Discordance between fat mass index and body mass index is associated with reduced bone mineral density in women but not in men: the Busselton Healthy Ageing Study

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1 **Mini abstract**

2 The obesity-BMD relationship is complex. In 3,045 middle-aged adults, we found that in
3 women (but not men) with discordant FMI/BMI categories, higher body fat for BMI was
4 associated with lower BMD, suggesting that increased fat mass without an accompanying
5 increase in lean mass may be deleterious to bone.

Abstract

Purpose: The relationship between obesity and BMD is complex. Fat mass index (FMI, fat mass (kg)/height (m)²) is a more accurate measure of fatness than BMI, and depending on body composition, some individuals have discordant BMI/FMI categories. We examined associations between FMI, BMI and BMD in participants in the Busselton Healthy Ageing Study.

Methods: Body composition and BMD of hip, spine and total body were measured using DXA in 3,045 participants (1,644 female) aged 45-67 years. Using standard BMI/FMI categories, participants were classified as underweight/fat deficit, normal, overweight/excess fat, obese I and obese II-III.

Results: BMI and FMI categories were concordant in 77.3% of females and 71.2% of males. There were 12.9% females and 13.2% males in a higher FMI than BMI category (high body fat for BMI), whereas 9.8% females and 15.6% males were in a lower category (low body fat for BMI). Females with high body fat for BMI had significantly lower covariate-adjusted BMD at the femoral neck, total hip and total body (differences of 3.8%, 5.1% and 2.6%, respectively, all $P < 0.05$) than females with low body fat for BMI, and lower total body BMD than women with concordant FMI/BMI (by 1.4%, $P = 0.04$). In males, BMD did not differ significantly between those who were concordant or discordant for FMI/BMI categories.

Conclusion: In women (but not men) with discordant FMI/BMI categories, higher body fat for BMI was associated with lower BMD, suggesting that increased fat mass without an accompanying increase in lean mass may be deleterious to bone.

Introduction

Obesity is a serious public health problem, and the relationship between obesity and bone health is complex. While body weight and body mass index (BMI) have been shown to positively correlate with bone mineral density (BMD) and bone mineral content (BMC) in linear regression analyses [1, 2], there is also evidence that obesity may not be protective against osteoporosis and may even be detrimental to bone health [3, 4]. In a large, population-based study of 832,775 postmenopausal women classified by BMI categories, the rate of hip and pelvis fractures was significantly lower in overweight and obese women than in women with normal or low BMI, but proximal humerus fractures were significantly more common in obese women than normal/underweight women [5]. Furthermore, in women who sustained hip, clinical spine or pelvic fractures, this occurred at a significantly younger age in obese women than in women with normal or low BMI [5]. In a study of 5,025 men and women aged 47-50 and 71-75 years, it was found that in women the association between fat mass and femoral neck BMD was weaker in participants with fat mass above the population median (22.2 kg) compared with those with fat mass below the median [6]. Furthermore, in a recent study of 176 women aged 18-45 years, vertebral strength estimated from quantitative computed tomography (QCT) measurements was related to BMI in an inverted U-shape, with a negative association between BMI and estimated vertebral strength in obese women, who also had a higher predicted vertebral fracture risk than lean controls in several biomechanical models (standing, holding and lifting weights) [7].

Body weight and BMI are convenient measurements for clinical epidemiology, but they do not separate fat mass from lean mass. Linear regression models have been used to evaluate the relationships of lean and fat mass (as measured by dual energy x-ray absorptiometry (DXA)) with BMD, and have provided important information on the independent

significance of lean and fat mass [8-15], but could not determine the influence of excess body fat relative to body size (as reflected by BMI) on bone health. The use of body fat percentage as a measure of body fatness is also likely to be confounded by lean body mass, because at the same fat mass, body fat percentage decreases with increased lean mass [16]. It has been proposed to establish different healthy body fat percentage ranges for each BMI category of underweight, overweight and obesity [17]. In recent years, fat mass index (FMI, fat mass in kg/height in m²) has been suggested to be a more accurate indicator of body fatness than BMI, as it is independent of other body components such as lean mass. The classification ranges for fat deficit, normal, excess fat and obese class I to III have been developed from the data collected in the American National Health and Nutrition Examination Survey (NHANES) [16]. Since both lean mass and fat mass contribute to body mass and thus to BMI, some individuals have discordant BMI and FMI categories, depending on their body composition. For example, if an increase in fat mass was not accompanied by proportional increase in lean mass, that individual would have higher FMI than BMI category.

