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Prior fragility fracture and risk of incident ischaemic cardiovascular events: Results from UK Biobank

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Abstract

Purpose—We aimed to investigate the relationship between prior fracture and risk of incident ischaemic cardiovascular events in a UK population-based cohort.

Methods—UK Biobank is a large prospective cohort comprising 502,637 men and women aged 40–69 years, with detailed baseline assessment. History of fracture was self-reported, and details of hospital admissions for ischaemic heart disease (IHD) (ICD-10:I20–I25) were obtained through linkage to UK Hospital Episode Statistics. Cox proportional hazards models were used to investigate the prospective relationships between prior fracture and hospital admission for men and women, controlling for age, BMI, smoking, alcohol, educational level, physical activity, systolic blood pressure, calcium and vitamin D use, ankle spacing-width, heel BUA, and HRT use(women).

Results—Amongst men a fragility fracture (hip, spine, wrist, or arm fracture resulting from a simple fall) within the previous five years was associated with a 35% increased risk of IHD admission (fully-adjusted HR:1.35;95%CI: 1.00,1.82; p=0.047), with the relationship

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Conflict of Interest:

J Paccou, S D'Angelo, E Curtis, A Rhodes, Z Raisi-Estabragh, K Walker-Bone, M Edwards, C Cooper, S Petersen and N Harvey declare that they have no conflict of interest in relation to this paper.

predominantly driven by wrist fractures. Associations with hospitalisation for angina in men were similar in age-adjusted models [HR:1.54;95%CI: 1.03,2.30), p=0.037], but did not remain statistical significant after full adjustment [HR:1.64;95%CI: 0.88,3.07); p=0.121]. HRs for admission with angina were lower in women, and neither age- nor fully-adjusted relationships attained statistical significance.

Conclusions—Prior fragility fracture is an independent risk factor for incident ischaemic cardiovascular events in men. Further work may clarify whether this association is causal or represents shared risk factors, but these findings are likely to be of value in risk assessment of both osteoporosis and cardiovascular disease.

Keywords

osteoporosis; epidemiology; fragility fractures; cardiovascular; heart

Introduction

Cardiovascular disease (CVD), together with cancer, is the leading cause of death in the developed world, and as with osteoporosis, it becomes more common with increasing age [1, 2]. Studies have suggested links between osteoporosis and CVD, and low bone mineral density has been associated with increased aortic calcification [3–5], risk of cardiovascular events and premature death [3]. Several studies have shown that CVD and vascular calcification are associated with decreased bone mineral density (BMD) and greater risk of fractures [6, 7]. Indeed, a diagnosis of CVD; whether ischaemic heart disease, heart failure, stroke or peripheral arterial disease, has been shown to be related to the subsequent risk of osteoporotic fracture (mostly of the hip), although the exact mechanism remains unclear [8–11]. Several studies have documented associations between chronic inflammation, osteoporosis [12,13] and cardiovascular disease [14], together with other conditions such as sarcopenia [15], diabetes/obesity [16] and dementia [17], suggesting one possible common mechanism. However, there is also evidence that risk factors for fracture and ischaemic heart disease overlap considerably [18, 19]. Here, we investigated the relationship between prior fracture and risk of incident cardiovascular events in both men and women, hypothesizing that participants with prior fragility fracture would have a higher risk of incident cardiovascular events than those without.

Methods

Study population

UK Biobank is a large prospective cohort with detailed baseline assessment. Between 2006 and 2010, more than 500,000 participants aged 40 to 69 were recruited nationwide. Data regarding lifestyle, environment, medical history, physical measures, and biological samples, were collected, and consent obtained for follow-up [20–22].

