence and incidence, such as the low incidence of femoral fracture in this study, may not be generalisable to the UK or overseas population [30], but effect sizes should still be generalisable. Moreover, we could not stratify our analyses by osteoporosis severity or osteopenia. Study strengths include that this is the largest study to address the associations between osteoporosis and a wide range of outcomes – cardiovascular and respiratory disease, cancer and all-cause mortality - by sex and adjusted by a large number of confounders. In addition, by performing a 2-year

land-mark analysis and sensitivity analyses excluding individuals with pre-existing disease, we were able to minimise the impact of reverse causation.

Conclusion

In conclusion, our results show evidence of a strong association of osteoporosis in men with all-cause mortality, as well as incidence and mortality from respiratory disease, in particular COPD. In contrast, these associations were only observed for respiratory incidence and mortality and COPD incidence in women, in addition to the CVD incidence. Importantly, all these associations persisted after comprehensive adjustment for age, BMI, and comorbidities. While CVD mortality risk also appears greater in men with osteoporosis versus those without osteoporosis, this risk is likely mediated at least in part by pre-existing chronic disease; similarly to breast cancer mortality in women. Therefore, compared with women, osteoporosis in men was associated with a wider range of adverse health outcomes and had stronger associations. These findings suggest management of osteoporosis should include screening for associated cardiovascular and respiratory disease risk, especially in men.

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474 **Table 1.** Cohort characteristics by osteoporosis and sex.

	Men				Women			
	Non-Osteoporosis		Osteoporosis		Non-Osteoporosis		Osteoporosis	
Sociodemographics								
Total, n (%)	143251	(47.7)	523	(11.4)	157224	(52.3)	4074	(88.6)
Age (years), mean (SD)	56.9	(8.2)	60.4	(6.8)	56.0	(8.1)	62.2	(5.4)
Deprivation Index, n (%)								
Lower	49489	(34.6)	154	(29.4)	53124	(33.8)	1429	(35.1)
Middle	48130	(33.6)	171	(32.7)	53761	(34.2)	1346	(33.0)
Higher	45632	(31.8)	198	(37.9)	50339	(32.0)	1299	(31.9)
Educational Level, n (%)								
College or University degree	56868	(47.5)	190	(47.6)	60855	(45.8)	1337	(43.1)
A levels/AS levels or equivalent	14933	(12.5)	47	(11.8)	19467	(14.6)	443	(14.3)
O levels/GCSEs or equivalent	27017	(22.6)	88	(22.1)	37391	(28.1)	987	(31.9)
NVQ / HND / HNC or equivalent	20876	(17.4)	74	(18.5)	15250	(11.5)	332	(10.7)
Ethnicity, n (%)								
White	136318	(95.2)	508	(97.1)	149304	(95.0)	3933	(96.6)
South Asian	2835	(2.0)	7	(1.3)	2258	(1.4)	66	(1.6)
Black	1917	(1.3)	3	(0.6)	2581	(1.6)	17	(0.4)
Chinese	345	(0.2)	1	(0.2)	568	(0.4)	9	(0.2)
Mixed background	1836	(1.3)	4	(0.8)	2513	(1.6)	49	(1.2)
Lifestyle								
BMI, n (%)								
Underweight (<18.5)	304	(0.2)	7	(1.3)	1157	(0.7)	111	(2.7)
Normal weight (18.5-<25.0)	37318	(26.0)	205	(39.2)	65102	(41.4)	2130	(52.3)
Overweight (25.0-<30.0)	71869	(50.2)	213	(40.7)	57634	(36.7)	1338	(32.8)
Obese (>30.0)	33760	(23.6)	98	(18.8)	33331	(21.2)	495	(12.2)
Waist circumference (cm),mean (SD)	96.3	(10.9)	95.0	(11.9)	83.8	(12.1)	81.0	(11.2)
Smoking, n (%)								
Never	71065	(49.6)	214	(40.9)	94361	(60.0)	2397	(58.8)
Previous	55819	(39.0)	221	(42.3)	49896	(31.7)	1361	(33.4)
Current	16367	(11.4)	88	(16.8)	12967	(8.3)	316	(7.8)
Dairy Products, n (%)								
Full cream	12302	(8.6)	52	(10.0)	7356	(4.7)	173	(4.2)
Semi-skimmed	97297	(67.9)	324	(62.0)	96197	(61.2)	2333	(57.3)
Skimmed	23987	(16.7)	88	(16.8)	37535	(23.9)	1053	(25.8)
Soya	3731	(2.6)	23	(4.4)	8681	(5.5)	268	(6.6)
Other type	1575	(1.1)	8	(1.5)	2152	(1.4)	76	(1.9)
Never/rarely consumed	4359	(3.1)	28	(5.3)	5303	(3.3)	171	(4.2)
Processed Meat, n (%)								
Never	8000	(8.6)	56	(10.7)	20452	(13.0)	660	(16.2)
Less than once a week	31159	(21.8)	116	(22.2)	60388	(38.4)	1593	(39.1)
Once a week	42779	(29.9)	142	(27.2)	44833	(28.5)	1075	(26.4)
2-4 times a week	52358	(36.5)	177	(33.8)	28873	(18.4)	669	(16.4)
5-6 times a week	7183	(5.0)	23	(4.4)	2154	(1.4)	61	(1.5)
Once or more daily	1772	(1.2)	9	(1.7)	524	(0.3)	16	(0.4)
Red meat (portion/week), mean (SD)	2.2	(1.5)	2.2	(1.6)	1.9	(1.3)	1.9	(1.4)
Fruit and Vegetables (g), mean (SD)	313.7	(197.9)	322.2	(206.9)	361.0	(189.6)	377.4	(197.1)
Alcohol, n (%)								
Daily or almost daily	37278	(26.0)	133	(25.4)	26332	(16.7)	694	(17.0)
Three or four times a week	38724	(27.0)	106	(20.3)	34014	(21.6)	802	(19.7)
Once or twice a week	36968	(25.8)	128	(24.5)	41035	(26.1)	958	(23.5)
One to three times a month	12428	(8.7)	50	(9.5)	20229	(12.9)	462	(11.3)