In a previous analysis of participants in the Busselton Healthy Ageing Study, we found positive relationships between each of lean mass or fat mass with BMD. However, in participants with higher BMI (based on tertiles), these relationships were attenuated in females and absent in males [18]. The aim of the present study was to examine further the relationship between body fatness and BMD, using discordance between FMI and BMI classification as a tool to identify subjects with higher or lower FMI for BMI categories and to investigate the influence of body fatness in relation to BMI on BMD in middle-aged adults.

Participants and methods

Participants

The Busselton Healthy Ageing Study is a study of non-institutionalised “baby boomers” (defined as those born from 1946 to 1964) resident in the Shire of Busselton, Western Australia, a coastal town in south-western Australia with a predominantly White population. The design and rationale of the study have been previously described [19]. All eligible residents listed on the electoral roll have been invited to participate; electoral registration is compulsory in Australia. Phase 1 of the study comprises a cross-sectional health survey, and will be followed by longitudinal studies. Between May 2010 and June 2013, 3,150 participants were recruited to the study for the baseline survey (comprising ~80% of those eligible) and of these 3,080 had a DXA examination. After excluding 35 of non-Caucasian ethnicity, 3,045 participants (1,401 male and 1,644 female) were included in this analysis. The study received ethics approval from the University of Western Australia Human Research Ethics Committee (Number RA/4/1/2203) and written informed consent was obtained from each participant.

DXA scans

DXA scans were undertaken to assess BMD of total hip, femoral neck, anterior-posterior spine (L1-L4) and whole body using a GE Lunar Prodigy Pro densitometer (Madison, WI, USA). The scans were analysed using enCORE Version 13 (GE Health) software with manual inspection of regions of interest and adjustment where necessary by two independent reviewers (MH and KZ). Body composition estimates including whole body fat mass (g) and lean mass (bone free) (g) were also obtained from the whole body DXA scan. Fat mass index (FMI) was calculated as fat mass (kg) / height (m²) and lean mass index (LMI) was calculated as lean mass (kg) / height (m²). Percentage body fat mass was calculated as (fat mass/total

mass) $\times 100$. Annual servicing and calibration according to manufacturer's specifications were carried out and calibration of the DXA machine using a phantom was performed prior to each scanning session. The precision error was $<2.0\%$ for each measured site at standard speed based on repeated scans in a random sample of 30 subjects. Using FMI reference ranges developed from NHANES, participants were classified into categories of fat deficit, normal, excess fat, obese I and obese II-III using FMI cut-offs of <3 , 3-6, 6-9, 9-12 and >12 for males and <5 , 5-9, 9-13, 13-17 and >17 for females [16].

Other assessments

Standing height and body weight were measured using standard anthropometric techniques with the participants lightly-clothed and shoeless. BMI was calculated as weight (kg) / height (m)². BMI between 18.5 and 24.99 kg/m² was regarded as normal, <18.5 underweight, 25–29.99 overweight, 30-34.99 obese I and ≥ 35 obese II-III according to WHO criteria [20]. Data on health history, medication use, and smoking habit (current, never or previous smokers) were collected using a questionnaire [19]. The questionnaire did not collect information on dietary history such as calcium and protein intake, but included a question regarding avoidance of dairy products. Physical activity level was assessed using the International Physical Activity Questionnaire (IPAQ), and categorised as low, medium and high according to the IPAQ scoring protocol [21]. Fasting blood samples were collected, and serum 25-hydroxyvitamin D (25OHD) was measured using the ARCHITECT 25-OH Vitamin D assay (Abbott Laboratories, Abbott Park, Illinois, US). One hundred and seventeen samples (randomly selected within 3 strata of 25OHD) were also assayed using isotope-dilution liquid chromatography/tandem mass spectrometry (LC-MS/MS) according to published methodology [22], and there was a strong correlation between the two techniques ($r^2 = 0.88$).

