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How does obesity influence the risk of vertebral fracture? Findings from the UK Biobank participants

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Disclosures

The authors have no conflicts of interest and nothing to disclose.

Abstract

Obesity and osteoporotic-related fractures are two common public health problems, although it is unclear how obesity affects the risk of vertebral fractures. The purpose of this study was to examine the association between different measures of obesity and the risk of vertebral fracture, and to establish the various clinical factors that can predict such risk. We analysed the data obtained from 502,543 participants in the UK Biobank (229,138 men and 273,405 women) who were aged 40-69 years. Imaging information was available in a subset of this cohort (5,189 participants, 2,473 men and 2,716 women). We further examined how bone mineral density (BMD) and geometry of the vertebrae were related to body fat measures. It was shown that a larger waist circumference, but not body mass index (BMI), was associated with an increase in fracture risk in men, but in women, neither BMI nor waist circumference affected the risk. Trunk fat mass, visceral adipose tissue (VAT) mass and limb fat mass were negatively associated with vertebral body BMD and geometry in men and women. BMD and geometry are related to the vertebral strength, but may not be directly related to the risk of fractures which are also influenced by other factors. The binary logistic regression equation established in this study may be useful to clinicians for prediction of vertebral fracture risks, and may provide further information to supplement FRAX which assesses general fracture risks.

Key words: body mass index, waist circumference, fat mass, spine, fracture risk assessment

Introduction

Obesity and osteoporosis are two very common public health problems. Obesity is sometimes thought to have a protective effect against osteoporotic fractures [1]. A higher body weight may impose larger mechanical loading on bone and consequently help improve bone health and reduce the risk of fracture [2]. However, recent studies show that when the mechanical loading effect of total body weight is accounted for, fat mass actually has a negative effect on bone health [3,4]. Recent epidemiological evidence also reveals that the relation between obesity and bone health may be site dependent [5]. Obesity has been shown to increase the risk of fractures at ankle and upper leg in postmenopausal women [5], but how it affects the risk in the vertebral column is still not clear.

Obesity is often believed to be beneficial to bone health because of the positive effect of mechanical loading conferred by body weight on bone formation[6]. However, adipose tissue may have negative effects on bone metabolism[6]. A number of previous studies have shown that fat mass was associated with the decrease of bone mass and bone quality at spine [7-9], leading to lower vertebral bone strength. The interaction of the different effects of mechanical loading and adiposity is still unclear[10]. The underlying mechanism between obesity and bone health is likely to be complex, and may be different in men and women. Obesity in men is more characterised by central adiposity in comparison to women. Visceral adipose tissue is particularly detrimental to bone health as it is associated with a number of hormones and cytokines that contribute to bone loss [6]. A number of studies have shown that obesity is more consistently associated with increased prevalence of vertebral fracture when obesity is assessed using visceral fat mass [11-13]. On the other hand, obesity has been found to be associated with increases in vertebral fracture risk in women, but not in men [11,13-16]. Waist circumference has been a reliable clinical parameter for predicting visceral fat[17], whereas BMI has stronger correlation with non-abdominal and abdominal subcutaneous fat[17]. The

correlation between obesity and the risk of vertebral fracture is likely to be dependent on whether obesity is measured by BMI or waist circumference. There is thus a need to clarify such correlation.

Vertebral body strength is related to its bone mineral density (BMD) and the geometry of the bone[18-21]. A number of previous studies have examined how fat mass influences vertebral body BMD, which is only a "proxy measure" of the risk of fractures [13,16,18]. It would be also useful to examine how fat mass affects the geometry of the vertebrae. The smaller vertebral size in women has been suggested as one of the reasons for the higher prevalence of vertebral fractures in women [22]. However, there is no information about how obesity may affect vertebral body geometry. There is clearly a need to study such relationship as it would provide additional insights into how fat mass may affect bone strength and potentially the risk of vertebral fractures.

