**Adiposity and bone microarchitecture in the GLOW Study**

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**Mini Abstract:** Low body mass index (BMI) is an established risk factor for fractures in postmenopausal women but the interaction of obesity with bone microarchitecture is not fully understood. In this study, obesity was associated with more favourable bone microarchitecture parameters but not after parameters were normalized for body weight.

**Abstract**

**Purpose:** To examine bone microarchitecture in relation to fat mass and examine both areal bone mineral density (aBMD) and microarchitecture in relation to BMI categories in the UK arm of the Global Longitudinal Study of Osteoporosis in Women.

**Methods:** 491 women completed questionnaires detailing medical history; underwent anthropometric assessment; high resolution peripheral quantitative computed tomography (HRpQCT) scans of the radius and tibia; and DXA scans of whole body, proximal femur and lumbar spine. Fat mass index (FMI) residuals (independent of lean mass index) were derived. Linear regression was used to examine HRpQCT and DXA aBMD parameters according to BMI category (unadjusted) and HRpQCT parameters in relation to FMI residuals (with and without adjustment for anthropometric, demographic and lifestyle covariates).

**Results:** Mean (SD) age was 70.9 (5.4) years; 35.0% were overweight, 14.5% class 1 obese, and 7.7% class 2/3 obese. There were significant increasing trends according to BMI category in aBMD of whole body, hip, femoral neck and lumbar spine (p≤0.001); cortical area (p<0.001), thickness (p<0.001), and volumetric density (p<0.03), and trabecular number (p<0.001), volumetric density (p<0.04) and separation (p<0.001 for decreasing trend) at the radius and tibia. When normalised for body weight, all HRpQCT and DXA aBMD parameters decreased as BMI increased (p<0.001). FMI residuals were associated with bone size and trabecular architecture at the radius and tibia, and tibial cortical microarchitecture.

**Conclusion:** Significant trends in HRpQCT parameters suggested favorable bone microarchitecture at the radius and tibia with increasing BMI but these were not proportionate to increased weight.

**Keywords:** Osteoporosis, Epidemiology, Adiposity, BMI, HRpQCT, DXA

**Introduction**

Osteoporosis is characterized by low bone mass and microarchitectural deterioration of bone tissue leading to increased bone fragility [1]. Osteoporotic fractures are associated with considerable morbidity, mortality and socioeconomic cost [2]. As the worldwide population is aging, the prevalence of osteoporosis is escalating and becoming a major public health issue [3], with data from US and UK suggesting that almost one in two women and one in five men will experience a fracture in their remaining lifetime from the age of 50 years [4, 5]. Economically, the cost of osteoporosis and fractures are projected to increase in the EU from €37.4 billion in 2010 to €46.8 billion by 2025 and, in the US, from $17 billion in 2005 to $25.3 billion by 2025 [2, 6].

While low body mass index (BMI) is well recognised as an important risk factor for fractures in postmenopausal women, the interaction of obesity with bone metabolism and microarchitecture is complex and not fully understood. BMI is incorporated in the fracture risk assessment tool (FRAX), and higher BMI is associated with lower future fracture risk. Higher BMI was traditionally considered protective against fracture through a direct effect of increased loading through body weight on bone mineral density, and because of reduced impact of falls as a result of increased soft-tissue padding [7]. However, accumulating evidence indicates that the relationship between BMI and fracture varies according to fracture site with lower rates of hip and pelvis fractures in obese individuals [8, 9], in contrast to a higher risk of some non-spine fractures including those of the proximal humerus, upper leg, and ankle, perhaps because bone mineral density, although higher in more adipose patients, does not show a rise commensurate with body size [8, 10-13].

The greater risk of lower limb fractures with obesity might therefore reflect biomechanical factors, but could also result from differences in bone structure. It is widely accepted that bone density is not the sole determinant of bone strength [14]; additional factors including bone geometry and bone micro-architecture may also be important. High-resolution peripheral quantitative computed tomography (HRpQCT) allows study of cortical and trabecular compartments of the bone and is not as affected by overlying soft tissue, providing a more reliable way to assess bone structure in obese individuals. Results of studies undertaken to date using this technology have been inconsistent, and studies have been performed mainly in obese children and adolescents [15-18]. One cross-sectional case-control study demonstrated that both obese men and women had higher volumetric BMD at the distal radius and distal tibia when compared to normal weight individuals [19]. In a modest sized study investigating associations between obesity and measures of bone microarchitecture in postmenopausal French women, Sornay-Rendu and collegues reported that obese women had higher volumetric BMD and higher values of cortical and trabecular architecture compared with normal weight women [13]. However, the increase of all parameters in obese women was lower relative to the excess of weight for BMI. Importantly it is not known whether associations between BMI and bone microarchitecture are the same between different classes of obesity (overweight, Class I, Class II/III, morbid obesity) at both weight bearing and non-weight-bearing skeletal sites in other populations.

Therefore, the aim of this study was to examine the relationships of bone microarchitecture with fat mass and to explore both areal bone mineral density (aBMD) and microarchitecture in relation to BMI categories (including obesity categories) in the UK arm of the GLOW study.

