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Total and visceral adiposity are associated with prevalent vertebral fracture in women but not men at age 62 years: the Newcastle Thousand Families Study

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Abstract

Low body weight is an established risk factor for osteoporosis and fracture but the skeletal risks of higher adiposity are unclear, and appear sex-specific and site-dependent. The aim of this study was to investigate associations of total fat mass (TFM), visceral adipose tissue (VAT) and C-reactive protein (CRP) with bone mineral density (BMD) and prevalent vertebral fracture (VF) in men and women aged 62 years. Three hundred and fifty two men and women aged 62.5 ±0.5 years from the Newcastle Thousand Families Study cohort, received DXA evaluations of femoral neck and lumbar spine BMD, of the lateral spine for vertebral fracture assessment, and of the whole body for TFM and VAT (GE Lunar CoreScan). Plasma CRP, FRAX scores, falls in the last 12 months and occupation at age 50 years were also included in the analysis. Vertebral fractures were less prevalent in women than in men (OR 0.33, $p < 0.001$) and BMD or FRAX scores did not differ between participants with and without VF. Women with VF were heavier, and had higher TFM, VAT and CRP than women without ($p<0.001$). In women, greater (+1 SD) TFM and VAT increased the odds of any grade VF (TFM: OR 1.06, $p = 0.001$; VAT: OR 2.50 $p = 0.002$), and greater VAT mass increased the odds of prevalent mild VF (OR: 2.60, $p = 0.002$). In contrast, there were no associations in men. In both sexes, after controlling for body weight, neither VAT or CRP were associated with BMD. In conclusion, irrespective of BMD, total and visceral adiposity were associated with prevalent VF in women but not in men. High fat mass, particularly if visceral, should be considered when assessing VF risk in women. Risk factors for VF in men require further investigation, particularly given their high prevalence.

Keywords: *obesity; bone; fracture; DXA; fat.*

Introduction

Vertebral fractures are amongst the most common consequences of bone fragility (1) and can cause significant morbidity that is comparable with morbidity post hip fracture (2). Their clinical relevance is attributed in part, to their association with disability and subsequent fractures. For instance, one prevalent vertebral fracture confers a 1.7 to 2.3-fold increase in the risk of any clinical fracture (3), a 4-fold increase or a new vertebral fracture (4) and a 1.5-2.0-fold increase in hip fracture (5). Despite their significance and unlike fractures of other skeletal sites, the majority of incident vertebral fractures do not reach clinical attention (6). As such, under-identification of this fracture type is a world-wide problem (6) and better prediction of risk is particularly important so that patients can be targeted for screening and intervention.

The widely-used World Health Organisation's (WHO) Fracture Risk Assessment tool (FRAX) predicts the 10 year probability of a fracture based on clinical risk factors (CRFs; age, low body mass index (BMI), previous fracture, parent hip fracture, current smoking, rheumatoid arthritis, glucocorticoid use, secondary osteoporosis, and > 3 units/day alcohol) with or without femoral neck bone mineral density (BMD) (7). Low BMI is included in the FRAX algorithms because evidence derived from early population-based studies indicate higher rates of fragility fracture in underweight women and lower rates of hip and radiological vertebral fracture in obese women (8). Greater body weight has plausibly been ascribed to protecting against bone loss and osteoporosis given the potential for bone mechanoadaption to greater loads (8,9). However, more recent research is challenging the perception that obesity is protective to bone health, with reports of elevated site and sex-specific fracture rates of the proximal humerus, ankle and upper leg despite BMD being within the normal range (10-12).

Obesity within the general population is accompanied by greater overall and central adiposity and low grade chronic systemic inflammation, which can negatively impact bone metabolism (13). Specifically, visceral adipose tissue is associated with an increased circulation of pro-inflammatory cytokines and oxidative stress (14,15), favouring a loss of bone mass through stimulated osteoclast activity (14). Recent research has explored associations between adiposity and bone in adults with the goal of advancing insights into the obesity-fracture relationship. The EPIC prospective study reported that higher total fat mass measured by DXA, is associated with a lower hip fracture risk in women, but not men (16). In the Tasmanian Older Adult Cohort study, a positive association between prevalent vertebral fracture and BMI, total fat mass and waist circumference was reported in women, while there was a negative relationship between prevalent vertebral deformities and total fat mass in men (17). Elsewhere, unfavourable associations between abdominal or visceral adiposity, BMD and non-spinal fractures have been reported mainly in women (18,19), but relationships with vertebral fracture have not yet been explored and it is not clear whether such associations are seen in men. The aim of the current study was to evaluate sex-specific associations of total fat mass, visceral adiposity and CRP with BMD and prevalent vertebral fracture in men and women aged 62 years from the Newcastle Thousand Families Study (NTFS) cohort. To enable comparison with the universal methods of fracture risk assessment, BMD and FRAX scores were also evaluated