Data analysis

Variables are presented as means $\pm$ standard deviations (SD), or means $\pm$ standard error of mean (SEM) for adjusted values by gender unless otherwise stated. Generalized additive models (GAM), which offer a greater flexibility to represent the relations between the dependent variable and predictor variables compared with linear regression, were used to generate graphic representations of the dose-response relations of each of FMI and BMI with BMD in each gender, adjusted for the following covariates: age, LMI (for the models for FMI only), smoking, alcohol consumption (≥ 3 units/day), smoking history (never/past/current), serum 25OHD, physical activity level and dairy avoidance. Comparisons between the three groups, low body fat for BMI (refers to those with lower FMI than BMI category), concordant FMI and BMI, and high body fat for BMI (refers to those with higher FMI than BMI category), were made by analysis of covariance (ANOVA) with Tukey's post hoc test and analysis of covariance (ANCOVA) adjusted for covariates listed above for GAM models (except for LMI) with Bonferroni post hoc test. The normality and independence of the residuals and the homogeneity of variance of each model were checked using residual plots (normal probability plot and plot of residuals vs predicted values). Statistical significance level was set at $P < 0.05$ (two-tailed). All analyses were performed using IBM SPSS (version 22, IBM, Chicago, IL, USA) and R (version 3.0.1, R Foundation for Statistical Computing, Vienna, Austria).

Results

Demographic details and key clinical data for all participants are shown in **Table 1**. The mean age of the participants was 56.9 ± 5.6 years (range 45.5-67.3) for males and 56.5 ± 5.5 years (range 45.7-67.2) for females. Although males had slightly but significantly higher BMI compared with females (28.4 ± 4.0 vs 27.8 ± 5.4 kg/m², $P < 0.001$), they had significantly lower FMI (8.1 ± 2.9 vs 11.4 ± 4.2 , $P < 0.001$). According to BMI categories, the prevalence rates of overweight, obese I and obese II-III are 53.4, 22.6 and 6.8% in males and 35.4, 19.9 and 9.9% in females, respectively. Males had significantly higher height, body weight, LMI, serum 25OHD and BMD at hip, femoral neck, spine and total body and significantly lower percentage body fat compared with females. Males were also more likely to be current or past smokers, to consume 3 units or more of alcohol per day and to have higher physical activity level.

Figure 1 shows a breakdown of male and female participants according to 5 categories of BMI and FMI. BMI and FMI categories were concordant in 71.2% of males and 77.3% of females. In females, 9.8% were in a lower FMI than BMI category (low body fat for BMI), whereas 12.9% were in a higher category (high body fat for BMI). For males, the corresponding figures were 15.6% and 13.2%.

Figure 2 depicts the dose-response relations of each of BMI and FMI with BMD in each gender using the generalized additive models. For BMI, a positive relationship with BMD at each site is apparent in both males and females, but the associations at each site appear weaker at higher values of BMI. For FMI, there is a positive relationship with BMD at all sites across all FMI values in males, whereas in females, BMD increases with FMI till FMI reaches about 20 kg/m², after which there is an apparent decline in BMD at femoral neck,

total hip and total body. In post-hoc partial correlation analyses (adjusted for age and LBM) in females with FMI ≥ 20 kg/m² (n =50), FMI negatively associated with total hip BMD (r = 0.290, P = 0.037), and had no significant correlations with total body, spine or femoral neck BMD (r = -0.230 to -0.070, P > 0.05). It should be noted that because of the higher prevalence of obese II-III and the higher FMI values in female participants compared with males, the values on the x axes differ between genders. In addition, the models in females explained a higher percentage of variance in BMDs (adjusted R² 0.133-0.236) compared with the models in males (adjusted R² 0.057-0.136).

Table 2 shows the comparison of characteristics between participants with higher, concordant or lower FMI for BMI category. Males with low body fat for BMI were younger, and had lower body weight and BMI and higher serum 25OHD concentrations compared with males with concordant FMI/BMI or high body fat for BMI. Females with low body fat for BMI were younger and shorter compared with those who had high body fat for BMI. In both genders, participants with low body fat for BMI were more likely to have a high physical activity level.

Table 3 shows the comparison of BMD between those with higher, concordant or lower FMI for BMI categories. In males, there were no significant BMD differences between the three groups in either the unadjusted or the covariate-adjusted analyses. In females, in the unadjusted analysis, those with high body fat for BMI had significantly lower femoral neck, total hip and total body BMD compared with those with concordant FMI and BMI (differences 2.5%, 3.0% and 1.6%, respectively) and low body fat for BMI (5.2%, 6.1% and 3.0%, respectively) (all P<0.05), but not spine BMD. In addition, those with concordant FMI and BMI had significantly lower total hip BMD compared with those with low body fat for

194 BMI (3.0%, $P=0.03$). After adjustment for age, smoking, alcohol consumption, serum
195 25OHD, physical activity level and dairy avoidance, BMD differences at the femoral neck,
196 total hip and total body remained significant between women with high and low body fat for
197 BMI (adjusted differences 3.8%, 5.1% and 2.6%, respectively, all $P<0.05$), as did whole body
198 BMD differences between women with high body fat for BMI and concordant FMI/BMI
199 (1.4%, $P = 0.04$).