**Methods**

*Study participants*

GLOW is a prospective, observational cohort study conducted through general physician practices in 10 countries. Study design and recruitment have been described in detail previously [20]. In brief, practices, representative of each region, were recruited through primary care networks and provided the names of women aged 55 years and older who had been seen by their physician in the past 24 months. The primary aim of GLOW was to characterize the descriptive epidemiology and health impact of osteoporosis-related fractures among women who were 55 years of age and older worldwide. Globally, GLOW enrolled over 60,000 women through over 700 physicians in 10 countries, and conducted annual follow-up for up to 5 years. In Southampton only, 1367 participants with baseline data and at least one follow-up questionnaire were invited, after completion of 5 years of follow-up, for a follow-up study which included DXA and HRpQCT. Participants were scanned between April 2014 and December 2017. Patients who were institutionalized or were not able to complete the study survey by themselves due to cognitive impairment, language barriers, or were too ill to complete the survey or attend for the scans were excluded.

*Questionnaires*

Information was collected using self-administered questionnaires and included details regarding smoking status, alcohol consumption, education level, medical diagnoses (participants were asked if a doctor or health provider had ever told them that they had any of the listed morbidities including type 2 diabetes mellitus and hypertension), falls, fractures, use of anti-osteoporotic medication (AOM), years since menopause and use of oestrogen or hormone replacement therapy (HRT). Information on possible confounders was taken from the questionnaires where it was available closest in time to the scan date. Participants were also asked to rate how physically active they were compared to other women of the same age out of the following responses: ‘very active’; ‘somewhat active’; ‘a little active’; and ‘not at all’. Participants were considered to be taking AOM if, from baseline to the 5 year-follow-up, they reported current use of alendronate, etidronate, ibandronate, pamidronate, risedronate, zoledronic acid, strontium ranelate, teriparatide, calcitonin, tibolone or raloxifene.

*Assessment of bone by HRpQCT*

Participants underwent a HRpQCT scan of the non-dominant distal radius and tibia using XtremeCT I, (Scanco Medical, Basserdorf, Switzerland) on the same day as the DXA scan; if there was a history of fracture on the non-dominant limb, the non-fractured limb was measured. A stack of 104 parallel HRpQCT slices were acquired with an isotropic voxel size of 82 µm. Each scan was assessed for motion artefact, and if present a second scan was performed. The quality of the measurements was assessed using a 5-point scale recommended by the manufacturer (1, excellent; 2, good; 3, acceptable; 4, poor; 5, unacceptable) [21]. Grade 5 images were excluded due to excessive motion artefact; the number of radius and tibia scans excluded for this reason were 102 and 16 respectively. Initial image analysis was carried out using the standard manufacturer’s method and Image Processing Language (IPL, Version 6.1, ScancoMedical). For this analysis, the standard evaluation and cortical porosity scripts were run to obtain estimates of the following parameters at the radius and tibia: total area and trabecular area, volumetric density, number, thickness and separation; cortical area, thickness, volumetric density and pores diameter; and cortical porosity [22].

*Anthropometry and DXA*

Height was measured to the nearest 0.1 cm using a Marsden stadiometer on the day of scanning; weight was measured to the nearest 0.1 kg using a Marsden MPPS-250 (Marsden Weighing Machine Group Limited, Rotherham, UK) digital floor scale. BMI (kg/m2) was calculated by dividing body weight by height2. BMI categories were defined as underweight (BMI < 18.5), normal (18.5 ≤ BMI < 25), overweight (25 ≤ BMI < 30), class 1 obese (30 ≤ BMI < 35), Class 2/3 obese (BMI ≥ 35), morbid obesity (BMI ≥ 35 and either hypertension or type 2 diabetes or both conditions). DXA Hologic Horizon W (software version Apex 5.5.3.1 [Vertec Scientific, Reading, UK]) was used to measure whole body fat and fat free mass, from which lean mass was estimated, as well as areal bone mineral density (aBMD, g/cm2) of the whole body, hip, femoral neck and lumbar spine.

*Derived measures*

Lean mass index (LMI, kg/m2) and fat mass index (FMI, kg/m2) were derived by dividing the corresponding measures by height2 (m). To obtain a measure of fat mass that was independent of lean mass, standardised FMI residuals were obtained from a linear regression model with FMI as the outcome and LMI as the predictor; the linear relationship between FMI and LMI was checked by a scatterplot.

*Statistical analysis*

The analysis sample comprised 491 individuals with non-missing values for BMI category or FMI residual and HRpQCT of at least one site, radius or tibia, scanned.

Skewed parameters were transformed prior to standardising. Mean (SD) z-scores for the HRpQCT parameters of the tibia and radius and DXA aBMD parameters were examined according to BMI category; tests for linear trends according to BMI category were also performed using linear regression. To investigate whether increases in bone parameters in higher BMI groups were in proportion to participants’ greater weight, these steps were repeated after dividing the bone parameters by body weight. The differences in parameters between participants with morbid obesity (Class 2/3 obese with hypertension or diabetes) and those with Class 2/3 obesity but without hypertension or diabetes were examined using t-tests.

Linear regression was used to examine the association between FMI residuals and HRpQCT parameters. The following models were implemented: unadjusted; adjusted for age at time of HRpQCT scan, physical activity, smoking status, alcohol consumption, education and use of AOM and oestrogen/hormone replacement (pill/skin patch); and additionally adjusted for total hip BMD. Analyses were conducted using Stata 15 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC); p<0.05 was regarded as statistically significant.

This research was performed in accordance with the Declaration of Helsinki and was approved by the UK Health Research Authority, reference 07/MRE01/30. All participants gave informed consent.