Materials and Methods

Participants

Three hundred and forty two men (n=152) and women (n=190) from the Newcastle Thousand Families Study birth cohort participated in the study. The NTFS was initiated in 1947 by Sir James Spence, when 1,142 children born in May and June that year to mothers resident in the

city of Newcastle upon Tyne were recruited in response to the high infant mortality rate and poverty levels in the city at that time (20). The birth cohort has been followed up at regular intervals with a multidisciplinary research focus (21-22) and the cohort has been described in detail at age 50 years (23). The current study evaluated participants during the most recent NTFS follow up wave in 2011, where 30% returned for a clinical examination having completed health and lifestyle questionnaires. The remainder of the sample could not be contacted, had moved away from the area, or had died. A favourable ethical opinion was obtained from the Sunderland Local Research Ethics Committee (Reference 09/H0904/40) and the research complied to the World Medical Association Declaration of Helsinki. All included study members gave their written informed consent.

Clinical measurements

Participants were asked to refrain from vigorous exercise during the preceding 24 h and for all physical measurements, were tested in light-weight clothing with shoes and jewellery removed. Body weight was measured to the nearest 0.1 kg using calibrated electronic scales and standing height was measured to the nearest 0.1 cm using a stadiometer. BMI (kg/m^2) was subsequently calculated [weight (kg)/height$(m)^2$] and scores were categorised according to the WHO criteria as underweight ($<18.5\ kg.m^{-2}$), normal ($18.5\text{-}24.9\ kg.m^{-2}$), overweight ($25\text{-}29.9\ kg.m^{-2}$) and obese ($>30\ kg.m^{-2}$).

Serum CRP, a marker of inflammation status, was measured from a blood sample drawn between 7am and 10:30am following an 8 h overnight fast and delivered to the laboratory for initial processing within one hour of the draw and was measured using an enzyme-linked immunosorbent assay (ELISA) method. The precision error of the test was 6.4%CV.

Fan beam dual energy X-ray absorptiometry (Lunar iDXA, GE Healthcare, Madison, WI) was used to evaluate BMD, vertebral fracture, total fat mass and visceral adipose tissue (VAT). Daily calibration and quality control observations were recorded according to manufacturer's guidelines throughout the duration of the data collection and no equipments drifts or faults were reported during the study period. Anterior-posterior lumbar spine (L1-L4) and left femoral neck BMD ($g.cm^{-2}$) were evaluated. For the lumbar spine scans, positioning was assisted with the GE-Lunar spine positioner which elevates the legs and opens the inter-vertebral spaces to allow clear visualisation of the vertebra. For the proximal femur scans, patient positioning was assisted using the GE-dual femur positioning device which allows both legs to be abducted and inwardly rotated 25^{o}.

The prevalence of VF was assessed using a lateral vertebral scan and vertebral fracture assessment (VFA) software (EnCore version 15.0). Participants were scanned in the left lateral decubitus position according to the manufacturers guidelines and in doing so, were positioned on their left side with the knees and hips flexed at a 90^{0} angle, and with arms flexed and both hands joined together near the head. VFA scans were initiated at the location of the sacrum, targeting the T4-L4 segment of the spine. The acquired images were analysed by the automated software for thoracic and lumbar vertebral body morphometry. Six markers were placed on each vertebral body to measure the vertebral height in three planes; anterior (H_a), mid (H_m) and posterior (H_p). These were compared with those of other vertebrae (L1-L4), allowing the software to estimate the extent of any reduction in the anterior, middle or posterior vertebral height. The detection of vertebral fracture relies not only on the dimensions of the vertebral bodies but also on their overall appearance and comparison to neighbouring vertebrae. Visual verification was performed by an International Society for Clinical Densitometry certified clinical densitometrist with specific training and experience in vertebral fracture identification. Verification included the observation of correct placement of

markers on the vertebral bodies, and differentiation between genuine vertebral fracture and deformities due to other pathology such as degenerative disease, or a normal variant. Contrast and brightness were adjusted using the Clear View image enhancement facility and a second reader (radiographer) was consulted when further verification was needed. Vertebral deformities were then graded using the semi-quantitative Genant scale, according to their severity as grade 1 (mild), grade 2 (moderate) and grade 3 (severe). Grade 1 corresponds to a 20-25% reduction in any vertebral height; grade 2 a 25-40% reduction in vertebral height and severe represents a >40% reduction in vertebral height.