Although the risk of vertebral fracture is possibly related to mechanical loading and adiposity as discussed above, various other clinical factors will need to be considered in order to provide an accurate prediction of the risk of vertebral fractures. They may include history of prior fractures, age, gender, smoking, alcohol use, glucocorticoid use, rheumatoid arthritis, and secondary osteoporosis. FRAX has been developed to evaluate osteoporotic fracture risk in untreated postmenopausal women and men aged >50 years [23], although the algorithm is not specifically developed for vertebral fractures. Some previous studies attempted to predict vertebral fracture risk [24,25]. They showed that fracture risks are related to morphological factors such as vertebral sizes or kyphosis. But clinically this information may not be available for fracture prediction. Their sample sizes were also generally small with limited power. This study will further explore the prediction of vertebral fractures considering a range of clinical factors as used in FRAX.

The aim of this study was to (1) to examine the association between obesity and the risk of vertebral fracture, and whether this association was influenced by the methods of measuring obesity, (2) to predict the risks of vertebral fractures using various clinical factors, and (3) to study how vertebral BMD and geometry, which are both related to vertebral strength, are associated with body fat measures.

Materials and methods

Study design and sample

UK Biobank is a health resource aiming to provide data for researchers around world to study the cause of a wide range of diseases such as cancer, cardiovascular diseases, diabetes, arthritis, osteoporosis, eye disorders, depression and dementia (https://www.ukbiobank.ac.uk). UK Biobank is based on a prospective cohort consisting of around 500,000 UK volunteer participants aged 40-69 years who were first recruited and assessed during 2006-2010. Subsets of this original cohort were then repeatedly assessed overtime during several time periods. The current study was based on datasets collected from two time periods: 2006-2010 and 2014-2019. It was conducted in November 2016 after approval was obtained to access the data.

Full dataset - 502,543 participants (229,138 men and 273,405 women) aged 40-69 years who were assessed using self-completion questionnaire and physical measurements during 2006-2010. The current study used this data set to examine the incidence of vertebral fractures in participants with different body weights.

Data subset - A subset of this cohort, 5,189 participants (2,473 men and 2,716 women) was followed up in an imaging study (2014 – 2019) that provided dual-energy X-ray absorptiometry (DXA) data of the body. This allows us to further study BMD and geometry

of the vertebrae of the participants, as these data were not available for every participant in the full data set.

Clinical Information From the Full Dataset

Anthropometric measurements

Height (standing), weight, and waist circumference (WC) were obtained for all participants.

Incidence of fractures

Each participant was asked to fill in a self-completion questionnaire in baseline assessment which included questions asking whether they had fractured/broken bones in the last 5 years and where the fractured bone sites were (e.g. spine, hip, wrist, leg, ankle, arm, or others).

Other information

Categorical data including smoking status (never, previous, or current smoker), daily alcohol consumption of three or more units (yes or no), history of rheumatoid arthritis (yes or no), secondary osteoporosis (yes or no), type 2 diabetes (yes or no), hormone-replacement therapy (yes or no), and menopause (yes or no) which were obtained from self-completion questionnaire.

Imaging Information from the Data subset

Vertebral body BMD and geometry

DXA images (GE-Lunar iDXA, Madison, WI, USA) were collected to obtain numerical measures of vertebral body size, and areal bone mineral density (BMD) at whole spine (C4 to L4) and lumbar spine (L1 to L4) in the anterior-posterior (AP) direction. The measures from lumbar spine AP scan included L1-L4 BMD, L1-L4 area (i.e. the estimated projected area of L1-L4 in the AP scan), L1-L4 average height (i.e. the vertebral height from the bottom of L4

to the top of L1), and L1-L4 average width (i.e. the average width of the four lumbar vertebrae L1-L4). The measures from whole spine AP scan included spine BMD, and spine bone area. The vertebral body BMD and geometry data were obtained from 5,189 participants (male = 2,473, female =2,716).

Body composition

Body composition data were also obtained from this data subset. The measures used in this study included trunk fat mass, visceral adipose tissue (VAT) mass, and limb fat mass which is the sum of leg fat mass and arm fat mass. These measurements were not normalised to body weight or height.