**Results**

*Participant characteristics*

Baseline participant characteristics of the study sample are presented in Table 1. Mean (SD) age at scan was 70.9 (5.4) years. Mean (SD) BMI was 26.8 (5.0) kg/m2; 35.0% were overweight (25 ≤ BMI < 30), 14.5 % were class 1 obese (30 ≤ BMI < 35) and 7.7% were class 2/3 obese (BMI ≥ 35). Only 4.5% of the sample were class 2/3 obese and had hypertension or type 2 diabetes. Mean (SD) values for whole body fat mass and FMI were 29.5 (9.1) kg and 11.5 (3.6) kg/m2 respectively. The number of participants with fractures at certain sites and falls according to categories of BMI is presented in eTable 1 (Online Resource).

*FMI residuals in relation to HRpQCT parameters*

Associations between FMI residuals and HRpQCT parameters are presented in Table 2. At the radius, FMI residuals were positively associated with trabecular number and negatively associated with total area, trabecular area and trabecular separation in unadjusted and adjusted models (p<0.01 for all associations); apart from trabecular separation, these associations were robust when additionally adjusted for total hip aBMD. FMI residuals were positively associated with cortical thickness (p<0.05) in unadjusted analysis only.

At the tibia, FMI residuals were positively associated with cortical volumetric density (p<0.003) and negatively associated with total and trabecular area (p<0.03), cortical porosity (p<0.02) and cortical pores diameter (p<0.03); these associations were robust in all models. FMI residuals were positively associated with cortical area (p<0.004), cortical thickness (p<0.02) and trabecular number (p<0.03) and negatively associated with trabecular separation (p<0.05) in unadjusted and adjusted analysis but not after adjustment for total hip aBMD.

*DXA aBMD parameters in relation to BMI category*

The DXA aBMD parameters according to BMI category are presented in Table 3. All DXA aBMD parameters increased with increasing BMI category (p-values for trend ≤0.001). However, this trend was reversed for all DXA aBMD parameters after normalizing values for body weight (p-values for trend <0.001) (Table 4).

*HRpQCT parameters in relation to BMI category*

The HRpQCT parameters at the radius and tibia according to BMI category are presented in Table 3. There were significant trends in cortical and trabecular parameters at both radius and tibia according to BMI category. At the radius, there was a significant increase in cortical area (p<0.001), thickness (p<0.001) and volumetric density (p<0.03) and trabecular number (p<0.001) and volumetric density (p<0.003), and a decrease in trabecular separation (p<0.001) as BMI category increased. At the tibia there was a significant increase in cortical area (p<0.001), thickness (p<0.001), volumetric density (p<0.001), and trabecular microarchitecture: trabecular number (p<0.001), and trabecular volumetric density (p<0.04) as well as decrease in cortical pores diameter (p<0.001), trabecular thickness (p<0.01) and trabecular separation (p<0.001) parameters as BMI category increased. However, at the tibia this pattern was reversed in morbid obesity with a less favorable profile for some of the tibial parameters (compared to other class 2/3 obese participants without hypertension or type 2 diabetes), mainly of the trabecular compartment: lower trabecular number (p<0.01), higher trabecular separation (p<0.01) and lower trabecular volumetric density (p<0.03); and higher cortical pores diameter (p<0.05); these parameters did not differ significantly between participants with morbid obesity and those with normal BMI. When normalised for body weight, all HRpQCT parameters decreased as BMI category increased (p<0.001) (Table 4).

**Discussion**

In this study, we found that in postmenopausal women there were significant trends in HRpQCT parameters suggesting favorable bone microarchitecture at both radius and tibia with an increase of BMI category. However, when normalised for body weight, all HRpQCT and DXA aBMD parameters decreased as BMI increased, illustrating that, for parameters where higher values are indicative of better bone health, these improvements were not proportional to the increase in body weight. Similar FMI patterns were observed at both sites. At the tibial site, despite the positive association with cortical vBMD and negative association with porosity, which we would expect to be associated with greater bone strength, the effect sizes were relatively small.

Excess body weight due to obesity has traditionally been considered to have a positive effect on bone with a well-described association of high BMD with obesity [11, 23]. Similarly, in our study, an increase of aBMD assessed by DXA was observed with increased BMI. However, a higher aBMD in people with a higher BMI may represent appropriate adjustment of the skeleton to increased body weight, but not relate to greater bone strength [24]. Lower rates of hip, pelvis, and wrist fractures in obese individuals may result from the protective effects of increased soft-tissue padding and differences in fall characteristics [8, 9, 25], whereas a higher risk for ankle, upper leg and humerus fractures might reflect biomechanical factors, but could also represent relative reduced parameters at the highest BMIs [8, 10-13]. We found significant increases in cortical area, thickness, cortical volumetric density and trabecular number and decreases in trabecular separation parameters at the radius as BMI category increased. At the tibia there was significant increases in cortical area, thickness, volumetric density and trabecular microarchitecture parameters: trabecular number, trabecular volumetric density and decreases in trabecular separation and thickness parameters as BMI category increased. However, at the tibia this pattern was reversed in morbid obesity with a fall in some tibial parameters (compared to participants without hypertension or diabetes who were class 2/3 obese) mainly of the trabecular compartment i.e. trabecular volumetric density (due to lower trabecular number and higher trabecular separation). We did see differences in relationships at the radius and tibia which require validation in other samples. This may reflect technical differences in acquisition at the two sites, or differences due to the weight bearing/non-weight bearing nature of the two sites. Fracture risk in the GLOW global cohort was reported to be increased at the ankle and upper leg in obese women, which may also be relevant [8].