Lean tissue mass (LTM), total fat mass (TFM) and visceral adipose tissue (VAT) measurements were derived from total body DXA. Participants were placed in the supine position on the scanning table, aligning with the central horizontal axis. The arms were positioned parallel to, but not touching the body, with a 1cm space in between the thigh and the hand to enable the estimation of VAT. The forearms were pronated with hands face down in accordance with the NHANES protocol. The legs were fully extended and feet were secured with a canvas and Velcro support to avoid foot movement during the scan acquisition. Scans were conducted using standard (153mm/sec) or thick (80mm/sec) mode depending on body stature. The regions of interest (ROI) for the total body cut-offs were manually adjusted according to the manufacturer's instructions. The ROI over the android region for the assessment of VAT mass was automated by the CoreScan software (EnCore version 15.0) (25,26). The iDXA CoreScan application uses a validated model derived from DXA and CT images, which computes VAT by subtracting subcutaneous abdominal fat from total abdominal fat (27). As well as being validated against CT, iDXA VAT is highly correlated with criterion MRI measurements of VAT (28) and robust associations with cardiometabolic risk (29) and glucose intolerance (30) have been demonstrated.

Precision estimates for iDXA measurements are 0.4%CV for lumbar spine BMD (26), 0.9%CV for femoral neck BMD (26), and 0.8%CV for TFM (31). Precision of VAT mass in individuals who have a BMI that is between 25.5 and 42.4 $kg.m^{-2}$ is 0.5%CV (32).

FRAX scores and other variables

In addition to age, sex and BMI, individual FRAX scores were included in the analyses (8). Information on previous fracture, parent hip fracture, current smoking, rheumatoid arthritis, glucocorticoid use, secondary osteoporosis, and alcohol consumption, were self-recorded by participants in the NTFS general health questionnaire. FRAX scores indicating the 10 year probability of a major osteoporotic fracture and hip fracture were subsequently calculated from femoral neck BMD and the aforementioned CRFs. Information on falls within the last 12 months were acquired from responses to the NTFS health questionnaire (*"Have you fallen in the last year?"*) and recorded as 'yes' or 'no'. The incidence of prior clinical vertebral and hip fractures were also acquired via the NTFS health questionnaire. Social class descriptive data were derived from responses to a social class questionnaire at age 50 years, and participants were classified as manual, non manual or not in employment.

Statistical analysis

All analyses were done using SPSS version 22.0 (IBM Corporation, US). The data are expressed as means and their standard deviations (SDs) and/or percentages, and there were no missing data. Comparison of the male-female proportion in the original birth cohort and the current wave was made by Chi Square. Sex-specific means and standard deviations of means (SD) were derived for all variables and differences in continuous variables between those with and without vertebral fracture were computed using independent student T-tests. Relationships between variables and the number of total, mild (deformity) or moderate to

severe VF and BMD were explored using Spearman's rank correlation coefficients and variables with a value $p<0.05$ (two tailed test) were included in the regression models. There were no height or weight adjustments for analysis between variables and VF. Partial correlations were used to adjust for body weight when exploring relationships of BMD with TFM, lean mass and VAT mass. Logistic regression was used to ascertain the effects of continuous and categorical variables on the likelihood of prevalent VF, as the dichotomous dependent variable. Significant associations are identified at $p<0.05$.

Results

The mean age of the cohort at the time of testing was 62.5 (0.5) years and cohort co-morbidities are given in Table 1. There were fewer male (44% v 51%) and more female (49% v 56%) participants in the current sample compared to the original 1947 cohort ($p = 0.008$). One hundred and ninety seven participants provided information on social class at age 50 years (professional or non manual [I - IIIn): n=198; manual or unskilled: n=89 (IIIm -V); not in employment: n=10). Most women were using hormone replacement therapy (HRT) (60%). Six men and five women had previously had a clinical vertebral fracture. Two men and one woman had previously suffered a hip fracture.

Table 1. Cohort co-morbidities at age 62 years.