Data analysis

Participants (N= 502,543) were categorised into underweight, normal weight, and obese using body mass index (BMI) and waist circumference (WC). When BMI was used, both male and female participants were categorised according to the same criteria, i.e. underweight ($BMI < 25\ kg/m^2$), normal weight ($25\ kg/m^2 \leq BMI < 30\ kg/m^2$), and obese ($BMI \geq 30 kg/m^2$). When waist circumference was used, male and female participants were categorised using different criteria. Female were categorised as underweight ($WC < 80$ cm), normal weight ($80cm \leq WC < 88cm$), and obese ($WC \geq 88cm$), while male were categorised as underweight ($WC < 94$ cm), normal weight ($94cm \leq WC < 102cm$), and obese ($WC \geq 102cm$) [26].

The association of the various categories of BMI and waist circumference with incidence of vertebral fracture was examined in males and females using chi-square tests.

The relation between vertebral fractures and various clinical risk factors were studied using full dataset, including age, gender, body weight and height, history of hip and other limb fractures (they were studied separately as the risks of fractures were site dependent [14]),

smoking, alcohol consumption, rheumatoid arthritis, type 2 diabetes and secondary osteoporosis. The significance of these relations was examined using chi-square tests for categorial data and logistic regression for continuous data. The odd-ratios of each risk factor was determined.

Multivariate logistic regression was employed to predict the risks of vertebral fractures using the factors identified above (enter method). However, only factors which were statistically significant related to the fracture risks were entered into the regression equation.

The imaging data subset provided further information which allowed us to study fat mass, vertebral body BMD and geometry which were not available in full data set. Linear regressions were employed to look at how BMD and geometry were related to trunk fat mass, visceral adipose tissue, and limb fat mass. Each of these fat mass measures was entered into regression analysis individually, while using age, weight, height, smoking status, hormone-replacement therapy (for females only), and menopause (for females only) as covariates. Linear regression analysis was conducted on male and female separately. Multi-collinearity between independent variables was checked by variance inflation test (VIF <10).

SPSS 22.0 (IBM, Armonk, NY, USA) was used for all statistical analysis. Data from any participant with missing values were not included in the statistical analysis. The level of statistical significance was set at $p < .05$.

Results

Obesity and risk of vertebral fracture

Characteristics of participants in full data set and imaging subset are shown in Table 1 and 2 respectively. The ethnic background for majority of participants is white (94.1% for baseline assessment and 96.9% for imaging study).

There were 479 vertebral fractures in 229,138 male participants and 645 vertebral fractures in 273,405 female participants in the previous five years, which result in the incidence rate of vertebral fracture at 4.2 per 10,000 per year in men and 4.7 per 10,000 per year in women.

Chi-square analysis was conducted on BMI data from 496, 812 (226,945 male and 269,867 female) participants out of 502,543 participants and waist circumference data from 500, 383 (228,062 male and 272,321 female) participants out of 502,543 participants, due to missing data. There was no significant association between BMI and incident vertebral fracture in male $\chi^2 = 0.94$, $p = .625$ or in female $\chi^2 = 4.28$, $p = .118$ (Table 3). There was a significant association between waist circumference and incident vertebral fracture in male $\chi^2 = 8.51$, $p = .014$, but not in female $\chi^2 = 0.71$, $p = .701$ (Table 4). Obese men (WC $\geq$ 102 cm) had higher vertebral fracture incidence (5.0 per 10,000 per year) than normal weight men (3.7 per 10,000 per year) and underweight men (3.8 per 10,000 per year).

The odd-ratios of the various clinical risk factors are shown in Table 5. All these factors were entered into the logistic regression equation, with the exception of alcohol consumption and type 2 diabetes which were not shown to be significantly related to vertebral fracture risks. The logistic regression model was found to be statistically significant (omnibus test, p=.000), and was therefore a good predictor of vertebral fractures.

Vertebral body BMD and geometry

Due to missing values, the multiple linear regression analysis was conducted on data from 4,849 participants (2,277 male and 2,572 female).

Vertebral body BMD and geometry generally showed negative association with VAT mass, trunk fat mass and limb fat mass in both males and females ($p<.05$) (Table 6). However,

spine bone area appeared to show positive association with VAT mass and trunk fat mass, but its association with limb fat mass remained negative ($p<.01$).

The association of limb fat mass with vertebral body BMD and geometry, compared to VAT mass and trunk fat mass, appear to be stronger with larger correlation coefficients. It should also be noted the associations between L1-4 BMD and VAT mass were weak and not statistically significant in both males and females ($p>.05$).

