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Low Bone Mineral Density is Associated with Increased Risk for Myocardial Infarction in Men and Women

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Abstract

Summary The association between bone mineral density (BMD) and myocardial infarction (MI) was investigated in 6872 men and women. For both men and women lower BMD in the femoral neck and hip was associated with increased risk of MI largely independent of smoking, hypertension, hypertriglyceridemia and diabetes.

Purpose The relationship between bone mineral density (BMD) and cardiovascular disease isn't completely understood. The objective of this prospective study was to investigate the risk of myocardial infarction (MI) in relation to bone mineral density and to determine if cardiovascular risk factors could explain this association.

Methods Dual X-ray absorptiometry (DEXA) was performed in 5490 women and 1382 men to determine total hip and femoral neck bone mineral density (BMD, g/cm²) and estimate femoral neck volumetric BMD (vBMD, g/cm³). During a mean follow-up time of 5.7 years 117 women and 79 men suffered an initial MI.

Results After adjustment for age and BMI, lower BMD of the femoral neck and total hip was associated with increased risk of MI for both women (hazard ratio (HR)=1.33, 95% confidence interval (CI): 1.08-1.66 per standard deviation (SD) decrease in femoral neck BMD) and men (HR=1.74, 95% CI: 1.34-2.28 per SD decrease in total hip BMD). After additional adjustment for smoking, hypertension, hypertriglyceridemia and diabetes the associations were slightly attenuated in men (HR=1.42-1.88 in the age and BMI-adjusted model versus 1.33-1.77 in the fully adjusted model) while similar attenuations were seen in women (HR=1.06-1.25 versus 1.05-1.22).

Conclusion Lower BMD was associated with an increase in MI risk for both men and women. Women had consistently lower HRs compared to men in all models. Adjusting for smoking, hypertension, hypertriglyceridemia and diabetes did not distinctively weaken these associations.

Key Words Bone density, Myocardial infarction, Cohort study, Men, Women

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Introduction

Cardiovascular diseases (CVD) are taking a huge toll on the aging population, and they are the greatest cause of mortality in the Western world [1]. Traditional risk factors for CVD are age, hypertension, smoking, hyperlipidemia, abdominal fat mass, low physical activity and diabetes [2-5]. Another burden of the elderly population is osteoporosis, which annually causes millions of fractures worldwide, leading to decreased quality of life and increased morbidity and mortality [6]. Osteoporosis shares several of the aforementioned risk factors for CVD, and though originally seen as unrelated diseases, recent studies have discovered several common features. Suggested common etiologies are smoking [7], hypertension [8], hyperlipidemia [9,10] and atherosclerosis [11,12].

Previous studies that have investigated the association between bone mineral density (BMD) and incident CVD have mostly been performed on postmenopausal women [13-17], suggesting an association between lower BMD and a higher incidence of CVD. However, studies including men have shown conflicting results concerning the association between BMD and CVD. Although cross-sectional studies of men with prior myocardial infarction or stroke revealed lower BMD than controls [15,18], several longitudinal studies have failed to find an association between BMD and CVD [16,19]. In studies that did find an inverse association between BMD and CVD, this finding only held true for a subgroup of the male population [20] or was markedly attenuated after adjustment for shared risk factors [21], suggesting that shared risk factors might explain the association between BMD and CVD.

Furthermore, there is no consensus on which bone site best reflects bone health in relation to CVD; in fact, previous studies highlight a wide array of bone sites, ranging from the phalanges [19] and metacarpals [16] to the femoral neck and spine [20]. Several of these measured bone sites are only used in clinical practice for fracture diagnostics. In contrast, the femoral neck is vital in the assessment of osteoporosis [6], and because it is often the only investigated bone site in practice, its association with the risk of myocardial infarction is of interest.

The purpose of this study was to investigate BMD and volumetric BMD (vBMD) of the femoral neck and BMD of the total hip as risk factors for incident myocardial infarction in a large cohort of men and women and whether these associations can be explained by shared risk factors of osteoporosis and CVD.