Special occasions only	9755	(6.8)	47	(9.0)	22302	(14.2)	650	(16.0)
Never	8098	(5.7)	59	(11.3)	13312	(8.5)	508	(12.5)
Sleep, n (%)								
Normal 7-9 h/d	106057	(74.0)	316	(60.4)	118215	(75.2)	2900	(71.2)
Short sleep <7 h/d	35180	(24.6)	157	(30.0)	36620	(23.3)	1099	(27.0)
Long sleep >9 h/d	2014	(1.4)	49	(9.4)	2389	(1.5)	75	(1.8)
TV viewing (h), men (SD)	2.7	(1.5)	1	(0.2)	2.7	(1.5)	2.9	(1.6)
Total PA (min/week), mean (SD)	3088.7	(3359.2)	2672.5	(2996.4)	2656.9	(2751.5)	2659.1	(2736.4)
Handgrip Strength (kg), mean (SD)	39.6	(8.7)	35.1	(9.0)	23.6	(6.1)	20.4	(5.8)
Health								
SBP (mmHg), mean (SD)	140.9	(17.4)	139.2	(18.1)	134.6	(19.1)	137.0	(19.2)
C-reactive protein (mg/L), mean (SD)	2.3	(4.1)	3.2	(5.4)	2.5	(4.1)	2.5	(4.4)
HDL cholesterol (mmol/L), mean(SD)	1.3	(0.3)	1.3	(0.4)	1.6	(0.4)	1.7	(0.4)
Vitamin D (nmol/L), mean (SD)	49.9	(21.2)	58.9	(22.3)	49.6	(20.8)	62.2	(22.3)
Steroid, n (%)	1523	(1.1)	50	(9.6)	1642	(1.0)	152	(3.7)
Vitamin/mineral supplements, n (%)	7714	(5.4)	43	(8.2)	11525	(7.3)	394	(9.7)
Comorbidities, n (%)	0.1	(0.4)	0.3	(0.5)	0.1	(0.4)	0.2	(0.5)
CVD, n (%)	48276	(33.7)	198	(37.9)	38367	(24.4)	1104	(27.2)
COPD, n (%)	2206	(1.5)	25	(4.9)	1935	(1.2)	116	(2.9)
Cancer, n (%)	8527	(6.0)	62	(11.9)	13390	(8.5)	598	(14.7)
Hypothyroidism, n (%)	2256	(1.6)	12	(2.3)	11455	(7.3)	384	(9.4)
Hyperthyroidism, n (%)	450	(0.3)	2	(0.4)	1769	(1.1)	67	(1.6)
Cushing's syndrome, n (%)	3	(0.0)	1	(0.2)	33	(0.0)	5	(0.1)
Femoral fracture, n (%)	24	(0.0)	0	(0.0)	16	(0.0)	0	(0.0)
Eating disorders, n (%)	10	(0.0)	0	(0.0)	198	(0.1)	19	(0.5)
Rheumatoid arthritis, n (%)	939	(0.7)	14	(2.7)	1865	(1.2)	101	(2.5)
Inflammatory bowel disease, n (%)	44	(0.0)	0	(0.0)	52	(0.0)	3	(0.1)
Crohn's disease, n (%)	380	(0.3)	14	(2.7)	457	(0.3)	39	(1.0)
Ulcerative colitis, n (%)	726	(0.5)	19	(3.6)	781	(0.5)	37	(0.9)
Liver disease, n (%)	265	(0.2)	8	(1.5)	261	(0.2)	23	(0.6)
Kidney chronic disease, n (%)	352	(0.3)	8	(1.5)	319	(0.2)	16	(0.4)
Diabetes, n (%)	9004	(6.3)	29	(5.5)	4871	(3.1)	126	(3.1)
Hypogonadism, n (%)	663	(0.5)	5	(1.0)	-		-	
Menopause, n (%)	-		-		93446	(70.1)	3408	(97.3)