Discussion

A strength of the present study is that it utilised data from a large cohort and attempted to answer the important clinical question of how obesity may affect the risk of vertebral fractures. BMI and waist circumferences are commonly used clinical measures to assess obesity, but only waist circumference appear to influence the risk of vertebral fractures in men. Obese men with waist circumference over 102 cm had a significantly higher vertebral fracture incidence compared with men of normal weight and underweight. We also showed that trunk fat mass, VAT mass and limb fat mass were negatively associated with vertebral body BMD and geometry, but the negative association was strongest for limb fat mass.

The current study provides important clinical information about how various clinical risk factors are related to and may predict the risk of vertebral fractures. These risk factors are in agreement with previous findings [27]. The binary regression equation derived in the present study may be used by clinicians to predict the risk of vertebral fractures, providing information additional to FRAX which assesses the general risk of fractures. It is noteworthy to mention that a previous history of hip fractures is the most significant predictive factor

among all the variables in the equation. This finding is in agreement with those of previous studies that the risks of fractures of these two body regions are closely related [28].

The current study provides support to previous findings that obesity measured by BMI was not associated with vertebral fracture risk [5,29]. However, in previous studies, there were inconsistent observations about the effect of BMI on the risk of fractures. Some studies reported BMI was associated with increased risk [9,15,16] while others found BMI was negatively correlated with the risk [14]. When obesity was measured by different measures, especially those related to central adiposity such as waist circumference, trunk fat mass, and VAT mass, previous literature is more consistent in showing that obesity is associated with increased prevalence of vertebral fracture [11-13]. This is in line with the findings in this study. Therefore, our study, together with the others, suggest that central adiposity may be an important risk factor for the risk of vertebral fracture. In addition, the binary regression equation revealed that the risk of vertebral fractures is higher in men than women, and this in general agreement with the observation reported previously[13]. However, previous studies reported that obesity only affects the risks in women but not in men [11,12,14,16]. This is in contrast to our finding that waist circumference affects men only. The effect of obesity in different genders is likely to be affected by how we measure or define obesity. Another explanation is that we looked at the risk of vertebral fractures, whereas the previous studies examined other anatomical cites.

Our findings are in line with a previous study which found that lumbar spine BMD was negatively associated with trunk fat mass and limb fat mass, but not with abdominal fat mass [30]. However, some previous studies found that lumbar spine BMD was negatively correlated with VAT mass [4,7,8,31]. The different findings may be due to different methods used in measuring vertebral body BMD and VAT mass. While the data employed in the current study was based on DXA measurement[30], computed tomography (CT) was used in those studies

where different results were found [4,7,8,31]. Although DXA is a valid method to estimate body composition, it may not be as accurate as CT when assessing abdominal fat [32].

There were few studies that have examined the effect of fat mass on vertebral geometry and their findings are inconsistent. One recent study found that whole body fat mass was negatively associated with anterior-posterior vertebral diameter of lumbar spine in both men and women aged 60 to 64 years [33], while another study found that there was no association between total body fat mass and cross-sectional area of lumbar vertebrae in teenagers and young adults [34]. The current study provided clear evidence that fat mass had negative association with vertebral geometry in the lumbar spine and the whole spine.

The results from imaging data subset showed that limb fat and trunk fat mass had a greater effect on vertebral body BMD and geometry than VAT fat mass, suggesting that visceral fat may have less influences on vertebral strength in comparison to other fat tissues. However, the results from the full dataset showed that waist circumference, which is related to visceral fat, is the only measure which is related to the risk of vertebral fracture in men. These two observations may appear to be in disagreement, but this clearly shows that BMD and the risk of fractures are not directly related to each other. Obese subjects have been found to have increased prevalence of vertebral fracture due to poor bone quality, despite normal BMD [9]. The risk of fractures is clearly not affected by BMD only but also a range of clinical factors including smoking, alcohol use, glucocorticoid use, rheumatoid arthritis, and secondary osteoporosis [23]. Moreover, in obese patients, the accuracy of measurement of BMD using DXA images has been shown to be adversely influenced by the thickness of VAT [35]. The above findings suggest that it may not be adequate to use BMD to assess the risk of vertebral fracture especially in obese subjects.