Demographic and clinical assessment

Participants completed a series of computer-based questionnaires followed by face-to-face interviews with trained research staff. Details of the assessments and variables are publicly

available (<http://biobank.ctsu.ox.ac.uk/crystal/>), and a transcript of the questionnaire may be downloaded (http://www.ukbiobank.ac.uk/wp-content/uploads/2011/06/Touch_screen_questionnaire.pdf?phpMyAdmin=trmKQIYdjjnQIgJ%2CfAzikMhEnx6). Information collected included socio-demographics (gender, age, ethnicity, and educational attainment), lifestyle factors (including smoking status, alcohol consumption and physical activity) and self-reported physician-diagnosed comorbidities (e.g. hypertension, diabetes and cancer). Details regarding calcium and vitamin D use and hormonal replacement therapy (HRT) in women were also obtained. The questionnaire asked participants to report any doctor's diagnosis of cardiovascular comorbidities such as coronary artery disease (combining angina and heart attack), stroke, and diabetes, and for all regular medications to be listed. Weight and height measurements were obtained for calculation of BMI (kg/m^2); systolic and diastolic blood pressures (SBP, DBP) were measured using the Omron HEM-7015IT digital blood pressure monitor. History of fracture was self-reported. All participants were asked if they had fractured or broken a bone in the past five years and if yes, at which of the following specific sites: ankle, leg, hip, spine, wrist, arm or other bones. A further question asked if the fracture resulted from a simple fall (low-trauma fracture). Combining this information, 'fragility fracture' was defined as a low-trauma (occurring as a result of a fall) fracture involving the hip, spine, wrist or arm. 'Other' and 'unknown' fractures were excluded from subsequent analyses. Broadband ultrasound attenuation (BUA) (db/MHz) and speed of sound (SOS) (m/s) were measured at least twice on each calcaneum with a SAHARA sonometer (Hologic, Marlborough, USA) and left and right mean values used for analysis. Intermalleolar distance ("ankle spacing width") was also recorded, as soft tissue thickness may influence heel ultrasound indices. Measures of BUA were available for 485,899 of the 502,664 participants who attended the health examination and completed the health and lifestyle questionnaire.

Ascertainment of outcomes

Information on incident hospital admission for ischaemic heart disease (IHD: I20-I25) and for acute myocardial infarction (I21) or angina (I20, which includes both unstable and stable angina) was obtained through linkage to UK Hospital Episode Statistics (HES). The remaining ICD10 codes included: subsequent myocardial infarction within 4 weeks after a first event; complications of myocardial infarction; other acute ischaemic heart disease, and chronic ischaemic heart disease. HES data are produced through coding and central reporting of diagnoses underlying hospital admissions nationwide. All study subjects were followed up until any ischaemic cardiovascular event, death, or until 29th February 2016, yielding a mean follow-up time of 7 years and a maximum time of 10 years.

Statistical analyses

Baseline characteristics were analysed in men and women separately, reporting mean (standard deviation) or median (interquartile range) for continuous variables and number (percent) for categorical variables, and testing for differences between the cohort with and without a previous fragility fracture.

We explored associations between previous fracture/fragility fracture and (i) hospital admission for ischaemic heart disease, (ii) hospital admission for acute myocardial

infarction or iii) hospital admission for angina, using Cox proportional hazards models, with results expressed as Hazard Ratio (HR) and 95% Confidence Interval (95%CI). In further analyses, we explored the associations between previous fragility fracture and hospital admission for either ischaemic heart disease, myocardial infarction or angina using competing-risk regression models, with death from any cause as competing risk event. We used a similar approach to investigate associations between previous fragility fracture and risk of death due to ischaemic heart disease, accounting for risk of death from any other cause. Competing-hazard models generate sub-hazard ratios (SHRs) instead of hazard ratios and treat death from any cause as competing risk as participants who experience this event cannot have a subsequent outcome, unlike those who are lost at follow-up (censored). The interpretation of SHR is similar to the HR of a Cox regression, with estimates higher than 1 indicating an increased risk of the outcome controlling for the fact that the competing risk events can also occur. Results from both approaches are reported firstly adjusted for age, and then adjusted for age, BMI, smoking, alcohol, educational level, physical activity, SBP, medications for cholesterol/diabetes, calcium and vitamin D use, ankle spacing width, heel BUA and HRT (women). All analyses were performed separately for men and women and were performed using Stata v 14.2 (StataCorp, College Station, Texas, USA).