BMI, body mass index; CVD, cardiovascular disease; COPD, chronic obstructive pulmonary disease; SBP, systolic blood pressure; C-RP, C-reactive protein; HDL, High-density lipoprotein cholesterol.

Figure legends

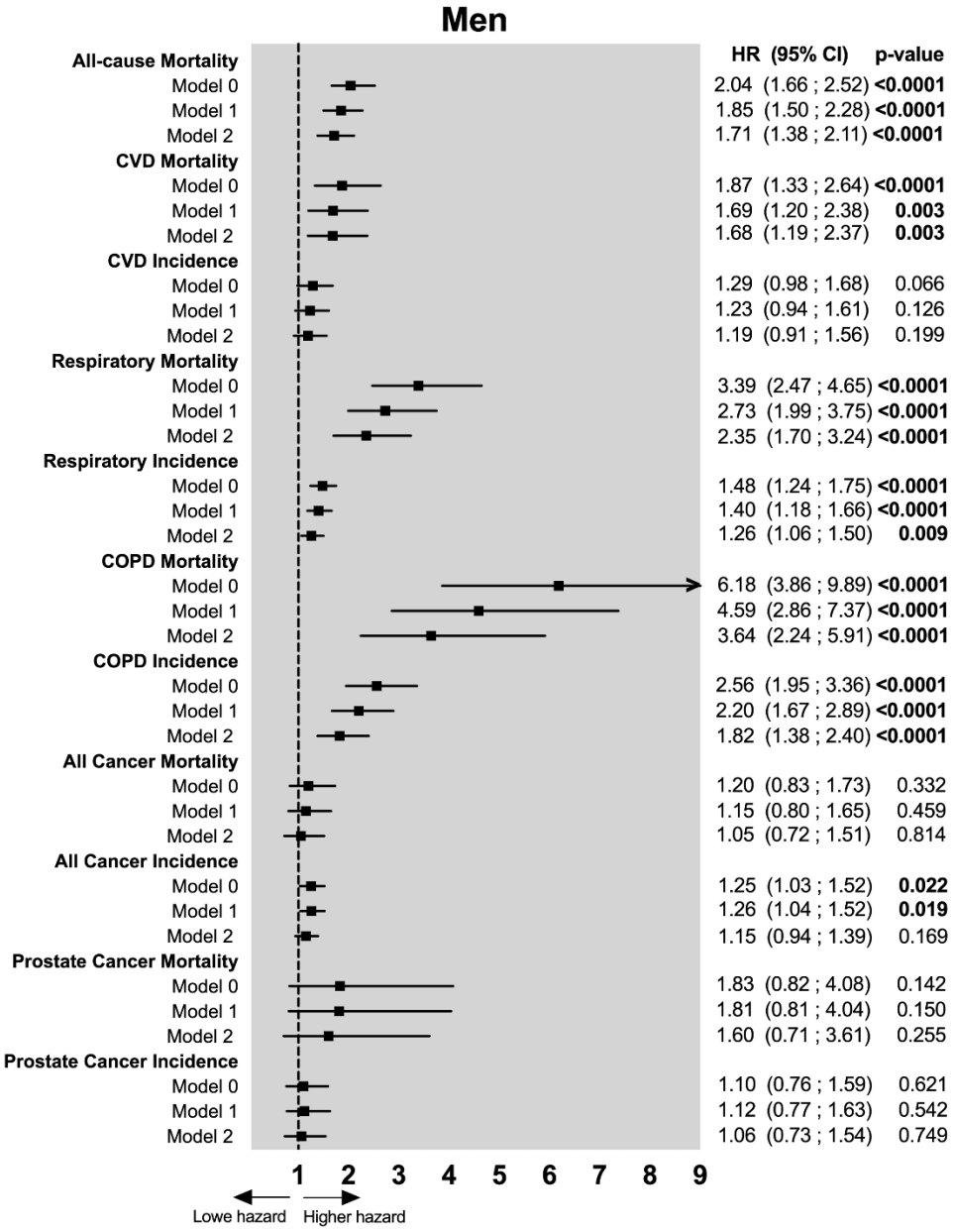


Figure 1. Cox proportional hazard model of the association of osteoporosis with all-cause mortality, CVD, respiratory diseases and cancer mortality and incidence in men.

Data are presented as adjusted HR and 95% CI. The reference group were men without osteoporosis at baseline assessment. Model 0 was adjusted for age, deprivation index, ethnicity and education. Model 1 additionally adjusted by BMI, smoking, grip strength,

total physical activity, sedentary time, sleep duration and dietary intake. Model 2 was adjusted as in model 1 but also included systolic blood pressure, C-reactive protein, cholesterol, medication (including diuretic), vitamin D, vitamin or calcium and micronutrients supplementation, corticosteroid, hormone replacement therapy (HRT), bone fractures, and prevalent comorbidities. Participants with prevalent CVD, respiratory diseases and cancer at baseline were excluded from the analyses if the diiseases was used as an outcome (i.e. for the CVD mortality and incidence outcomes, participants with baseline medical diagnoses of heart diseases were excluded). Significant associations ($p < 0.05$) are highlighted in bold. CVD, cardiovascular disease; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; CI, confidence interval.