In this study we observed weak associations between fat mass and vertebral body BMD and geometry in both men and women. This implies there are other factors which may also influence BMD and geometry. Biomechanical factors may play a role in the associations between obesity and vertebral fracture risk. Spinal loads depend on trunk mass and the distance between trunk centre-of-mass to the vertebrae, both of which were found to be significantly larger in the obese subjects [36,37]. It has been shown that for the same body weight a larger waist circumference, which is related to increased visceral fat mass, can significantly move the centre-of-mass forward and increase the spinal loads [38]. It is possible that the increased spinal loads, together with the reduced BMD and smaller vertebral geometry associated with obesity, are responsible for the increased incidence of vertebral fractures.

The current study has some limitations. The incidence of vertebral fracture was obtained from self-report questionnaire, and there was no information about how the reported vertebral fractures were diagnosed. It is possible that not all vertebral fractures were reported in the questionnaire as vertebral fracture is generally underdiagnosed [39]. However, the incidence rate of vertebral fracture observed in the current study is comparable to a previous study that was based on medical records [40]. This previous study found that for a UK population of 5 million adults the incidence rate of vertebral fracture was 3.2 per 10,000 per year for men and 5.6 per 10,000 per year for women, while our study found that the incidence rate was 4.0 per 10,000 per year for men and 4.7 per 10,000 per year for women. Another limitation of the current study is that the logistic regression equation was derived from data obtained within a short period of time (between 2006-2010), and therefore does not represent the prospective risks as compared to FRAX which provides a 10-year risk prediction. However, the model is the only one at the moment that can assess vertebral fracture risk, and may be used clinically in conjunction with FRAX. Finally, low serum vitamin D level in the obese may be an

important factor that may contribute to bone fragility [7], but we were unable to include this as a risk factor in our analysis as this was not available from the UK Biobank.

Conclusion

The results of the present study showed that obese men with waist circumference (WC) over 102 cm had a significantly higher vertebral fracture incidence compared with men with normal weight (94 cm ≤ WC < 102 cm) and underweight (WC < 94 cm). Trunk fat mass, VAT mass and limb fat mass were negatively associated with vertebral body BMD and geometry in men and women. BMD and geometry are related to the vertebral strength, and they may not be directly related to the risk of fractures which are also influenced by other factors. The binary logistic regression equation established in this study may be clinically useful for the prediction of fracture risks.

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Table 1 Characteristics of participants in the full data set (mean ± S.D.)

	Male (N=229,138)	Female (N=273,405)
Age	56.75±8.19	56.35±8.00
Weight (kg)	85.93±14.37	71.46±14.09
Height (m)	1.76±0.68	1.62±0.63
BMI (kg/m^2)	27.84±4.25	27.09±5.19
Waist circumference (cm)	96.96±11.35	84.72±12.55
Previous smoker	87614	85458
Current smoker	28612	24367
Rheumatoid arthritis (yes)	1706	3952
Secondary osteoporosis (yes)	3041	6205
Type 2 diabetes (yes)	2030	1347
Menopause (yes)		165,411
Hormone-replacement therapy (yes)		103,921

Table 2 Characteristics of participants in the data subset (mean ± S.D.)

	Male (N=2,473)	Female (N=2,716)
Age	61.89±7.09	60.82±7.17
Weight (kg)	84.51±13.39	69.50±12.74
Height (m)	1.76±0.66	1.63±0.63
BMI (kg/m^2)	27.28±3.99	26.38±4.86
Waist circumference (cm)	93.85±10.23	82.29±11.59
VAT mass (g)	1698.41±949.57	780.51±583.32
Trunk fat mass (g)	15378.56±6199.79	14005.97±6026.61
Limb fat mass (g)	8684.01±3056.76	12024.89±3998.66
L1-L4 BMD (g/cm^2)	1.25±0.19	1.14±0.18
L1-L4 area (cm^2)	66.06±6.23	54.19±5.20
L1-L4 average width (cm)	4.64±0.39	4.08±0.72
L1-L4 average height (cm)	14.24±0.82	13.30±0.82
Spine BMD (g/cm^2)	1.19±0.15	1.02±0.15
Spine bone area (cm^2)	212.03±25.47	182.27±20.48
Current and previous smoker	1,072	967
Menopause (yes)		2,014
Hormone-replacement therapy (yes)		1,073