Results

Characteristics of the participants

Of the 502,637 participants recruited to UK Biobank, 482,672 individuals (median age 58 years, 54.6% women) had complete data on fracture in the previous five years and BUA. We excluded people who either had hospital admission records (HES) for the studied cardiovascular diseases (ICD10 codes I20-I25) before completing the baseline questionnaire, or, when recruited, reported to have been previously diagnosed by a doctor with myocardial infarction or any form of angina. This left a dataset of 456,694 participants (55.9% women). A total of 43,008 participants (9.4%) reported a previous fracture in the past five years: 25,702 (10.1%) in women and 17,306 (8.6%) in men. Fragility fracture was recorded in 10,018 participants; 7,684 in women and 2,334 in men. Table 1 summarises the baseline characteristics including the number of prior hip (n=765), spine (n=980), arm (n=4,578) and wrist (n=8,800) fractures.

Women with fragility fractures were older than those without ($p<0.001$). For both men and women, the proportion of current smokers was higher in the group with a previous fragility fracture. The use of medication for cholesterol or diabetes was significantly higher among those with a previous fragility fracture. Online Supplementary Tables 1 and 2 summarise the characteristics of the participants by sex, stratified by the reporting of prior hip or spine fracture.

Prior fracture and hospitalisation for ischaemic heart disease (IHD) events

In total, 3238 women and 6768 men suffered from an incident IHD event during the follow-up period, while 888 women and 2349 men were admitted to hospital with an acute myocardial infarction and 1045 women and 1338 men with angina. Table 2a and Figure 1

show the relationships between prior fracture, fragility fractures, and incident ischaemic cardiac outcomes.

Thus for both men and women there were modest associations between prior fracture (irrespective of trauma involved) and incident IHD admission, but these did not remain statistically significant in fully-adjusted models. Among men, a fragility fracture within the previous five years was associated with 35% increased risk of admission for IHD (fully adjusted HR: 1.35; 95%CI: 1.00, 1.82; $p=0.047$). Associations with hospitalisation for angina in men followed a similar pattern the age-adjusted models, with a 54% increase in risk with prior fragility fracture [HR: 1.54; 95%CI: 1.03, 2.30), $p=0.037$], but did not remain statistical significant after full adjustment [HR: 1.64; 95%CI: 0.88, 3.07); $p=0.121$]. The hazard ratios for angina were a little lower in women, but neither the age-adjusted nor fully adjusted relationships were statistically significant. With acute myocardial infarction as the outcome neither the age-adjusted nor fully adjusted models yielded any significant associations with prior fragility fracture in men or women. Table 3 demonstrates that accounting for mortality as a competing risk did not materially alter the associations for any outcome.

Site specific associations between prior fracture and incident IHD admission

The number of wrist fractures was greater than that of arm fractures and far greater than that of hip or spine fractures; whilst there were no statistically significant associations between prior fracture of the hip, spine or arm and incident IHD admission, there was a strongly statistically significant relationship between fracture of the wrist and incident IHD admission amongst men (Table 2b): (55% increased risk); fully adjusted HR 1.55 (95%CI: 1.17, 2.04), $p=0.002$. Amongst women, there was a relationship of similar magnitude, albeit less statistically robust, for prior arm fracture, which was associated with a 46% increased risk of IHD admission: fully adjusted HR: 1.46 (95%CI: 0.95, 2.22), $p=0.081$.

Prior fragility fracture and risk of death following admission for ischaemic heart disease

In total, IHD accounted for 492 deaths in men and 120 deaths in women. In a model accounting for the competing hazard of death from other causes, there was no evidence of an association between prior fragility fractures in the previous five years and risk of death following admission for ischaemic heart disease in either sex. Fully adjusted HR women: 0.59 (95%CI: 0.08,4.56), $p=0.62$; and for men: 1.66 (0.61,4.54), $p=0.32$.

Discussion

We have demonstrated, in the very large population-based UK Biobank cohort, that a history of prior fragility fracture (occurring at hip, spine, wrist or arm as the result of a simple fall) predicts incident ischaemic cardiovascular events in men, independently of a wide range of covariates, and that this relationship appeared to be driven primarily by prior wrist fractures. In this relatively young cohort, adjustment for the competing hazard of death did not materially alter the risk estimates, and indeed we did not observe any relationships between prior fragility fracture and ischaemic cardiac mortality in either sex.