In previous work, Sornay-Rendu and colleagues reported greater volumetric BMD at the distal radius and distal tibia resulting from greater trabecular volumetric density and trabecular thickness and greater cortical volumetric density (due to lower cortical pores) in obese postmenopausal women, compared to a non-obese control group [13]. Evans et al. compared bone density and microarchitecture in younger (age 25-40) and older (age 55-75) obese men and women to a non-obese control group [19]. Greater differences in BMD and HRpQCT measurements between obese and normal adults were observed in the older adults than the younger adults with greater volumetric BMD at the distal radius and distal tibia in obese, compared to non-obese individuals in the older age group. In the younger group, obese adults had greater volumetric BMD than normal BMI adults at the tibia only. Older obese individuals had favorable cortical and trabecular compartment parameters with thicker cortices, higher cortical volumetric density, higher trabecular volumetric density, and higher trabecular number than normal weight adults at both sites scanned, whereas in the younger group the higher volumetric BMD in obese participants was due to greater trabecular density, due to higher trabecular number and lower trabecular separation at the radius and tibia. Those results suggest that obesity may protect against age‐related bone loss, and also increase peak bone mass. However, no BMI categories of obesity were distinguished in these studies. Sukumar et al performed a study of 211 women of a wider age range (25-71) and BMI classified into 3 categories (normal weight, obese-class 1 and obese-class 2/3) measuring bone parameters by pQCT. In contrast to our findings, they reported that women with Class 2/3 obesity had reduced cortical but increased trabecular volumetric density at the tibia measured by pQCT [26]. However, in that study, the negative association between BMI and cortical volumetric BMD was significant only in the premenopausal (p<0.001) and not in the postmenopausal (p=0.1) women. It is possible that cortical volumetric BMD does not decline as dramatically in obese compared to in leaner women with aging, or other ageing factors (e.g. menopause) overriding the obesity ‘effect’ through cortical thinning and reduced density.

We observed some differences in FMI patterns at the radius and tibia. At the distal radius and tibia, FMI residuals were associated with parameters of bone size and trabecular architecture, whereas at the distal tibia only, FMI residuals were also associated with cortical compartment parameters. The existing literature has shown some positive relationships (among women and after accounting for LMI) between adiposity and bone geometry, however the specific compartments affected have varied and studies are few [15, 16]. Edwards and colleagues reported positive relationships among women between FMI and trabecular number and cortical area in tibia and only trabecular number in the radius [17]. Interestingly, in the current study, at the distal tibia, FMI residuals were associated more strongly with cortical compartment parameters and bone size, in contrast to the study by Edwards et al., that indicated a stronger association with the trabecular compartment. In that study participants were recruited from the Hertfordshire Cohort Study (HCS). Women of the HCS were older (mean [SD] age of 76.4 [2.6] compared to 70.9 [5.4] for GLOW participants).

Morbid obesity has been associated with an excessive increase of leptin levels [27]. Associations between leptin and BMD are complex, with human and murine studies yielding conflicting results and leptin exerting positive and negative effects on bone metabolism, depending on whether it acts directly on bone cells or indirectly (via the hypothalamus and autonomic nervous system), respectively [27-35]. Circulating leptin levels may be affected by inflammatory cytokines [29, 30]. Obesity is considered to be a low grade pro-inflammatory state, associated with greater concentrations of pro-inflammatory cytokines, which are inversely associated with BMD and positively associated with bone resorption [32-35]. In obesity, adipose tissue becomes inflamed, both via increased production of inflammatory cytokines by mature adipocytes and through infiltration of adipose tissue by macrophages [33]. It has been suggested that most adipokines, in morbidly obese humans, are derived from nonfat cells [34, 35]. We observed that the trend of favorable bone microarchitecture at both radius and tibia with an increase of BMI category is reversed at the tibia at the level of morbid obesity. Blood samples were not available in our study to test cytokines levels, though such research would be valuable.

There are limitations to our study. These are observational data that demonstrate trends and associations, but not causality between obesity, fat mass and bone microarchitecture. In addition, our study populations of postmenopausal women were UK community-dwelling subjects; of those who participated in the present study, 14.4% had a prevalent fracture between age 45 years and the GLOW baseline whereas this proportion was higher (21.8%, p<0.001) among the wider UK arm of GLOW who did not participate in the current study, suggesting a healthy participant effect; and our findings need to be tested in other populations. Furthermore, information on possible confounders was not available at the time of the scans, but was taken from the questionnaires where it was available closest in time to the scan date. Moreover, it is recognized, that performing a higher number of statistical tests increases the risk of chance findings. However, the Bonferroni correction would not be the preferred approach here, as limitations of this method have been identified such as the increased likelihood of type II errors (potentially resulting in important clinical findings being deemed non-significant) and that the interpretation of findings depends on the number of other tests performed [36]. In light of these limitations, the effect sizes and p-values reported in tables in this study enable readers to judge the clinical and statistical significance of our findings. BMI may be considered a suboptimal measure of obesity, as body fat distribution could affect bone density and microarchitecture. Finally, the numbers of individuals at the extreme BMI categories are small and the Pearson correlation coefficient between FMI and BMI was 0.97. Unfortunately, the high correlation between these variables and the small number of participants with values in some of the BMI categories prevented an analysis of fat mass in relation to bone microarchitecture within different BMI categories. Larger studies of obese women are required.