	Men, n=152	**Women, n=190**
Use of glucocorticoids (>3 months)	9 (5.9%)	12 (6.3%)
Parental fracture	11 (7.2%)	10 (5.3%)
Previous fracture	24 (15.8%)	32 (16.8%)
Rheumatoid arthritis	1 (0.7%)	1 (0.5%)

Current smoking	21 (13.8%)	19 (10.0%)
Alcohol consumption >3 units/daily	31 (20.4%)	23 (12.1%)
Falls within last 12 months	22 (14.5%)	33 (17.4%)

Table 2. Anthropometric, bone and C-reactive protein results for men and women aged 62 years, with and without prevalent vertebral fracture *(VF = vertebral fracture; BMD = bone mineral density).*

	Men, n=152			**Women, n=190**		
	No VF	*VF*	*P*	*No VF*	*VF*	*p*
Height (cm)	173.2 ± 7.2	173.9 ± 6.8	0.586	162.2 ± 6.6	162.2 ± 7.5	0.987
Weight (kg)	82.6 ± 15.5	85.9 ± 15.7	0.185	71.9 ± 12.3	79.5 ± 18.3	0.003
Body mass index ($kg.m^{-2}$)	27.5 ± 4.9	28.3 ± 4.4	0.278	27.3 ± 4.7	30.1 ± 6.3	0.001
Femoral neck BMD ($g.cm^{-2}$)	0.946 ± 0.155	0.942 ± 0.123	0.863	0.922 ± 0.144	0.945 ± 0.140	0.339
Lumbar spine BMD ($g.cm^{-2}$)	1.200 ± 0.165	1.212 ± 0.158	0.619	1.100 ± 0.181	1.147 ± 0.176	0.127
FRAX hip fracture (fx)	1.4 ± 1.8	1.2 ± 1.5	0.439	1.2 ± 1.9	0.9 ± 1.1	0.285
FRAX major osteoporotic fx	6.9 ± 4.3	6.4 ± 3.3	0.431	8.3 ± 3.9	8.1 ± 3.5	0.726
Lean tissue mass (kg)	52.7 ± 6.3	54.2 ± 6.3	0.161	38.0 ± 4.4	40.1 ± 5.5	0.020
Total fat mass (kg)	27.9 ± 9.7	29.5 ± 9.7	0.355	28.9 ± 9.5	35.4 ± 12.5	0.001
Visceral adipose tissue mass (g)	2.08 ± 1.18	2.24 ± 1.02	0.305	0.93 ± 0.62	1.38 ± 0.87	0.001
C-reactive protein (mg/l)	5.16 ± 6.88	6.09 ± 22.9	0.760	3.04 ± 2.63	3.96 ± 2.79	0.050

Prevalent vertebral fracture

Logistic regression indicated that the prevalence of VF was significantly lower in women than in men (OR = 0.33, 95% confidence interval 0.21 - 0.53). For both sexes, grade 1 deformities were most common and prevalent in 58 (38%) men and 37 (20%) women. Grade 2 and/or grade 3 VF were prevalent in 41 (27%) men and 19 (10%) women. Sex-specific comparisons of demographics between those with and without VF are given in Table 2. Women with prevalent VF were heavier, had greater LTM, TFM and VAT mass, and higher levels of CRP compared to women without VF ($p<0.05$, Table 2). There were no differences in variables, including social class, between men with and without prevalent VF (Table 2).

In women, the number of grade 1 VF increased as BMI, TFM and VAT mass increased ($p<0.005$). The number of grade 2 and grade 3 VF increased only with VAT mass ($R = 0.179$; $p = 0.03$). The effects of a) TFM and CRP and b) VAT mass and CRP on the likelihood of prevalence of any grade VF and of VAT mass on the prevalence of c) grade 1 and d) grade 2-3 VF in women were assessed and the models are presented in Table 3. Regression model *a* and model *b* explained 12.2% and 11.7% (Nagelkerke's R^2) of variance and correctly classified 77% and 75% of cases respectively. The *wald* criterion demonstrated that in the respective models only TFM and VAT mass made significant contributions and CRP was not a significant predictor. For every 1 SD increase in TFM (10.7 kg) and VAT (0.72 kg) the odds for prevalent vertebral fracture increased by a factor of 1.06 and 2.50 respectively. Analysis of VF by grade indicated that VAT was more predictive of grade 1 ($R^2= 0.11$, OR: 2.6, $p = 0.002$) than of grade 2-3 ($R^2= 0.06$, OR: 1.9, $p = 0.08$) VF (Table 3).