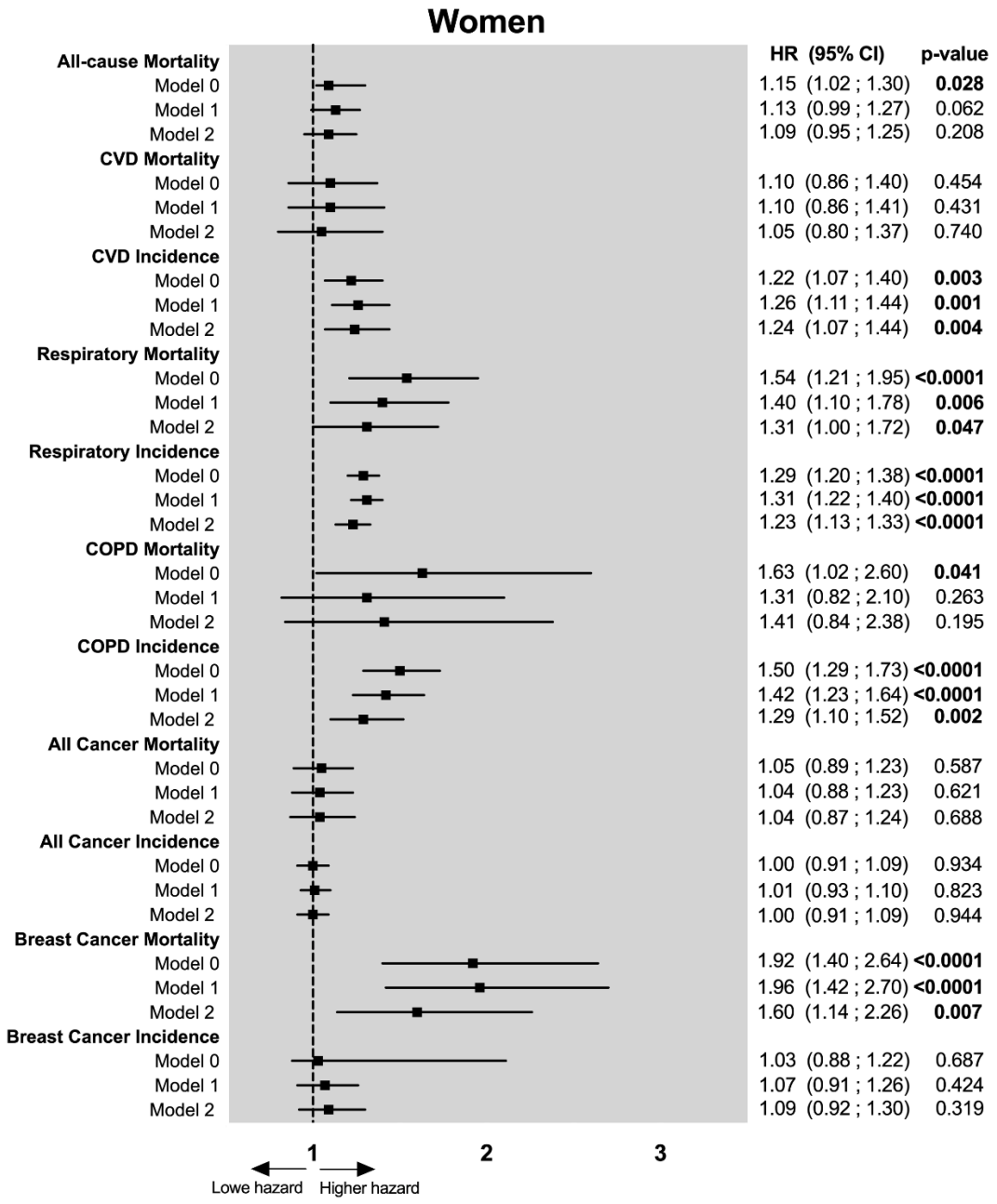