Table 3 Contingency table showing the number of vertebral fractures in different BMI categories in males and females

	BMI (kg/m^2)			
Male	<25	25-30	≥ 30	Total
Vertebral fracture	119	223	128	470
No vertebral fracture	56,634	112,023	57,818	226,475
Total	56,753	112,246	57,946	226,945
Female	<25	25-30	≥ 30	Total
Vertebral fracture	267	227	131	625
No vertebral fracture	105,405	99,656	64,181	269,242
Total	105,672	99,883	64,312	269,867

Note: $\chi^2 = 0.94$, p = .625 for male; $\chi^2 = 4.28$, p = .118 for female

Table 4 Contingency table showing the number of vertebral fractures in different waist circumference categories in males and females

	Waist circumference (cm)			
Male	<94	94 -102	≥ 102	Total
Vertebral fracture	176	124	174	474
No vertebral fracture	91,851	66,243	69,519	227,588
Total	92,016	66,361	69,685	228,062
Female	<80	80-88	≥ 88	Total
Vertebral fracture	237	168	237	642
No vertebral fracture	104,406	68,168	99,105	271,679
Total	104,643	68,336	99,342	272,321

Note: $\chi^2 = 8.51$, p = .014 for male; $\chi^2 = 0.71$, p = .701 for female

Table 5 Coefficients (B) of the various predictive variables in the logistic regression equation and odds ratios of these variables

Predictive factor	B (S.E.)	Odds ratio [95% Confidence interval]
Constant	-3.690 (0.836)	
Age (years)	0.011(0.004)**	1.012 [1.004, 1.019]
Gender[1]	0.221(0.087)*	1.248 [1.052, 1.479]
Weight (kg)	-0.005(0.002)*	0.995 [0.991, 1.000]
Height (cm)	-0.019(0.005)**	0.981 [0.971, 0.990]
History of hip fracture[2]	2.419(0.184)**	11.237 [7.833, 16.121]
History of fractures other than hip and vertebrae[2]	1.428 (0.066)**	4.169 [3.662, 4.747]
History of smoking[2]	0.275 (0.061)**	1.316 [1.167, 1.484]
Rheumatoid Arthritis[2]	0.778 (0.184)**	2.178 [1.518, 3.126]
Secondary osteoporosis[2]	0.347 (0.183)*	1.415 [0.988, 2.027]

Note: R^2 = .001 (Cox & Snell) .040 (Nagelkerke). Model $\chi^2(7)$ = 615.850 p=.000
[1]Variable code (0=female, 1=male)
[2]Variable code (0=no, 1=yes)
*Significance of the predictive variables *p<.05; **p<.01*

Table 6 Association between fat mass, vertebral BMD and geometry in male (N=2,277) and female (N=2,572) participants

	VAT mass (g)	Trunk fat mass (g)	Limb fat mass (g)
Male			
L1-L4 BMD (g/cm^2)	-0.036	-0.148**	-0.284**
L1_L4 area (cm^2)	-0.123**	-0.148**	-0.287**
L1-L4 average width (cm)	-0.237**	-0.489**	-0.281**
L1-L4 average height (cm)	0.085**	0.063	-0.058
Spine BMD (g/cm^2)	-0.084*	-0.226**	-0.370**
Spine bone area (cm^2)	0.248**	0.235**	-0.212**
Female			
L1-L4 BMD (g/cm^2)	0.035	-0.071	-0.450**
L1_L4 area (cm^2)	0.023	-0.133**	-0.420**
L1-L4 average width (cm)	-0.018	-0.178**	-0.189**
L1-L4 average height (cm)	0.093**	0.195**	-0.167**
Spine BMD (g/cm^2)	0.054*	-0.086	-0.436**
Spine bone area (cm^2)	0.346**	0.518**	-0.406**

Note: values are the standardised regression coefficients from linear regression models adjusted for age, weight, height, smoking status, hormone-replacement therapy (for female only), and menopause (for female only). *p<.05; **p<.01