In women, use of HRT was not associated with BMI, lean mass, total fat mass, or VF prevalence ($p > 0.14$). In both men and women, there were no associations of VF with FRAX scores or the number of falls in the last 12 months ($p = 0.080$ and 0.786 respectively). Falls were not associated with BMI, lean mass, total fat mass and VAT mass ($p >0.40$).

Table 3. Logistic regression outputs for predictors of prevalent vertebral fracture in women aged 62 years.

	B	**Wald**	***P***	**ExpB**	**95% CI**
Model a (any grade)					
Total fat mass	0.056	12.05	0.001	1.058	*1.025 - 1.092*
CRP	0.015	0.048	0.827	1.015	*0.885 - 1.164*
Model b (any grade)					
Visceral adipose tissue mass	0.917	13.10	0.001	2.053	*1.523 - 4.113*
CRP	0.019	0.025	0.785	1.019	*0.890 - 1.167*
Model c (grade 1 deformity)					
Visceral adipose tissue mass	0.955	9.23	0.002	2.598	*1.403 - 4.811*
Model d (grades 2-3 VF)					
Visceral adipose tissue mass	0.654	0.113	0.08	1.923	*0.925 - 3.995*

Bone mineral density

Body weight, and all body composition and adiposity markers correlated positively with FN and LS BMD in both men and women ($p < 0.05$). After adjusting for body weight, only LTM was associated with LS BMD in men ($R = 0.206$, $p = 0.017$). In both men and women, CRP was not associated with BMD, and variables did not differ according to employment (manual or non manual) at age 50 years ($p>0.10$). In women, there were no associations between BMD and HRT (femoral neck $R = - 0.140$, $p = 0.064$; lumbar spine $R = - 0.102$, $p=0.176$).

Discussion

Our study explored relationships of total and visceral adiposity with BMD and prevalent vertebral fracture in a cohort of men and women aged 62 years. Low BMI is an established

risk factor for osteoporosis and fracture, but the skeletal risks associated with obesity are unclear, and appear to be sex-specific and site-dependent (17,19). Previous studies have reported that obesity and total fat mass are predictive of non spine fractures in women (18,19) and in men (33), and that total fat mass is positively associated with prevalent vertebral fracture in women, but not in men (17). Our primary finding was that both total and visceral fat mass, a marker of poor metabolic health, were associated with an increased likelihood of prevalent vertebral fracture in women, but not in men. Levels of CRP, a marker of inflammation, were also greater in women with prevalent vertebral fracture and there were no associations with femoral neck or lumbar spine BMD, or with FRAX scores.

We are the first to report a positive, sex-specific relationship between visceral adipose tissue mass and vertebral fracture, and in the absence of any association between visceral fat and BMD. Our findings also support the accumulating evidence that higher body weight and BMI increase the likelihood of vertebral fracture in postmenopausal women, irrespective of positive associations between body weight and BMD (34,35). Recently, Machado and colleagues demonstrated the potential negative influence of visceral adiposity on non-spine fracture risk in 433 non obese elderly women (mean age 72 years) over a 4.3 year follow-up. The odds ratio was 1.42 (95% CI 1.09 - 1.85), which is greater than the 1.001 (95% CI 1.000 - 1.003) in the current study (mean age 62 years). Several other groups have examined proxy measures of visceral fat in relation to fracture risk and reported similar findings. In the Tasmanian Older Adults Cohort Study, Laslett et al. (17) found positive associations between trunk fat and prevalent vertebral fracture in postmenopausal women (mean age 63 years). In 61,677 postmenopausal women, Meyer et al. have recently demonstrated significant associations between waist circumference and an increased hip fracture risk after adjusting for BMI (36).

The relationship between greater body weight and fracture has been suggested to involve an imbalanced load to strength ratio (37) and an elevated risk of falling (38), although we did not find associations between the number of falls in the last 12 months and the prevalence or number of vertebral fractures. Lean tissue mass also constitutes a major compartment of total body weight and in agreement with others, positive relationships between lean mass and BMD were observed in this cohort. However, the relationship between body weight and vertebral fracture in women appeared determined by fat mass. An adverse effect of adipose tissue on skeletal integrity is plausible because of the adipocyte-derived pro-inflammatory state that favours bone resorption (13-15). A common marker of indicator of inflammation is CRP, which we found to be on average, normal in women (<6 mg/l), lower in women than in men (5.6 v 3.2 mg/l), and unrelated to BMD. However, levels were significantly higher in women with prevalent vertebral fracture compared to those without, and were positively correlated with total and visceral fat. Elsewhere, CRP has shown to be predictive of non spine fractures in men and women (39), although in our regression models, visceral and total fat mass were more significant and there were no effects found in men.