In conclusion, we have observed a significant trend suggesting favorable cortical and trabecular microarchitecture with increased BMI category in postmenopausal women at both radius and tibia. At the tibia, this pattern was reversed in morbid obesity with less favorable tibial parameters mainly of the trabecular compartment. Furthermore, for bone parameters where higher values indicate better bone health, improvements in these parameters with increased BMI category were not in proportion to the increase in body weight. There were different FMI patterns at the radius and tibia; FMI residuals were associated with parameters of bone size and trabecular architecture at the radius and tibia, whereas at the tibia only, FMI residuals were associated with cortical compartment parameters. Understanding better the relationships between obesity, fat mass and bone microarchitecture, and impact of morbidity, may give insights into targeted interventions for prevention of osteoporotic fractures later in life.

**Declarations:**

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All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards

Informed consent was obtained from all individual participants included in the study.

**Availability of data and material** Not applicable

**Code availability** Not applicable

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|  |  |  |
| --- | --- | --- |
| **Table 1. Participant characteristics** **of the analysis sample (n=491)** | | |
|  |  |  |
| **Participant characteristic** | **Mean (SD) / N(%)** | **Obs** |
| Age at scan (years) | 70.9 (5.4) | 491 |
| Height (cm) | 160.3 (6.2) | 491 |
| Weight (kg) | 68.6 (12.7) | 491 |
| BMI (kg/m2) | 26.8 (5.0) | 491 |
|  |  |  |
| BMI categories: Underweight (BMI < 18.5) | 10 (2.0%) | 491 |
| Normal (18.5 ≤ BMI < 25) | 200 (40.7%) |
| Overweight (25 ≤ BMI < 30) | 172 (35.0%) |
| Class 1 obese (30 ≤ BMI < 35) | 71 (14.5%) |
| Class 2/3 obese (BMI ≥ 35) | 38 (7.7%) |
|  |  |  |
| Whole body fat mass (kg) | 29.5 (9.1) | 409 |
| Fat mass index (kg/m2) | 11.5 (3.6) | 409 |
| Whole body total aBMD (g/cm2) | 1.01 (0.10) | 412 |
| Total hip aBMD (g/cm2) | 0.84 (0.11) | 466 |
| Femoral neck aBMD (g/cm2) | 0.69 (0.10) | 459 |
| Total lumbar spine aBMD (g/cm2) | 0.92 (0.15) | 473 |
|  |  |  |
| Physically active\*: Not at all / a little | 65 (13.4%) | 484 |
| Somewhat | 249 (51.4%) |
| Very | 170 (35.1%) |
|  |  |  |
| Current smoker | 29 (6.0%) | 483 |
|  |  |  |
| Alcoholic drinks per week: None | 122 (25.3%) | 483 |
| 1-6 | 194 (40.2%) |
| 7-13 | 113 (23.4%) |
| >13 | 54 (11.2%) |
|  |  |  |
| Education: Below GCSE | 124 (25.3%) | 491 |
| CSE O level / GCSE | 165 (33.6%) |
| A Level | 61 (12.4%) |
| Degree | 141 (28.7%) |
|  |  |  |
| Use of anti-osteoporotic medication | 78 (17.1%) | 455 |
| Ever used oestrogen / hormone replacement therapy | 243 (50.8%) | 478 |
|  |  |  |
| Years since last menstrual period: <10 | 150 (31.4%) | 477 |
| 10-19 | 212 (44.4%) |
| 20-29 | 89 (18.7%) |
| >29 | 26 (5.5%) |
|  |  |  |
| Hypertension\*\* | 206 (42.9%) | 480 |
| Type 2 diabetes\*\* | 26 (5.4%) | 483 |
| Morbid obesity: Class 2/3 obese and hypertension/diabetes | 22 (4.5%) | 491 |
|  |  |  |
| Obs: Number of non-missing observations | |  |
| \*Asked how physically active compared to other women of the same age | |  |
| \*\*Ever told by health professional |  |  |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Table 2. Standard deviation difference in mean HRpQCT parameters (95%CI) per standard deviation increase in fat mass index residuals** | | | | | | | |
|
| **HRpQCT parameter** | **Unadjusted** | | **Adjusted\*** | | **Additionally adjusted**  **for hip BMD** | | |
| **Estimate**  **(95% CI)** | **P-value** | **Estimate**  **(95% CI)** | **P-value** | **Estimate**  **(95% CI)** | **P-value** | |