There are few studies examining links between prior fracture and incident ischaemic heart disease, and we are not aware of specific data relating to wrist fracture in this context. Thus in a large case-control study of 8,758 Taiwanese hip fracture patients (mean age 70 years), hip fracture was independently associated with a greater risk of acute myocardial infarction (HR = 1.29; 95%CI: 1.12, 1.48; $p < 0.001$) [23]. In the placebo group of the MORE trial of raloxifene [19], increased incidence of cardiovascular events was reported in postmenopausal women (mean age 66.5 years) with prior vertebral fractures. One recent study reported that amongst 2,101 patients hospitalised with a hip fracture (mean age 63.9 years), there was a 53% increased risk of stroke (adjusted HR: 1.53; 95%CI: 1.17, 2.01; $p = 0.002$) compared with 6,303 randomly selected controls matched on sex, age and year of index healthcare use over a one-year follow-up period [24]. Conversely, several studies have shown cross-sectional associations between low bone mineral density and vascular calcification, for example at the aorta. The diagnosis of various manifestations of cardiovascular or cerebral vascular disease, such as coronary artery disease, heart failure, stroke, dementia [25,26] have all been associated with increased incident fracture risk, a direction of associations which is perhaps intuitively easier to understand given the potential effect of these conditions on mobility. It should be noted that the age distribution of participants in these studies is generally somewhat greater than in our cohort which is likely to have limited our ability to ascertain associations across both sexes and specific cardiac or fracture diagnostic categories. The younger age of our cohort is consistent with the predominance of wrist fractures over those of the hip and spine. (The reporting of spine fractures will also reflect that only a minority of these come to clinical attention) [1]. Our observation of relationships between prior wrist fracture, but not other sites, and incident IHD in men may thus partly reflect lower power to detect associations with hip or spine fractures in the context of an underlying association between bone fragility and ischaemic cardiac disease. The stronger association for fractures occurring as a result of a fall compared with all fractures irrespective of the magnitude of trauma involved (albeit independent of heel BUA as a surrogate measure of bone strength) would support this. Conversely, there may be contributions from factors unrelated to bone fragility which increase specifically risk of both wrist fracture and IHD: whilst we adjusted comprehensively for such potential effects, this specificity of association, and elucidation of underlying mechanisms will require further investigation.

Whilst the available literature is consistent with our findings of links between bone fragility and cardiovascular disease, it should be noted that both conditions are common in elderly individuals and have previously been regarded as independent age-related disorders [1, 2]. As such both osteoporosis and cardiovascular disease share some common risk factors such as lack of physical activity, smoking, alcohol use, glucocorticoids, diabetes [27,28]. It is therefore possible that the observed associations simply reflect the presence of such common risk factors. However, some studies have suggested overlap in the etiological mechanisms of these diseases [18, 19]. For example, bone metabolism and vascular physiology share several regulatory factors, and the process of vascular calcification in many ways resembles that of bone formation [29,30]. Although the pathophysiology of this observed association of fragility fracture and future development of CVD remains poorly understood, progress continues to be made investigating the potential roles of both chronic inflammation and

oxidative stress. Elevated levels of C-reactive protein and inflammatory cytokines have been shown to be associated with CVD, fracture risk [31] and poorer trabecular microarchitecture in men [32]. Secondly, oxidative stress is associated with severe atherosclerosis and low bone stiffness [33]. Further work will be required to elucidate the extent to which such mechanisms explain observations such as those presented here.

The existing data linking prior fracture to incident cardiovascular events have focused mainly on women, and we could not identify any other studies in which sex differences in these relationships have been documented. The much lower incidence of cardiovascular events amongst women than men may have limited our ability to detect associations amongst female participants. However, our findings are consistent with recent epidemiological data from the UK Clinical Practice Research Datalink, which demonstrate that the excess mortality following a fracture is greater in men than women compared to mortality rates in the general population [34,35].