The higher prevalence of vertebral fracture in men observed in this study is consistent with previously published data on vertebral deformities (17). Despite a 3-fold higher prevalence of vertebral fracture in men compared to women, our data indicated that there were no relationships between prevalence or number of vertebral deformities and any of the established CRFs or adiposity markers in men. Elsewhere, others have reported associations between adiposity markers and fracture in older women but not in older men (17,37), and the MrOS Study team observed no associations between visceral fat and non-spine fracture in 749 men aged over 65 years (30). The reasons for such dimorphism are indeterminate. It has been suggested that the relationship between trunk adiposity and

vertebral deformities in women could be related to breast size and therefore could explain the sex differences (17). In the current study, we assessed visceral adipose mass using the iDXA CoreScan programme, which unlike the standard trunk evaluation, only includes the abdominal region. It may be possible that men with vertebral fracture had occupations involving more physical work compared to men without and to women, and as such the vertebral fractures may represent occupational trauma. Although we did not find any differences in the prevalence or number of vertebral fractures in men between the manual and non manual employment classes, the employment data was derived from information gathered at age 50 years. A future direction for research would be an in depth evaluation of earlier life occupational categories prior to any possible employment changes, for example, following closure of the local coal mines and ship yards in and around Newcastle upon Tyne, and a move towards a more service-based economy (40).

There are some differences between our cohort and those from the literature, such as age and mean BMI. Our sample is heavier than those investigated previously (17,41), with an average BMI of 28.0 $g.cm^{-2}$ (28.3 and 30.1 $kg.m^{-2}$ for men and women with prevalent vertebral fracture). The risk for fragility vertebral fracture rises exponentially with age and most previous studies exploring vertebral fracture in men have examined prevalence and incidence in older cohorts. The NTFS cohort at the time of data collection wave were comparatively young at age 62 years, and mean BMD was normal at both the spine and femoral neck. Follow-up work is planned for the cohort with a view to exploring changes in BMD, body composition, and other CRFs in relation to all fracture incidence in further follow-ups.

Vertebral fractures identified as grades 1-3 were included in the current study. It has been suggested that some grade 1 vertebral deformities may not represent vertebral fracture, such as those deformities based on only short vertebral height (42), which are

more common in overweight or obese postmenopausal women (43). We employed a semi-quantitative approach and excluded deformities with continuous SVH. Grade 1 deformities were included in the analysis because these can represent progressive vertebral deformity from loading ensued microcracks (44) and because mild vertebral deformities without clinical symptoms, have been found to be a risk factor for subsequent vertebral fracture and non vertebral fracture in older women (45). Moreover, older men with prevalent mild vertebral deformity have also been reported to have a greater risk of further fracture (46). It is however, recognised that the sensitivity and specificity for the detection of grade 1 vertebral deformities by VFA is lower than for the higher grades (47, 48). None-the-less, the associations with VAT and TFM remained when analysis was conducted only for grade 2 and 3 VF.

There are a number of limitations to our study. First, it is recognised that abdominal CT is the gold standard for the accurate assessment of visceral adiposity, with a greater resolution than DXA and providing three dimensional imaging as opposed to two. For the current study, DXA was considered to be a more suitable tool for screening because of its significantly lower radiation dose and on the basis that validation studies have demonstrated excellent agreement with both CT and MRI (25, 27-28). Secondly, we were unable to assess time since the fracture or antecedent factors relating to vertebral fracture and are unable to make any inferences about cause and effect relationships. Longitudinal investigations are needed to address causality. Third, there was a small discrepancy in the gender representation of the cohort, with 7% less male and 7% more female participants than those recruited from birth in 1947. This may reflect greater geographical mobility or mortality in males. Finally, caution should be taken when making inferences given that the study was performed among members of a birth cohort born in Newcastle upon Tyne, UK who were aged 61 - 63 years. However, this age group has particular public health

importance because the risk of fracture is increased compared to younger ages, and effective risk factor modification (e.g. exercise and diet for fat loss) is still likely to be viable.

In conclusion, there is a significant and positive association between the prevalence and number of vertebral fractures and total and visceral adiposity in women but not in men at age 62 years. The aetiology of vertebral fracture unrelated to BMD, in men remains uncertain and given the high prevalence, warrants further investigation, particularly into occupational trauma. Given the rising global rates of obesity (49), the association between adiposity and vertebral fracture risk also warrants further and timely investigation so that those at risk can be better identified.

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