|  |  |  |  |  |  | |  |
| **Radius** |  |  |  |  |  | |  |
| Total area | **-0.23 (-0.34,-0.13)** | **<0.001** | **-0.19 (-0.32,-0.07)** | **0.002** | **-0.19 (-0.31,-0.06)** | | **0.003** |
| Trabecular area | **-0.23 (-0.34,-0.12)** | **<0.001** | **-0.19 (-0.31,-0.06)** | **0.003** | **-0.17 (-0.29,-0.04)** | | **0.010** |
| Cortical area | 0.04 (-0.07,0.15) | 0.432 | 0.04 (-0.08,0.16) | 0.531 | -0.02 (-0.13,0.08) | | 0.660 |
| Cortical thickness | **0.11 (0.00,0.22)** | **0.046** | 0.09 (-0.03,0.21) | 0.159 | 0.03 (-0.09,0.15) | | 0.614 |
| Cortical volumetric density | 0.09 (-0.02,0.20) | 0.120 | 0.08 (-0.04,0.20) | 0.195 | 0.03 (-0.09,0.14) | | 0.651 |
| Cortical porosity | -0.02 (-0.12,0.09) | 0.763 | -0.04 (-0.16,0.08) | 0.514 | -0.06 (-0.18,0.07) | | 0.354 |
| Cortical pores diameter | -0.09 (-0.19,0.02) | 0.110 | -0.09 (-0.21,0.03) | 0.141 | **-0.14 (-0.26,-0.01)** | | **0.035** |
| Trabecular volumetric density | 0.10 (-0.01,0.21) | 0.079 | 0.09 (-0.03,0.21) | 0.132 | 0.01 (-0.09,0.12) | | 0.787 |
| Trabecular number | **0.15 (0.04,0.26)** | **0.006** | **0.18 (0.06,0.30)** | **0.003** | **0.12 (0.01,0.22)** | | **0.035** |
| Trabecular thickness | -0.01 (-0.12,0.10) | 0.819 | -0.02 (-0.14,0.11) | 0.773 | -0.08 (-0.21,0.04) | | 0.178 |
| Trabecular separation | **-0.16 (-0.26,-0.05)** | **0.005** | **-0.18 (-0.30,-0.05)** | **0.005** | -0.10 (-0.21,0.00) | | 0.058 |
|  |  |  |  |  |  | |  |
| **Tibia** |  |  |  |  |  | |  |
| Total area | **-0.15 (-0.24,-0.05)** | **0.003** | **-0.13 (-0.24,-0.02)** | **0.023** | **-0.15 (-0.26,-0.03)** | | **0.013** |
| Trabecular area | **-0.16 (-0.26,-0.06)** | **0.001** | **-0.14 (-0.25,-0.03)** | **0.010** | **-0.15 (-0.26,-0.04)** | | **0.010** |
| Cortical area | **0.15 (0.05,0.24)** | **0.002** | **0.15 (0.05,0.25)** | **0.003** | 0.09 (0.00,0.19) | | 0.054 |
| Cortical thickness | **0.15 (0.05,0.24)** | **0.003** | **0.13 (0.03,0.23)** | **0.014** | 0.08 (-0.02,0.18) | | 0.101 |
| Cortical volumetric density | **0.17 (0.08,0.26)** | **<0.001** | **0.21 (0.11,0.31)** | **<0.001** | **0.16 (0.06,0.25)** | | **0.002** |
| Cortical porosity | **-0.12 (-0.22,-0.03)** | **0.013** | **-0.16 (-0.27,-0.06)** | **0.002** | **-0.14 (-0.25,-0.03)** | | **0.010** |
| Cortical pores diameter | **-0.13 (-0.23,-0.03)** | **0.009** | **-0.13 (-0.24,-0.01)** | **0.029** | **-0.13 (-0.25,-0.01)** | | **0.027** |
| Trabecular volumetric density | 0.02 (-0.07,0.12) | 0.646 | 0.02 (-0.09,0.13) | 0.768 | -0.07 (-0.17,0.03) | | 0.165 |
| Trabecular number | **0.13 (0.03,0.23)** | **0.009** | **0.13 (0.02,0.24)** | **0.020** | 0.05 (-0.05,0.15) | | 0.318 |
| Trabecular thickness | **-0.10 (-0.19,0.00)** | **0.045** | -0.10 (-0.21,0.01) | 0.078 | **-0.13 (-0.24,-0.01)** | | **0.027** |
| Trabecular separation | **-0.12 (-0.22,-0.02)** | **0.019** | **-0.11 (-0.22,0.00)** | **0.044** | -0.03 (-0.13,0.07) | | 0.574 |
|  |  |  |  |  |  | |  |
| P: P-value; CI: Confidence interval | | | | | | | |
| \*Adjusted for age at time of HRpQCT scan, physical activity, smoking status, alcohol consumption, education and use of anti-osteoporotic medications and oestrogen/ hormone replacement (pill/skin patch) | | | | | | | |
| Higher fat mass index residuals indicate greater fat mass index than expected, given lean mass index | | | | | | | |
| Estimates were obtained from linear regression models | | | | | | | |
| Significant associations (p<0.05) are highlighted in bold | | | | | | | |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Table 3: Mean (SD) standardised HRpQCT and DXA aBMD parameters according to BMI category** | | | | | |  |  |  |
| **HRpQCT radius parameter** | **Underweight** | **Normal** | **Overweight** | **Class 1** | **Class 2/3** | **Morbid obesity** | **P-values for trend** | **P-value\*** |
| **(n=4)** | **(n=160)** | **(n=139)** | **(n=54)** | **(n=27)** | **(n=13)** |