Materials and methods

Total cohort

Using the bone mineral database (described below), 5490 women and 1382 men who fulfilled the inclusion criteria and had measured their hip and femoral neck BMC and BMD were included in the present study. For each subject, the date of the bone mass measurement was set as the baseline date. The inclusion criteria was age between 30-75 at baseline and no previous myocardial infarction before baseline as defined by the MONICA database (described below). The end of the study for all subjects was either January 1, 2007, the date of their 76th birthday, the date of myocardial infarction or the date of death, whichever came first. Using the MONICA database, 93 individuals with myocardial infarction (MI) prior to baseline

were excluded from the study. After the exclusion, 196 cases of prospective myocardial infarctions were identified in the study population.

Background data were retrieved from the VIP database (described below) and were available for 2730 women and 574 men. Because some subjects did not have all background variables measured because of analyzing or input errors, the number measured for each variable is presented separately in **Table 1**. The pulse pressure was calculated as the mmHg difference between the systolic and diastolic blood pressures. Hypertension was defined as use of antihypertensive medications, a diastolic blood pressure ≥ 90 mmHg or systolic blood pressure ≥ 140 mmHg. Diabetes was defined as self-reported diabetes, a fasting glucose value of ≥ 7.0 mmol/L or ≥ 12.1 mmol/L glucose after a glucose tolerance test. Hypertriglyceridemia was defined as triglycerides > 2 mmol/L.

BMD database

Since 1991, dual energy X-ray absorptiometry (DEXA) has been used at the Sports Medicine unit, Umeå University, Sweden, to assess bone mineral density and body composition. BMD (g/cm^2), bone mineral content (BMC, grams) and bone area (cm^2) were measured using a Lunar DPX-L until 1998 when a Lunar IQ was used instead (GE Lunar, GE Healthcare, Waukesha, WI). Volumetric BMD (vBMD, g/cm^3) in the femoral neck was estimated by assuming that the femoral neck is cylindrical in size [22]. By scanning one person several times with repositioning between measurements, the coefficient of variation (CV, SD/mean) was determined. The CVs were approximately 1% for the hip and femoral neck BMD and BMC. The equipment was calibrated each day using a

standardized phantom, and it was regularly evaluated using a spine phantom. No drifts in BMD measurements were detected. About 90% of the scans during the study period were performed by the same technician.

VIP database

The Västerbotten Intervention Programme (VIP) is an ongoing community intervention programme inviting all residents of Västerbotten county aged 40, 50 and 60 years of age to a health screening and counseling [23]. Its purpose is to reduce morbidity and mortality from CVD and diabetes. At this health investigation, height and weight are measured in light clothing, and blood pressure (BP) is measured using a mercury sphygmomanometer after 5 minutes of rest in a supine position. Also, blood samples are obtained and analyzed for glucose, triglycerides and total cholesterol. Subjects are instructed to fast for at least 8 hours before the blood sample is taken. A 75 gram oral glucose tolerance test is performed in all subjects without known diabetes and with a fasting glucose level below 7.0 mmol/L. Finally, the participants are asked to fill in a very comprehensive questionnaire regarding smoking, eating habits, diseases and medication.

MONICA database

MONICA Northern Sweden (Multinational Monitoring of Trends and Determinants for Cardiovascular Diseases) is a project initially initiated by the WHO in 1985 to monitor time trends and risk factors and the incidence of CVDs. The incidence of stroke and MI are registered and validated in Västerbotten and Norrbotten in northern Sweden. Initially, subjects under the age of 65 who suffered a MI were included, but from

2000, patients 65-75 years of age were also included [24]. To identify subjects aged 65-75 who suffered a MI before 2000, the BMD database was merged with the hospital registry at the University Hospital of Northern Sweden, Umeå. The hospital records of patients with a MI diagnosis were then validated according to the MONICA criteria [24].