We studied a very large population-based cohort assessed in detail and with uniform methodology, with outcome events linked through hospital records. However there are some limitations that should be considered in the interpretation of our results. Firstly, prior fracture was ascertained by self-report. However, UK Biobank is not predicated on any individual disease so there is no reason why individuals might preferentially report such events. Secondly, we relied on hospital event linkage for outcome data and therefore may not have captured out-patient events, or general practice consultations for conditions such as angina pectoris. Furthermore we were not able to validate diagnoses using clinical data such as ECGs and troponin levels. However, hospital admission for ischaemic cardiac diagnoses is likely to yield a more reliable outcome than its antecedents, and direct clinical validation in a study of this scale is not feasible. Thirdly, we cannot exclude the possibility of selection bias towards a healthy population, as is common with such studies, and which is likely to have reduced the incidence of cardiovascular events. The relatively low mortality rate is consistent with the minimal effect of accounting for mortality in competing hazard models. Finally, this was a relatively young cohort in terms of fractures, although not for ischaemic heart disease. It is therefore not clear how generalizable our findings are to older, frailer populations.

In conclusion, this study supports prior fragility fracture, particularly of the wrist, as an independent risk factor for incident cardiovascular events in men. Further work is required to elucidate whether this association is causal or represents shared risk factors. Nonetheless, these findings are likely to be of value in risk assessment of both osteoporosis and cardiovascular disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Mini Abstract

In the large UK Biobank population-based cohort, we found that amongst men, but not women, prior fragility fracture was associated with increased risk of admission with ischaemic heart disease.