| Total area | 0.01 (1.24) | 0.07 (0.99) | -0.08 (1.09) | 0.04 (0.89) | -0.05 (0.76) | 0.00 (0.90) | *0.522* | *0.741* |
| Trabecular area | 0.18 (1.11) | 0.10 (0.98) | -0.09 (1.10) | 0.00 (0.88) | -0.15 (0.79) | -0.09 (0.92) | *0.153* | *0.718* |
| Cortical area | -1.07 (1.20) | -0.20 (0.94) | 0.05 (1.00) | 0.23 (1.08) | 0.60 (0.74) | 0.53 (0.73) | ***<0.001*** | *0.673* |
| Cortical thickness | -1.02 (0.86) | -0.18 (0.95) | 0.06 (1.04) | 0.21 (1.00) | 0.46 (0.76) | 0.41 (0.77) | ***<0.001*** | *0.739* |
| Cortical volumetric density | -0.55 (0.65) | -0.11 (0.94) | 0.06 (1.05) | 0.05 (1.12) | 0.32 (0.76) | 0.30 (0.70) | ***0.020*** | *0.872* |
| Cortical porosity | 0.04 (0.88) | 0.03 (0.98) | -0.06 (1.08) | 0.03 (0.96) | 0.08 (0.81) | 0.03 (0.59) | *0.948* | *0.774* |
| Cortical pores diameter | 0.52 (0.84) | 0.07 (1.07) | 0.00 (0.94) | -0.13 (0.97) | -0.17 (0.96) | -0.10 (0.88) | *0.088* | *0.711* |
| Trabecular volumetric density | -0.64 (0.48) | -0.09 (1.01) | -0.04 (0.96) | 0.16 (1.05) | 0.53 (0.96) | 0.41 (1.07) | ***0.002*** | *0.552* |
| Trabecular number | -0.88 (0.76) | -0.16 (0.95) | -0.07 (0.96) | 0.36 (1.00) | 0.68 (1.06) | 0.42 (1.09) | ***<0.001*** | *0.218* |
| Trabecular thickness | -0.05 (1.12) | 0.07 (0.95) | -0.02 (1.08) | -0.22 (0.98) | 0.14 (0.94) | 0.15 (1.12) | *0.399* | *0.959* |
| Trabecular separation | 0.87 (0.64) | 0.15 (0.95) | 0.08 (0.93) | -0.34 (1.07) | -0.69 (1.08) | -0.44 (1.08) | ***<0.001*** | *0.248* |
|  |  |  |  |  |  |  |  |  |
| **HRpQCT tibia parameter** | **Underweight** | **Normal** | **Overweight** | **Class 1** | **Class 2/3** | **Morbid obesity** | **P-values for trend** | **P-value\*** |
| **(n=10)** | **(n=196)** | **(n=166)** | **(n=69)** | **(n=36)** | **(n=22)** |
| Total area | 0.53 (1.10) | 0.04 (0.99) | -0.11 (1.00) | 0.05 (1.02) | 0.07 (0.97) | 0.06 (1.09) | *0.666* | *0.925* |
| Trabecular area | 0.64 (1.04) | 0.07 (0.98) | -0.11 (1.00) | -0.00 (1.02) | -0.05 (1.00) | -0.03 (1.13) | *0.141* | *0.865* |
| Cortical area | -0.97 (1.13) | -0.24 (0.92) | 0.02 (0.93) | 0.39 (1.03) | 0.74 (0.95) | 0.54 (0.99) | ***<0.001*** | *0.111* |
| Cortical thickness | -1.02 (1.06) | -0.20 (0.95) | 0.05 (0.96) | 0.27 (0.98) | 0.58 (1.03) | 0.46 (1.13) | ***<0.001*** | *0.421* |
| Cortical volumetric density | -0.65 (1.34) | -0.15 (0.92) | 0.08 (0.99) | 0.20 (1.06) | 0.26 (1.08) | 0.17 (1.22) | ***<0.001*** | *0.521* |
| Cortical porosity | 0.02 (0.68) | 0.12 (0.97) | -0.08 (0.98) | -0.14 (0.99) | -0.04 (1.27) | -0.02 (1.39) | *0.076* | *0.898* |
| Cortical pores diameter | 0.24 (0.82) | 0.15 (0.95) | 0.04 (1.01) | -0.38 (1.04) | -0.29 (0.98) | -0.03 (0.97) | ***<0.001*** | ***0.046*** |
| Trabecular volumetric density | -0.48 (0.90) | -0.06 (1.07) | 0.01 (0.97) | 0.15 (0.91) | 0.15 (0.91) | -0.11 (0.89) | ***0.037*** | ***0.028*** |
| Trabecular number | -0.17 (1.07) | -0.23 (1.03) | 0.00 (0.92) | 0.40 (0.88) | 0.51 (1.02) | 0.16 (0.96) | ***<0.001*** | ***0.009*** |
| Trabecular thickness | -0.54 (0.88) | 0.15 (1.01) | 0.02 (1.04) | -0.24 (0.87) | -0.31 (0.85) | -0.34 (0.77) | ***0.006*** | *0.784* |
| Trabecular separation | 0.24 (1.04) | 0.21 (1.04) | 0.00 (0.91) | -0.37 (0.92) | -0.46 (1.02) | -0.11 (0.96) | ***<0.001*** | ***0.007*** |
|  |  |  |  |  |  |  |  |  |
| **DXA aBMD parameter** | **Underweight** | **Normal** | **Overweight** | **Class 1** | **Class 2/3** | **Morbid obesity** | **P-values for trend** | **P-value\*** |
| **(n=10)** | **(n=199)** | **(n=172)** | **(n=71)** | **(n=38)** | **(n=22)** |
| Whole body total aBMD | -0.21 (1.24) | -0.12 (1.04) | -0.04 (0.94) | 0.37 (1.00) | 0.27 (0.80) | 0.19 (0.90) | ***0.001*** | *0.548* |
| Total hip aBMD | -0.86 (0.95) | -0.27 (0.91) | 0.01 (0.96) | 0.44 (0.99) | 0.72 (0.98) | 0.68 (1.08) | ***<0.001*** | *0.777* |