Statistics

Data are presented as mean $\pm$ standard deviation (SD). Differences between two groups were estimated using the Student's *t*-test for independent samples and the Mann-Whitney *U* test for the not normally distributed variables. The correlation between risk factors was evaluated using Pearson's correlation coefficient. Variables not normally distributed were first transformed using the natural logarithm. The relationships between BMD, vBMD and the risk of MI were determined using Cox proportional hazards models. Logistic regression was used to investigate the relationship between the different estimates of bone mass and the different risk factors for MI, such as hypertension, diabetes, hypertriglyceridemia and smoking. A *p*-value less than 0.05 was considered significant. SPSS for the PC (version 17.0, SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

Results

The cohort consisted of 6872 men and women. During a mean follow-up of 5.7 ± 4.1 years, 117 women and 79 men suffered a first ever MI. Analyses were stratified by sex since earlier studies have found different associations between bone density and CVD in men and women. Anthropometric data and background variables of

the cohort are presented separately for men and women in **Table 1**.

The association between the different estimates of bone density at baseline and the risk of MI after adjustment for age and BMI is presented in **Table 2**. Data is presented per 1 SD decrease in bone density variables. For both women and men all estimates of bone density were associated with the risk of MI after adjusting for age and BMI. Femoral neck BMD, vBMD and total hip BMD was in women associated with a HR of 1.33 (95% CI: 1.08-1.66), 1.33 (1.07-1.64) and 1.28 (1.02-1.60) respectively. For men the corresponding HRs were 1.56 (1.22-2.00), 1.42 (1.11-1.82) and 1.74 (1.34-2.28) respectively.

To investigate the relationship between traditional CVD risk factors and bone density variables, a partial correlation was performed after adjusting for age and BMI, except for the correlations between BMI and bone density variables that were only adjusted for age, as seen in **Table 3**. For both women and men, a significant positive association was found between the different measures of bone density and BMI (♀ $r=0.20-0.45$, ♂ $r=0.17-0.35$, $p<0.01$ for all). For women the bone density measures was inversely correlated to both systolic and diastolic blood pressure (BP) (BMD of the femoral neck $r=-0.05$, $p=0.01$ for both systolic and diastolic BP). Also, an inverse correlation was found for BMD of the femoral neck and total cholesterol ($r=-0.06$, $p<0.01$). No significant correlations were found in men.

Using a logistic regression, the association between the bone density measures and smoking, hypertension, hypertriglyceridemia, diabetes or treatment for any of these conditions was

investigated in **Table 4** and adjusted for age and BMI. For women lower bone density was associated with increased risk of prevalent hypertension (femoral neck vBMD, OR=1.17 95% CI: 1.06-1.29), diabetes (femoral neck BMD, OR=1.19 95% CI: 1.02-1.39) and smoking (total hip BMD, OR=1.21 95% CI: 1.08-1.34) while lower bone density reduced the risk of having hypertriglyceridemia (total hip BMD, OR=0.81 95% CI: 0.69-0.95). In men lower bone density was associated with increased risk of prevalent hypertension (femoral neck BMD, OR=1.34 95% CI: 1.09-1.65).

In **Table 5**, the importance of hypertension, hypertriglyceridemia, diabetes and smoking in the associations of bone density and the risk of MI were investigated using Cox regression analyses in a subcohort consisting of 2526 women and 478 men, including 54 women and 43 men who suffered a MI. Complete background data were available for all subjects concerning the conditions above. No significant differences were seen when comparing the subcohort to the total cohort as seen in **Table 2** with respect to either anthropometric or bone density measures.

In women when analyzing the subcohort only adjusted for age and BMI no significant associations were found between the bone mass measures and MI risk with slightly attenuated HRs (HR=1.28-1.33 in the total cohort versus 1.06-1.25 in the subcohort). Additional adjustment for hypertension, hypertriglyceridemia, diabetes and smoking did not distinctively change the hazard ratios when comparing to the age and BMI-adjusted model (HR=1.06-1.25 in the age and BMI-adjusted model versus 1.05-1.22 in the fully adjusted model). Age and diabetes were

significantly associated with MI risk in the final model.