Discussion

In this community-based study of middle-aged individuals, we found that when participants were categorised according to BMI and FMI, there was discordance in 29% of males and 23% of females, such that 10% of males and 13% of females had a higher fat mass (by FMI criteria) than predicted by BMI. After adjustment for relevant covariates, females with high body fat for BMI had significantly lower BMD at the femoral neck, total hip and total body than women with low body fat for BMI, and lower total body BMD than women who were concordant for FMI/BMI. In men, however, BMD did not differ significantly between groups based on FMI/BMI discordance.

The role of body composition on bone health has been extensively researched, but findings on the effect of fat mass on BMD have been controversial. This could be largely due to the inter-correlation of body weight, lean mass and fat mass, and the complex relationships of obesity and bone, including the positive impact of mechanical loading and the negative impact of excess body fat on bone metabolism. Our study used discordance between FMI and BMI classification as a tool to identify subjects with excess or low body fat relative to BMI, since if an increase in fat mass is accompanied by a proportional increase in lean mass, FMI and BMI categories would be concordant. Our study suggests that increased fat mass, without an accompanying increase in lean mass (as reflected in FMI/BMI discordance), may have detrimental effects on BMD at the femoral neck, total hip and total body in middle-aged women. Consistent with this, in a previous study of 4,489 white participants aged 19 to 90 years, in each BMI category (18.5-25, 25-30, >30 kg/m²), total body BMC decreased with increased body fat percentage quartiles [3]. In a large study of 7,137 Chinese men and 6,833 women aged 25–64 years, fat mass was negatively associated with whole body and total hip BMC across 5 kg strata of body weight [23]. In our study, we did not observe differences in

lumbar spine BMD between the different FMI for BMI categories. Previous studies have shown that obese individuals are more prone to have fractures at appendicular bones such as ankle, lower limb and humerus [5, 24], thus it is possible that cortical bone rather than trabecular bone is preferentially affected by obesity.

There are several possible mechanisms by which obesity could have a negative impact on bone health. Firstly, obesity and osteoporosis could have shared genetic determinants, as several shared genomic regions for body fat mass and BMD have been identified using bivariate whole-genome linkage scan [25]. Secondly, adipocytes and osteoblasts are derived from a common precursor, the mesenchymal stem cell; thus molecules that activate osteoblast differentiation can inhibit adipogenesis [26] and vice versa. For example, a role of the Wnt pathway in these process has been suggested in recent years [27]. Thirdly, excessive fat mass (especially visceral fat) is associated with increased proinflammatory cytokines [28] and reduced serum insulin-like growth factor I (IGF-I) levels [29], which result in increased bone resorption and reduced bone formation. In addition, the changes in adipocyte-derived cytokines secretion in obesity such as increased production of leptin and decreased production of adiponectin could affect bone formation [4]. Furthermore, excessive body fat is associated with lower vitamin D status [30] and increased parathyroid hormone concentration [31]; both could have negative impact on BMD.

We observed that discordance between FMI and BMI was associated with lower BMD in women but not men. This could be because men with high body fat for BMI also had higher body weight than those with lower body fat for BMI (Table 2), such that the positive effect of increased mechanical loading may have compensated for the negative impact of excess fat on bone metabolism. By contrast, in females these two groups had similar body weight and BMI,

further suggesting that those with high body fat for BMI had increased fat mass without an accompanying increase in lean mass. Indeed, as shown in Figure 2, a negative association of FMI with BMD at high FMI was observed in females but not males. As women in the present study are at the age of peri- or post-menopausal, it is possible that the effect of high fat for BMI only becomes apparent when other factors such as oestrogen deficiency are driving bone loss [32]. In addition, men and women have different percentage of body fat (Table 1), there were more very fat women than men (9.9% vs 6.8% for obese II-III category using BMI cut-off), and both BMI and FMI explained a greater proportion of the variance in BMD in women than in men. These factors may explain the sex difference in our results.