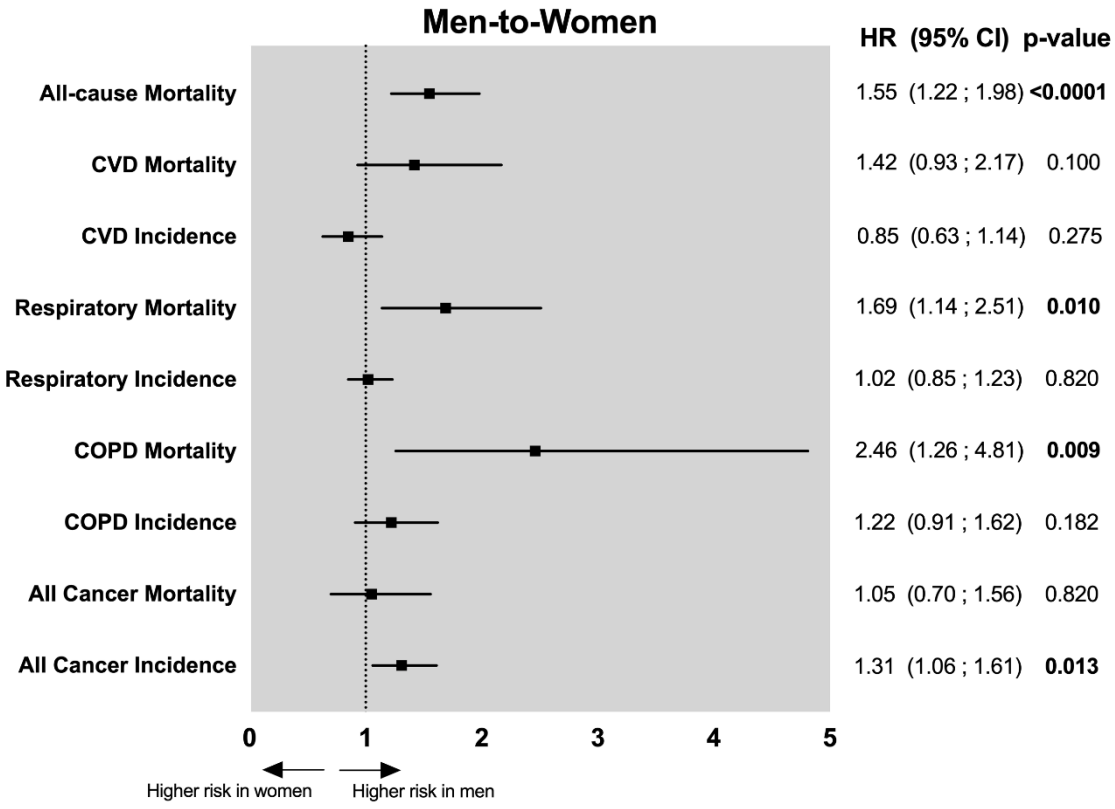