In the subcohort of men all bone density measures were significantly associated to MI risk in the age and BMI adjusted model with slightly increased HRs (HR=1.42-1.74 in the total cohort versus 1.42-1.88 in the subcohort). After additional adjustment for prevalent hypertension, hypertriglyceridemia, diabetes and smoking the hazard ratios for the bone density measures were slightly attenuated (HR=1.42-1.88 in the age and BMI-adjusted model versus 1.33-1.77 in the fully adjusted model) but still significant ($p<0.01$). Age, diabetes and hypertriglyceridemia were significantly associated to MI risk in the final model.

Discussion

In this prospective study of a large cohort of both women and men, a 1 SD decrease in BMD of the femoral neck in women was associated with a 1.3-fold increase in MI risk, while in men a 1 SD decrease in total hip BMD was associated with a 1.7-fold increase in MI risk. These associations were largely independent of smoking, hypertension, hyperlipidemia and diabetes.

Although several studies have investigated the association of BMD to CVD no previous study has investigated the association of BMD and vBMD to MI. The studies that have investigated the association between bone mass and CVD have used composite outcomes often including both MI and stroke and/or other aspects of CVD. A recent prospective study by Farhat *et al.* investigated the risk of incident CVD (MI, angina pectoris, stroke, transient ischemic attack, peripheral vascular disease and carotid artery disease) in a cohort consisting of 2310 men and women. They

investigated BMD of the femoral neck using DXA and vBMD of the spine using QCT [20]. After adjustment for potential confounders (e.g. education, physical activity, BMI, cholesterol, blood pressure) they could show that in black women a 1 SD decrease in femoral neck BMD was associated with a HR of 1.44 (95% CI: 1.10-1.90) in relation to the risk of incident CVD, but no significant associations were found in white women. For white men, the HR for 1 SD decrease in spine vBMD was 1.39 (95% CI: 1.03-1.87) in relation to the risk of incident CVD, with no significant associations in black men. The events were self-reported and validated whenever patients reported an event. In another recent prospective study, Szulc *et al.* investigated the risk of MI and/or stroke in 744 men older than 50 years and assessed the BMD of the femoral neck, spine, whole body and radius [21]. They found that the lowest quartiles of spine BMD, total body BMD and radius BMD were associated with a doubled risk of a cardiovascular event compared to the other three quartiles. In contrast, femoral neck BMD was not significantly associated with CVD risk. After adjustment for potential confounders the hazard ratios were markedly weakened. The events were self-reported and validated whenever reported. Samelson *et al.* investigated the association of BMD and the risk of coronary heart disease (MI, angina pectoris, death by coronary disease, coronary insufficiency) in 1236 women and 823 men and assessed BMD of the metacarpals [16]. They found that women in the lowest quartile of metacarpal cortical area had a 1.37-fold increased risk of coronary heart disease compared to the highest quartile. Adjusting for potential confounders did not significantly change these results. No associations were found in men. In

summary the bone sites most frequently used are the femoral neck and spine; most studies have found an inverse relationship at some bone site, but no bone site have been consistently associated with the risk of MI.

Because BMD of the femoral neck is the most often used bone site when diagnosing osteoporosis, it is surprising that only one study found an association with CVD, and only in a subgroup [20]. In other studies, no associations were found for femoral neck BMD. In contrast, our results suggest that femoral neck BMD is associated with the risk of CVD for both men and women. One factor that can influence the results is the studied outcome. Farhat and Szulc both used a composite outcome including both MI and stroke, and Samelson studied incidences of MI, angina pectoris, coronary insufficiency or coronary disease death. The diseases in these composite outcomes are all influenced by cardiovascular risk factors, but to different degrees, and may signify different severity and time aspects of CVD (e.g. angina pectoris vs. MI). In our study, we solely investigated the risk of incident MI, drawing information from the MONICA register, ensuring high validity and well-defined incident MIs. Other reasons for inconsistent results in previous studies can be the use of self-reported events, studies of mixed populations with respect to both ethnicity and sex, and lack of statistical power.