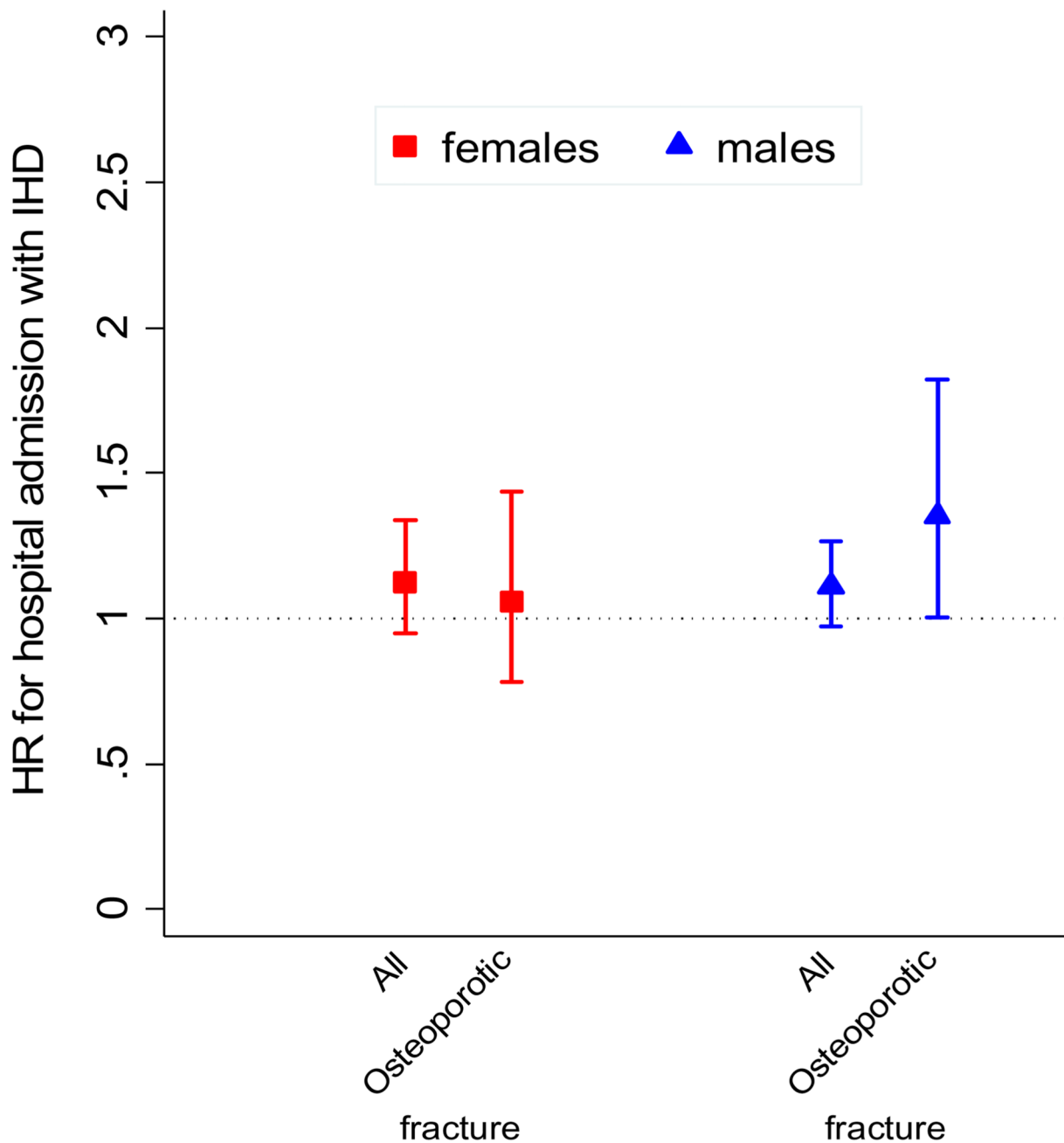


Figure 1. Risk of first hospital admission for ischaemic heart disease associated with history of any fracture or osteoporotic fracture in the 5 years prior to the baseline assessment. Data are hazard ratio and 95%CI, adjusted for age, BMI, smoking, alcohol, educational level, physical activity, systolic blood pressure, calcium and vitamin D use, heel BUA, ankle spacing width, and HRT (women).

Table 1

Characteristics of the participants, by fragility fracture status and sex

Characteristics	Women (n=7684)		Men (n=2334)		p-value ⁺
	Without fragility fracture (N=247768)	With fragility fracture (n=7684)	Without fragility fracture (N=198908)	With fragility fracture (n=2334)	
Demographic characteristics					
Age [median(IQR)], years	57.0 (50.0,63.0)	61.0 (56.0,65.0)	58.0 (50.0,63.0)	58.0 (49.0,63.0)	0.07
BMI [mean(SD)], kg/m ²	26.0 (23.4,29.6)	26.2 (23.6,29.6)	27.2 (24.9,29.9)	27.3 (24.8,30.2)	0.12
Ethnicity (%)					
White	94.5	97.4	94.4	94.7	0.57
Qualification (%)					
College or University degree	38.3	37.1	42.1	41.5	0.89
A levels/AS levels	14.5	13.5	12.6	12.0	
O levels/GCSEs	28.4	30.2	22.5	23.1	
CSEs or equivalent	6.6	5.0	6.7	6.8	
NVQ or HND or HNC	5.3	5.7	10.8	11.4	
Other professional qualification	6.9	8.5	5.3	5.1	
Lifestyle factors					
Alcohol consumption (%)					
at least 3 times per week	37.2	37.6	52.1	52.4	0.81
Smoking (%)					
Never	59.9	57.0	50.3	47.4	<0.001
Ex	31.0	33.3	37.1	35.1	
Current	8.8	9.2	12.3	16.8	
Not known	0.4	0.5	0.4	0.6	
Taking medication for cholesterol/diabetes [n (%)]	26656 (10.8)	1098 (14.3)	34663 (17.4)	472 (20.2)	<0.001
Physical activity [median (IQR)], days a week	1.0 (0.3,0)	1.0 (0.3,0)	2.0 (0.3,0)	2.0 (0.4,0)	0.56
Systolic blood pressure [mean(SD)], mmHg	135.1 (19.2)	138.2 (19.3)	141.1 (17.4)	141.0 (17.8)	0.63
Fracture site (n)					
Hip		439		326	

Characteristics	Women		Men		p-value [†]
	Without fragility fracture (N=247768)	With fragility fracture (n=7684)	Without fragility fracture (N=198908)	With fragility fracture (n=2334)	
Spine		581		399	
Wrist		6281		2519	
Arm		2909		1669	

* t test used in case of normality, Mann-Whitney U test used in case of non-normality of the distribution, chi 2 test used for categorical variables

Table 2a

Prior fracture in the past 5 years and the risk of incident hospital admission with ischaemic heart disease, acute myocardial infarction or angina in men and women.