None of the male participants, and only 0.9% of female participants were classified as underweight according to BMI. Thus, although low body weight in individuals is a risk factor for osteoporosis and fracture, this is not a common risk factor in this cohort. In contrast, using either BMI or FMI classification, there were about 30% participants classified as obese in both male and female, confirming that obesity is a serious public health problem in this community. In addition, we found that 15% of men and 20% of women in the normal weight BMI category had excess body fat according to FMI categories. Ageing is associated with changes in body composition, with an increase in percentage body fat and reductions in lean mass and BMD, not necessarily accompanied by changes in weight or BMI [33]. It has been suggested that older people at greatest health risk are those who are simultaneously sarcopenic and obese [34]. In recent years, osteosarcopenic obesity, a condition of the simultaneous presence of osteopenia/osteoporosis, sarcopenia and increased adiposity, has received attention. Postmenopausal women classified as having osteosarcopenic obesity had been reported to have reduced functionality, which could lead to increase fracture risk [35]. Thus the prevalence of osteoporosis in the obese population should receive greater attention,

and there may be value in increasing protein intake in combination with resistance training from middle age to preserve both lean body mass and bone mass with the aims of preventing age-related bone loss and future fracture[36] .

Strengths of our study include its large sample size and community-based nature, being representative of middle-aged Australians in general [19]. The narrow age range of participants and restriction of the analysis to Caucasians minimized potential confounding effects of age and ethnicity on the evaluation of body fatness and BMD [37, 38]. Our study also has limitations. Firstly, it is observational and cross-sectional, and it cannot be assumed that the relationships demonstrated between BMI/FMI and BMD are causal in nature. A longitudinal study would be informative. It is possible that the discordance in BMI/FMI could be due to lifestyle factors such as diet and physical activity. We adjusted for age, physical activity levels and several important lifestyle factors, but as detailed dietary intakes were not recorded in the study, we only adjusted for dairy avoidance in the analysis, and the significant associations observed may still be due to potential residual or uncontrolled confounders. Secondly, the age restriction and ethnic homogeneity of the cohort means the results may not be applicable to other age groups or ethnicities. However, middle-aged individuals such as ‘Baby Boomers’ aged 45-67 are an important group to study, because age-related changes in body composition are under way, and this group may respond to strategies to prevent age-related bone and muscle loss and future fracture. Thirdly, we used FMI cut-offs derived from an American study [16]. These have not been formally validated in Australians, but we think they are broadly applicable because the prevalence of overweight and obesity ($\text{BMI} \geq 25 \text{ kg/m}^2$) is similar for American non-Hispanic whites [39] and Australians [40] in both men (80.8% vs 80.6%) and women (61.3% vs 64.6%) of similar age. FMI cut-offs are based on BMI, and further research is required to establish their relevance to clinical outcomes.

300 Fourthly, the 95% CIs in Figure 2 were wider towards the high end of BMI and FMI due to
301 the smaller number of subjects with BMI and FMI in that range. However, even if subjects
302 with very high BMI (> 37.5 in males and > 42.5 in females) and FMI (> 12.5 in males and $>$
303 22.5 in females) were excluded, the weaker association at high BMI and FMI would still be
304 evident. It is known that measurement errors in BMD using DXA are larger in obese
305 individuals, and in a recent study of healthy volunteers, fat layering significantly affected
306 mean BMD values at the lumbar spine, but not at the femoral neck or total hip [41].
307

308 In conclusion, our study showed that there were 12.9% females and 13.2% males in a higher
309 FMI than BMI category (high body fat for BMI), whereas 9.8% females and 15.6% males
310 were in a lower category (low body fat for BMI). We found that in women but not men who
311 had high fat mass for BMI without an accompanying increase in lean mass, there was a
312 decrease in BMD at total hip, femoral neck and total body. Maintaining lean mass from
313 middle age onwards may be important for the prevention of osteoporosis and associated
314 fractures in later life.