As a shared etiology has been proposed between osteoporosis and CVD, in a first step we tested whether BMD was correlated to blood pressure (BP) and markers of glucose and lipid metabolism. We found that in women the bone density measures were inversely correlated to systolic and diastolic BP as well as to total cholesterol. Low

bone mass was also associated with prevalent hypertension, diabetes and smoking. In men, low bone density was associated with prevalent hypertension. While these factors each might contribute to both conditions, it is unclear if they can explain the deleterious association of low BMD and MI.

To test whether these shared risk factors between osteoporosis and CVD could explain the increase in MI risk associated with low BMD, a Cox regression analysis was made adjusted for smoking, hypertension, hypertriglyceridemia and diabetes. In men this did not markedly change the results. Femoral neck and total hip BMD were still significantly inversely associated to MI risk with only slightly attenuated HRs. Women had consistently smaller HRs than men across all models. Adjusting for the shared risk factors only slightly attenuated the HRs, comparable to the attenuations seen in men.

The underlying cause of a myocardial infarction is considered to be atherosclerosis. Atherosclerosis and osteoporosis are common in the elderly population, and thus are often observed in the same individual. However, epidemiological studies have found an age-independent relation between these diseases [11,25]. Shared risk factors between CVD and osteoporosis are involved in modifying the progression of atherosclerosis, suggesting that atherosclerosis might be the common pathophysiological link between CVD and osteoporosis. Taking the association between lipids and low BMD as an example, some studies have found an inverse association [26,27], while others have found a positive association [28,29]. However, controlling for vascular disease suggests that it is not lipids *per se* that is associated with

bone loss, but atherosclerosis [30]. Atherosclerosis is associated with demineralization [31], and the rate of atherogenesis is associated with the rate of bone loss [32]. Unfortunately we could not directly gauge the extent of atherosclerosis in the study population. In the present study the pulse pressure, a marker of arterial stiffness [33], was not associated to the bone mass measures and cannot explain the association between lower BMD and an increase in MI risk. Whether atherosclerosis is indicative of the deleterious implications of low bone mass on CVD risk is unclear.

The present study has its strengths and limitations. The strength of the present study is that it followed a large cohort of both men and women for several years. Detailed background data were available through a community intervention program [23]. The studied outcome was a single aspect of CVD, namely MI, and all incident MIs were registered and validated according to strict criteria, which ensured high validity [24]. The present study also has some limitations. First, the study population was not randomly selected from the general population but consisted mainly of subjects referred for DEXA measurement. However compared to the anthropometric data of the population-based VIP cohort, women had similar BMI, while men were only slightly lighter (weight - 2.3 kg, BMI -0.5 kg/m²). Also, the genetic risk markers for obesity and diabetes type 2 are comparable to those found in other populations [34]. Another limitation is that background variable data were not available for all subjects. However, when baseline characteristics of those with and without background variables were compared, only age (56.0 vs. 58.1 years) and height (165 vs. 166 cm) were significantly different. Measures of

bone mass and background variables were not performed at the same time, which may mean that the background variables changed during the time between measurements.

In conclusion, lower BMD of the femoral neck and total hip was associated with an increased risk of

MI in both men and women. Women had consistently smaller HRs compared to men in all models. These associations were largely independent of hypertension, diabetes, hypertriglyceridemia and smoking.