Figure 2. Cox proportional hazard model of the association of osteoporosis with all-cause mortality, CVD, respiratory diseases and cancer mortality and incidence in women.

The reference group were men without osteoporosis at baseline assessment. Model 0 was adjusted for age, deprivation index, ethnicity and education. Model 1 additionally adjusted by BMI, smoking, grip strength, total physical activity, sedentary time, sleep duration and dietary intake. Model 2 was adjusted as in model 1 but also included systolic

blood pressure, C-reactive protein, cholesterol, medication (including diuretic), vitamin D, vitamin or calcium and micronutrients supplementation, corticosteroid, hormone replacement therapy (HRT), bone fractures, menopause and prevalent comorbidities. Participants with prevalent CVD, respiratory diseases and cancer at baseline were excluded from the analyses if the diiseases was used as an outcome (i.e. for the CVD mortality and incidence outcomes, participants with baseline medical diagnoses of heart diseases were excluded). Significant associations ($p< 0.05$) are highlighted in bold. CVD, cardiovascular disease; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; CI, confidence interval.



F*igure 3. Men-to-women HR on all-cause mortality, CVD, respiratory diseases and cancer mortality and incidence.*

Data are presented as ratio of the HR of men-to-women and their 95% CI. Models were adjusted for all covariates included in the model 2. HR above 1 suggests a higher risk in men compared with women, whereas HR below 1 indicates a higher risk in women compared with men. Analyses were adjusted for age, deprivation index, ethnicity, education, BMI, smoking, grip strength, total physical activity, sedentary time, sleep duration, dietary intake, systolic blood pressure, C-reactive protein, cholesterol, medication (including diuretic), vitamin D, vitamin or calcium and micronutrients supplementation, corticosteroid, hormone replacement therapy, bone fractures and prevalent comorbidities. CVD, cardiovascular disease; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; CI, confidence interval

Supplementary Table 1. Cox proportional hazard model of the association with all-cause mortality, CVD, respiratory diseases and cancer mortality and incidence stratified by sex and with participants with prevalent diseases at baseline excluded (CVD, respiratory diseases and cancer).