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Table 1 Characteristics of male and female participants

	Male (n = 1401)	Female (n = 1644)	P value ^a
Age (year)	56.9 ± 5.6	56.5 ± 5.5	0.040
Height (cm)	176.0 ± 6.6	162.7 ± 6.1	<0.001
Weight (kg)	88.2 ± 13.5	73.4 ± 14.4	<0.001
BMI (kg/m ²)	28.4 ± 4.0	27.8 ± 5.4	<0.001
Lean mass index (kg/m ²)	19.4 ± 1.7	15.3 ± 1.6	<0.001
Fat mass index (kg/m ²)	8.1 ± 2.9	11.4 ± 4.2	<0.001
Percentage body fat	27.5 ± 6.7	39.9 ± 7.9	<0.001
Serum 25OHD (nmol/L)	84.5 ± 25.1	77.2 ± 24.0	<0.001
BMI category (%)			
Underweight	0	0.9	<0.001
Normal	17.3	33.9	
Overweight	53.4	35.4	
Obese I	22.6	19.9	
Obese II-III	6.8	9.9	
FMI category (%)			
Fat deficit	2.2	3.7	<0.001
Normal	21.6	27.6	
Excess fat	43.1	36.5	
Obese I	24.0	22.1	
Obese II-III	9.1	10.0	
Smoking (%)			
Never	43.9	51.8	<0.001
Past	44.5	39.2	
Current	11.6	9.1	
Alcohol consumption ≥ 3 units/d (%)	37.6	10.0	<0.001
Physical activity level (%)			
Low	20.8	26.7	<0.001
Moderate	27.6	39.4	
High	51.6	33.9	
Bone mineral density (g/cm²)			
Femoral neck	1.017 ± 0.135	0.948 ± 0.135	<0.001
Total hip	1.104 ± 0.145	0.992 ± 0.142	<0.001
Spine	1.266 ± 0.188	1.171 ± 0.173	<0.001
Total body	1.311 ± 0.098	1.188 ± 0.098	<0.001

Values are mean ± SD unless otherwise stated. ^a Student's t-test or chi-squared test.

Table 2 Comparison of characteristics by FMI-BMI classifications in middle-aged men and women

	Male (n = 1401)			Female (n = 1644)		
	High body fat for BMI (n = 185)	Concordant FMI and BMI (n = 998)	Low body fat for BMI (n = 218)	High body fat for BMI (n = 212)	Concordant FMI and BMI (n = 1271)	Low body fat for BMI (n = 161)
Age (year)	57.9 ± 5.5 ^a	57.1 ± 5.6 ^a	55.7 ± 5.4	57.3 ± 5.5 ^a	56.5 ± 5.5	55.8 ± 5.3
Height (cm)	176.3 ± 6.7	176.0 ± 6.5	175.9 ± 7.2	163.6 ± 5.9 ^a	162.7 ± 6.1	161.7 ± 5.7
Weight (kg)	90.1 ± 11.5 ^a	88.7 ± 13.9 ^a	84.3 ± 13.1	73.0 ± 10.3	73.9 ± 14.9 ^a	70.4 ± 14.5
BMI (kg/m ²)	29.0 ± 3.2 ^a	28.6 ± 4.1 ^a	27.2 ± 3.7	27.3 ± 3.6	28.0 ± 5.7	27.0 ± 5.6
BMI category (%)						
Underweight	-	-	-	-	1.1	-
Normal	20.0	17.6	13.7	52.4	31.5	29.2
Overweight	55.7	52.0	58.0	33.5	36.0	33.5
Obese I	24.3	22.2	22.8	14.2	20.8	19.9
Obese II-III	0 ^{a, b}	8.3	5.5	0 ^{a, b}	10.6	17.4
Lean mass index (kg/m ²)	18.1 ± 1.3 ^{a, b}	19.4 ± 1.6 ^a	20.4 ± 1.7	14.1 ± 0.9 ^{a, b}	15.3 ± 1.6 ^a	16.6 ± 1.5
Fat mass index (kg/m ²)	9.9 ± 2.2 ^{a, b}	8.2 ± 2.9 ^a	5.9 ± 2.3	12.1 ± 2.9 ^a	11.6 ± 4.3 ^a	9.4 ± 4.3
Percentage body fat	33.6 ± 4.4 ^{a, b}	27.8 ± 6.0 ^a	20.8 ± 5.8	44.0 ± 4.8 ^{a, b}	40.1 ± 7.5 ^a	33.0 ± 9.1
Serum 25OHD (nmol/L)	80.1 ± 24.1 ^a	83.7 ± 23.3 ^a	92.1 ± 31.6	76.7 ± 21.4	77.4 ± 24.3	75.9 ± 24.7
Smoking (%)						
Never/past/current	48.1/42.2/9.7	42.3/46.7/10.9 ^a	47.5/36.5/16.0	61.8/28.8/9.4 ^{a, b}	49.9/41.3/8.8	53.4/36.0/10.6
Alcohol consumption ≥ 3 units/day (%)	33.5	38.9	35.2	8.5	10.0	12.4
Physical activity level (%)						
Low/moderate/high	22.2/31.9/45.9 ^a	22.2/29.0/48.8 ^a	13.2/17.8/68.9	29.2/38.7/32.1 ^a	27.1/40.3/32.7 ^a	20.5/32.9/46.6