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Table 1. Descriptive characteristics of males and females in the cohort

Men	N	Mean ± SD	Women	N	Mean ± SD
Age (yr)	1382	53.1±12.3***	Age (yr)	5490	58.0±11.1
Weight (kg)		81.1±13.0***	Weight (kg)		68.1±12.8
Height (cm)		177±7***	Height (cm)		163±6
BMI (kg/m²)		25.8±3.7	BMI (kg/m²)		25.7±4.6
Systolic BP (mmHg)	538	130±18	Systolic BP (mmHg)	2668	128±18
Diastolic BP	538	80±12***	Diastolic BP	2668	78±10
Triglycerides (mmol/L)	461	1.48±0.77***	Triglycerides (mmol/L)	2522	1.31±0.77
Tot. Cholesterol	537	5.6±1.1*	Tot. Cholesterol	2680	5.7±1.2
F-glucose	538	5.8±1.4***	F-glucose	2680	5.5±1.0
Current smoker (%)	558	27.0	Current smoker (%)	2696	27.8
Hypertension	567	45.0	Hypertension	2718	43.8
Diabetes	572	15.6	Diabetes	2728	10.0
Hypertriglyceridemia	485	17.8	Hypertriglyceridemia	2548	11.8
Femoral neck BMD (g/cm²)	1382	0.93±0.16***	Femoral neck BMD (g/cm²)	5490	0.83±0.15
vBMD (g/cm³)		0.31±0.07***	vBMD (g/cm³)		0.33±0.06
Total hip BMD (g/cm²)	1382	0.99±0.17***	Total hip BMD (g/cm²)	5490	0.87±0.16

* Significantly different compared to women p<0.05

***Significantly different compared to women p<0.001

Table 2. The risk of MI using Cox proportional hazards models.

Women <i>Adjusted for age</i>				Men <i>Adjusted for age</i>		
	Hazard ratio	95% confidence interval	P-value	Hazard ratio	95% confidence interval	P-value
Femoral neck						
BMD	1.25	1.02-1.53	0.04	1.55	1.22-1.97	<0.01
vBMD	1.27	1.03-1.56	0.03	1.42	1.12-1.82	<0.01
Total hip						
BMD	1.15	0.94-1.41	0.17	1.67	1.30-2.13	<0.01

Women <i>Adjusted for age and BMI</i>				Men <i>Adjusted for age and BMI</i>		
	Hazard ratio	95% confidence interval	P-value	Hazard ratio	95% confidence interval	P-value
Femoral neck						
BMD	1.33	1.08-1.66	<0.01	1.56	1.22-2.00	<0.01
vBMD	1.33	1.07-1.64	0.01	1.42	1.11-1.82	<0.01
Total hip						
BMD	1.28	1.02-1.60	0.03	1.74	1.34-2.28	<0.01

Hazard ratios for the risk of MI per 1 SD decrease in bone mass variables is presented for men and women separately. The analyses included 5490 women and 1382 men, of whom 117 women and 79 men sustained a myocardial infarction.

Table 3. Partial correlations of bone mass variables.

Women	BMI		Systolic BP		Diastolic BP		Pulse pressure		Triglycerides		Tot. cholesterol		P-glucose	
Femoral neck														
	r	p	r	p	r	p	r	p	r	p	r	p	r	p
BMD	0.30	<0.01	-0.05	0.01	-0.05	0.01	-0.03	0.13	0.02	0.44	-0.06	<0.01	0.00	0.89
vBMD	0.20	<0.01	-0.04	0.04	-0.04	0.04	-0.03	0.19	0.02	0.28	-0.04	0.07	0.01	0.54
Total hip														
BMD	0.45	<0.01	-0.04	0.05	-0.03	0.09	-0.03	0.18	0.04	0.05	-0.03	0.10	0.01	0.78
Men	BMI		Systolic BP		Diastolic BP		Pulse pressure		Triglycerides		Tot. cholesterol		P-glucose	
Femoral neck														
	r	p	r	p	r	p	r	p	r	p	r	p	r	p
BMD	0.27	<0.01	-0.03	0.46	-0.01	0.87	-0.04	0.38	-0.03	0.50	-0.01	0.74	-0.01	0.81
vBMD	0.17	<0.01	-0.06	0.16	-0.03	0.46	-0.06	0.19	0.03	0.51	-0.01	0.76	0.03	0.56
Total hip														
BMD	0.35	<0.01	-0.01	0.88	0.02	0.63	-0.03	0.52	-0.01	0.83	-0.02	0.72	-0.01	0.82