	Men			Women		
	HR	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**
All-cause Mortality						
Model 0	2.50	(1.85 ; 3.38)	**<0.0001**	1.12	(0.94; 1.35)	0.213
Model 1	2.28	(1.69 ; 3.08)	**<0.0001**	1.09	(0.91 ; 1.10)	0.343
Model 2	2.02	(1.49 ; 2.76)	**<0.0001**	1.12	(0.92 ; 1.36)	0.275
CVD Mortality						
Model 0	1.67	(1.07 ; 2.63)	**0.025**	1.12	(0.86 ; 1.47)	0.397
Model 1	1.57	(0.99 ; 2.46)	0.052	1.14	(0.87 ; 1.49)	0.337
Model 2	1.47	(0.93 ; 2.32)	0.095	1.10	(0.82 ; 1.48)	0.524
CVD Incidence						
Model 0	1.22	(0.88 ; 1.70)	0.231	1.27	(1.11 ; 1.47)	**0.001**
Model 1	1.21	(0.87 ; 1.68)	0.249	1.32	(1.14 ; 1.52)	**<0.0001**
Model 2	1.16	(0.83 ; 1.61)	0.382	1.34	(1.14 ; 1.56)	**<0.0001**
Respiratory Mortality						
Model 0	2.79	(1.92 ; 4.05)	**<0.0001**	1.44	(1.11 ; 1.87)	**0.007**
Model 1	2.31	(1.59 ; 3.36)	**<0.0001**	1.34	(1.03 ; 1.74)	**0.030**
Model 2	2.07	(1.41 ; 3.02)	**<0.0001**	1.29	(0.96 ; 1.74)	0.089
Respiratory Incidence						
Model 0	1.44	(1.20 ; 1.72)	**<0.0001**	1.27	(1.18 ; 1.37)	**<0.0001**
Model 1	1.37	(1.15 ; 1.65)	**0.001**	1.29	(1.20 ; 1.39)	**<0.0001**
Model 2	1.26	(1.05 ; 1.51)	**0.012**	1.23	(1.13 ; 1.33)	**<0.0001**
COPD Mortality						
Model 0	4.31	(2.14 ; 8.69)	**<0.0001**	1.22	(0.62 ; 2.39)	0.564
Model 1	3.47	(1.71 ; 7.01)	**0.001**	1.02	(0.52 ; 2.02)	0.945
Model 2	3.02	(1.47 ; 6.21)	**0.003**	1.09	(0.51 ; 2.31)	0.825
COPD Incidence						
Model 0	2.43	(1.79 ; 3.31)	**<0.0001**	1.40	(1.19 ; 1.65)	**<0.0001**
Model 1	2.16	(1.59 ; 2.94)	**<0.0001**	1.35	(1.14 ; 1.59)	**<0.0001**
Model 2	1.88	(1.37 ; 2.57)	**<0.0001**	1.22	(1.01 ; 1.47)	**0.039**
All Cancer Mortality						
Model 0	1.17	(0.77 ; 1.79)	0.451	0.96	(0.78 ; 1.17)	0.661
Model 1	1.15	(0.75 ; 1.74)	0.522	0.96	(0.78 ; 1.18)	0.693
Model 2	1.11	(0.73 ; 1.70)	0.617	1.03	(0.83 ; 1.27)	0.803
All Cancer Incidence						
Model 0	1.26	(1.03 ; 1.56)	**0.028**	0.95	(0.86 ; 1.05)	0.340
Model 1	1.28	(1.04 ; 1.58)	**0.022**	0.97	(0.88 ; 1.07)	0.533
Model 2	1.20	(0.97 ; 1.48)	0.090	0.98	(0.88 ; 1.09)	0.657
Breast/Prostate Cancer Mortality						
Model 0	1.02	(0.25 ; 4.09)	0.978	1.57	(0.89 ; 2.75)	0.117
Model 1	1.04	(0.26 ; 4.19)	0.952	1.64	(0.93 ; 2.87)	0.087

Model 2	1.10	(0.27 ; 4.45)	0.895	1.65	(0.93 ; 2.94)	0.089
Breast/Prostate Cancer Incidence						
Model 0	1.00	(0.65 ; 1.53)	0.982	0.91	(0.74 ; 1.11)	0.335
Model 1	1.02	(0.67 ; 1.57)	0.921	0.94	(0.77 ; 1.15)	0.572
Model 2	0.99	(0.65 ; 1.53)	0.980	0.99	(0.80 ; 1.23)	0.951

For these analyses, we ran three incremental models that included different covariates. Model 0 included sociodemographic covariates: age, deprivation index, ethnicity and educational level. Model 1 was adjusted as in model 0 but also included lifestyle factors: BMI, smoking, grip strength, total physical activity, sedentary time, sleep duration and dietary intake of dairy products, alcohol, fruit and vegetables, red meat and processed meat. Model 2 was the same as Model 1 but also included health markers: systolic blood pressure, C-reactive protein, cholesterol, medication (including diuretic), vitamin D, vitamin or calcium and micronutrients supplementation, corticosteroid, hormone replacement therapy (HRT), bone fractures and prevalent comorbidities including hypothyroidism, hyperthyroidism, eating disorders, Cushing's syndrome, diabetes, rheumatoid arthritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, liver disease, kidney chronic disease, and femoral fractures at baseline. In this last model, hypogonadism and menopause were also included as sensitivity analyses for men and women, respectively. To minimise the potential contribution of reverse causality, all analyses were conducted using a landmark analysis excluding events occurring in the first 2-years of follow-up. Moreover, all participants with prevalent CVD, respiratory diseases and cancer at baseline were excluded from all analyses.