Values are mean ± SD unless otherwise stated. ^aSignificantly different from those with low body fat for BMI, ^bSignificantly different from those with concordant FMI and BMI category in the same sex, P < 0.05 (analysis of variance with Tukey's post hoc test).

Table 3 Comparison of bone mineral density (BMD) by FMI-BMI classifications

	Male (n = 1401)			Female (n = 1644)		
	High body fat for BMI (n = 185)	Concordant FMI and BMI (n = 998)	Low body fat for BMI (n = 218)	High body fat for BMI (n = 212)	Concordant FMI and BMI (n = 1271)	Low body fat for BMI (n = 161)
Unadjusted						
Femoral neck (g/cm ²)	1.003 ± 0.135	1.017 ± 0.134	1.028 ± 0.138	0.925 ± 0.135 ^{a, b}	0.948 ± 0.133	0.973 ± 0.146
Total hip (g/cm ²)	1.085 ± 0.139	1.105 ± 0.145	1.111 ± 0.147	0.964 ± 0.139 ^{a, b}	0.993 ± 0.140 ^a	1.023 ± 0.149
Lumbar spine (g/cm ²)	1.282 ± 0.207	1.267 ± 0.183	1.252 ± 0.195	1.159 ± 0.176	1.173 ± 0.171	1.171 ± 0.183
Total body (g/cm ²)	1.301 ± 0.097	1.312 ± 0.097	1.319 ± 0.102	1.170 ± 0.096 ^{a, b}	1.189 ± 0.096	1.205 ± 0.110
Covariates-adjusted						
Femoral neck (g/cm ²)	1.008 ± 0.010	1.018 ± 0.004	1.024 ± 0.009	0.931 ± 0.009 ^a	0.948 ± 0.004	0.966 ± 0.010
Total hip (g/cm ²)	1.087 ± 0.011	1.105 ± 0.005	1.109 ± 0.010	0.969 ± 0.009 ^a	0.993 ± 0.004	1.018 ± 0.011
Lumbar spine (g/cm ²)	1.280 ± 0.014	1.267 ± 0.006	1.254 ± 0.013	1.165 ± 0.012	1.173 ± 0.005	1.168 ± 0.014
Total body (g/cm ²)	1.303 ± 0.007	1.312 ± 0.003	1.317 ± 0.007	1.173 ± 0.006 ^{a, b}	1.189 ± 0.003	1.203 ± 0.007

Values are mean ± SD for unadjusted analysis and mean ± SEM covariates-adjusted analysis.

^aSignificantly different from those with low body fat for BMI, ^bSignificantly different from those with concordant FMI and BMI category in the same sex, P < 0.05 (analysis of variance with Tukey's post hoc test, or analysis of variance with Bonferroni post hoc test adjusted for age, smoking, alcohol consumption, serum 25OHD, physical level and dairy avoidance).

Figure legend

Figure 1 Number of male and female participants in each fat mass index (FMI) category by body mass index (BMI) category

Figure 2 Graphic presentation of the dose-response relationship between body mass index (BMI, Model 1) or fat mass index (FMI, Model 2) with bone mineral density (BMD) in male (A) and female (B) obtained by generalized additive regression models. Models adjusted for age, lean mass index (for the models for FMI only), smoking, alcohol consumption, serum 25OHD, physical level and dairy avoidance as covariates. Dotted lines represent 95% confidence intervals. The reference value for BMD (0 in the graph) is the value associated with the mean BMI or FMI for all subjects in each gender. Ranges from 0.5% to 99.5% percentiles of exposure variables are included. The rug plot along the bottom of each graph depicts each observation. Note the different values on the x-axes for females compared with males, reflecting the higher prevalence of obesity II-III and the higher FMI values in female participants.

Figure 1

Male (n = 1401)

Female (n = 1644)

Figure 2

A: Male

B: Female

Femoral neck

Total hip

Spine

Total body

Model 1: BMI

Model 2: FMI