Hospitalisation with ischaemic heart disease	Women		Men	
	<i>HR (95% CI)</i>	<i>p</i>	<i>HR (95% CI)</i>	<i>p</i>
N	3,238		6,768	
<i>Any fracture</i>				
Adjusted for age	1.16 (1.04,1.28)	0.005	1.11 (1.02,1.21)	0.015
Fully adjusted	1.13 (0.95,1.34)	0.179	1.11 (0.97,1.26)	0.121
<i>Fragility fracture</i>				
Adjusted for age	1.04 (0.87,1.24)	0.692	1.18 (0.96,1.45)	0.113
Fully adjusted	1.06 (0.78,1.43)	0.712	1.35 (1.00,1.82)	0.047
Hospitalisation with acute myocardial infarction				
N	888		2349	
<i>Any fracture</i>				
Adjusted for age	1.19 (0.98,1.45)	0.083	1.07 (0.92,1.24)	0.389
Fully adjusted	1.25 (0.92,1.70)	0.149	0.97 (0.78,1.22)	0.823
<i>Fragility fracture</i>				
Adjusted for age	1.07 (0.76,1.49)	0.706	1.01 (0.70,1.47)	0.944
Fully adjusted	1.20 (0.70,2.05)	0.508	1.09 (0.63,1.89)	0.748
Hospitalisation with angina				
N	1,045		1,338	
<i>Any fracture</i>				
Adjusted for age	1.31 (1.10,1.56)	0.003	1.23 (1.02,1.47)	0.029
Fully adjusted	1.31 (0.99,1.74)	0.057	1.21 (0.91,1.62)	0.185
<i>Fragility fracture</i>				
Adjusted for age	1.26 (0.95,1.68)	0.112	1.54 (1.03,2.30)	0.037
Fully adjusted	1.39 (0.88,2.22)	0.16	1.64 (0.88,3.07)	0.121

Fully adjusted models are adjusted for age, BMI, smoking, alcohol, educational level, physical activity, systolic blood pressure, calcium and vitamin D use, HRT (women) and additionally for heel BUA and ankle spacing width. HR: Hazard ratio.

Table 2b

Prior hip, spine, wrist or arm fracture in the past 5 years and the risk of incident hospital admission with ischaemic heart disease, acute myocardial infarction or angina in men and women.

Hospitalisation with ischaemic heart disease	Women		Men	
	HR (95% CI)	p	HR (95% CI)	p
<i>Hip fracture</i>				
Adjusted for age	0.80 (0.36,1.79)	0.590	0.69 (0.35,1.38)	0.300
Fully adjusted	1.11 (0.36,3.45)	0.858	-	
<i>Spine fracture</i>				
Adjusted for age	0.81 (0.38,1.70)	0.573	1.31 (0.81,2.10)	0.27
Fully adjusted	0.66 (0.16,2.64)	0.555	0.90 (0.37,2.16)	0.807
<i>Wrist fracture</i>				
Adjusted for age	1.03 (0.84,1.25)	0.8	1.36 (1.12,1.65)	0.002
Fully adjusted	0.96 (0.68,1.37)	0.841	1.55 (1.17,2.04)	0.002
<i>Arm fracture</i>				
Adjusted for age	1.14 (0.86,1.51)	0.366	1.03 (0.79,1.35)	0.837
Fully adjusted	1.46 (0.95,2.22)	0.081	0.92 (0.59,1.43)	0.715

Table 3

Prior fracture in the past 5 years and the risk of incident hospital admission with ischaemic heart disease in men and women, adjusting for the competing hazard of death from any cause.

Hospitalisation with ischaemic heart disease	Women		Men	
	SHR (95% CI)	<i>p</i>	SHR (95% CI)	<i>p</i>
N	3,238		6,768	
<i>Fragility fracture</i>				
Adjusted for age	1.04 (0.87,1.24)	0.674	1.18 (0.96,1.45)	0.110
Fully adjusted	1.06 (0.78,1.44)	0.694	1.35 (1.01,1.82)	0.046

Fully adjusted models are adjusted for age, BMI, smoking, alcohol, educational level, physical activity, systolic blood pressure, calcium and vitamin D use, HRT (women) and additionally for heel BUA and ankle spacing width. HR: Hazard ratio; SHR: Sub-distribution hazard ratio.