Adjusted for age and BMI, except for the analysis of BMI and bone mass. The analysis was made in a subpopulation of 2730 women and 574 men. Not all variables were measured in all individuals, and specific N per variable are presented in **Table 1**.

Table 4. Logistic regression analysis.

Women		Hypertension		Hyper-triglyceridemia		Diabetes		Smoking	
		OR (95% CI)	P	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	P
Femoral neck	BMD	1.14 (1.03-1.26)	<0.01	0.94 (0.81-1.10)	0.43	1.19 (1.02-1.39)	0.03	1.16 (1.04-1.29)	<0.01
	vBMD	1.17 (1.06-1.29)	<0.01	0.89 (0.77-1.03)	0.12	1.05 (0.90-1.22)	0.57	1.16 (1.04-1.29)	<0.01
Total hip	BMD	1.12 (1.01-1.24)	0.03	0.81 (0.69-0.95)	<0.01	1.11 (0.95-1.31)	0.19	1.21 (1.08-1.34)	<0.01
Men		Hypertension		Hyper-triglyceridemia		Diabetes		Smoking	
		OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	P
Femoral neck	BMD	1.34 (1.09-1.65)	<0.01	1.11 (0.83-1.48)	0.49	1.20 (0.92-1.56)	0.18	1.10 (0.88-1.39)	0.39
	vBMD	1.29 (1.05-1.58)	0.01	1.02 (0.77-1.35)	0.89	1.08 (0.84-1.40)	0.55	1.10 (0.88-1.39)	0.39
Total hip	BMD	1.22 (0.99-1.50)	0.06	1.04 (0.78-1.39)	0.79	1.23 (0.94-1.60)	0.13	1.17 (0.93-1.48)	0.17

The results are presented for 1 SD decrease in bone mass variables. Adjusted for age and BMI. The analysis was made in a subpopulation of 2730 women and 574 men. Not all variables were measured in all individuals, and specific N per variable are presented in **Table 1**.

Table 5. The risk of MI controlling for confounding factors.

Women		Total population^a, model 1^b	Subpopulation^{aa}, model 1	Subpopulation, model 2^{bb}
Femoral neck	BMD	1.33** (1.08-1.66)	1.25 (0.93-1.69)	1.22 (0.91-1.63)
	vBMD	1.33* (1.07-1.64)	1.17 (0.87-1.58)	1.15 (0.85-1.54)
Total hip	BMD	1.28* (1.02-1.60)	1.06 (0.77-1.46)	1.05 (0.77-1.44)

Men		Total population^a, model 1^b	Subpopulation^{aa}, model 1	Subpopulation, model 2^{bb}
Femoral neck	BMD	1.56** (1.22-2.00)	1.68** (1.19-2.38)	1.56** (1.10-2.20)
	vBMD	1.42** (1.11-1.82)	1.42* (1.03-1.97)	1.33 (0.96-1.85)
Total hip	BMD	1.74** (1.34-2.28)	1.88** (1.32-2.69)	1.77** (1.24-2.51)

^a Repeat of the analysis of 5490 women (including 117 MI) and 1382 men (including 79 MI) in Table 2

^{aa} Only includes the 2526 women (including 54 MI) and 478 men (including 43 MI) with complete background data with respect to ^{bb}

^b Adjusted for age and BMI

^{bb} Adjusted for age, BMI, diabetes, hypertriglyceridemia, hypertension and smoking

* p<0.05

** p<0.01

Flowchart describing the process of finalizing the study population and different subpopulations.