| Femoral neck aBMD | -0.39 (1.06) | -0.19 (0.96) | -0.02 (0.99) | 0.37 (0.99) | 0.55 (0.91) | 0.35 (0.94) | ***<0.001*** | *0.130* |
| Total lumbar spine aBMD | -0.26 (1.01) | -0.20 (0.99) | -0.01 (0.95) | 0.37 (0.96) | 0.52 (1.03) | 0.61 (1.15) | ***<0.001*** | *0.567* |
| BMI categories were defined as follows: Underweight (BMI<18.5); Normal (18.5≤BMI<25); Overweight (25≤BMI<30); Class 1 (30≤BMI<35); Class 2/3 (BM≥35)  Morbid obesity: Class 2/3 obese and hypertension/diabetes; this category was not used in the calculation of p-values for trend.  \*P-values for difference in parameter between participants with morbid obesity (Class 2/3 obese with hypertension or diabetes) and those with Class 2/3 obesity but without hypertension or diabetes. Significant p-values (p<0.05) are highlighted in bold. | | | | | | | | |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Table 4: Mean (SD) standardised HRpQCT and DXA aBMD parameters (divided by body weight before standardising) according to BMI category** | | | | | | | |
| **HRpQCT radius parameter** | **Underweight** | **Normal** | **Overweight** | **Class 1** | **Class 2/3** | **Morbid obesity** | **P-values for trend** |
| **(n=4)** | **(n=160)** | **(n=139)** | **(n=54)** | **(n=27)** | **(n=13)** |
| Total area | 1.54 (1.00) | 0.64 (0.76) | -0.19 (0.74) | -0.78 (0.61) | -1.52 (0.54) | -1.47 (0.59) | ***<0.001*** |
| Trabecular area | 1.45 (0.95) | 0.59 (0.81) | -0.18 (0.81) | -0.69 (0.66) | -1.39 (0.57) | -1.33 (0.64) | ***<0.001*** |
| Cortical area | 0.46 (1.11) | 0.38 (0.87) | -0.06 (0.95) | -0.55 (0.92) | -0.87 (0.89) | -0.93 (0.88) | ***<0.001*** |
| Cortical thickness | 0.33 (0.73) | 0.33 (0.89) | -0.04 (0.99) | -0.47 (0.87) | -0.84 (0.87) | -0.88 (0.88) | ***<0.001*** |
| Cortical volumetric density | 1.71 (0.34) | 0.67 (0.72) | -0.14 (0.67) | -0.94 (0.55) | -1.56 (0.62) | -1.55 (0.58) | ***<0.001*** |
| Cortical porosity | 0.80 (0.84) | 0.32 (0.94) | -0.12 (1.01) | -0.36 (0.89) | -0.62 (0.69) | -0.62 (0.50) | ***<0.001*** |
| Cortical pores diameter | 1.87 (0.49) | 0.68 (0.72) | -0.14 (0.62) | -0.92 (0.57) | -1.69 (0.49) | -1.66 (0.48) | ***<0.001*** |
| Trabecular volumetric density | 0.42 (0.63) | 0.31 (1.04) | -0.11 (0.91) | -0.39 (0.82) | -0.53 (0.78) | -0.63 (0.85) | ***<0.001*** |
| Trabecular number | 0.64 (1.13) | 0.45 (0.98) | -0.17 (0.89) | -0.48 (0.69) | -0.86 (0.70) | -0.99 (0.70) | ***<0.001*** |
| Trabecular thickness | 1.28 (0.66) | 0.57 (0.75) | -0.10 (0.84) | -0.89 (0.70) | -1.25 (0.79) | -1.22 (0.77) | ***<0.001*** |
| Trabecular separation | 1.42 (0.42) | 0.49 (0.74) | -0.01 (0.83) | -0.76 (0.80) | -1.49 (0.84) | -1.34 (0.96) | ***<0.001*** |
|  |  |  |  |  |  |  |  |
| **HRpQCT tibia parameter** | **Underweight** | **Normal** | **Overweight** | **Class 1** | **Class 2/3** | **Morbid obesity** | **P-values for trend** |
| **(n=10)** | **(n=196)** | **(n=166)** | **(n=69)** | **(n=36)** | **(n=22)** |
| Total area | 1.96 (0.65) | 0.66 (0.69) | -0.22 (0.64) | -0.83 (0.59) | -1.54 (0.64) | -1.46 (0.72) | ***<0.001*** |
| Trabecular area | 1.92 (0.72) | 0.60 (0.74) | -0.21 (0.70) | -0.76 (0.67) | -1.41 (0.70) | -1.31 (0.79) | ***<0.001*** |
| Cortical area | 0.35 (1.29) | 0.33 (0.98) | -0.07 (0.91) | -0.43 (0.86) | -0.74 (0.77) | -0.81 (0.78) | ***<0.001*** |
| Cortical thickness | 0.19 (1.22) | 0.33 (0.96) | -0.04 (0.91) | -0.47 (0.86) | -0.76 (0.89) | -0.76 (0.91) | ***<0.001*** |
| Cortical volumetric density | 1.54 (0.76) | 0.64 (0.74) | -0.13 (0.65) | -0.91 (0.57) | -1.55 (0.60) | -1.50 (0.58) | ***<0.001*** |
| Cortical porosity | 0.92 (0.70) | 0.45 (0.90) | -0.14 (0.85) | -0.59 (0.83) | -0.90 (0.95) | -0.83 (1.08) | ***<0.001*** |
| Cortical pores diameter | 1.70 (0.64) | 0.65 (0.69) | -0.12 (0.62) | -0.98 (0.58) | -1.58 (0.60) | -1.40 (0.58) | ***<0.001*** |
| Trabecular volumetric density | 0.80 (1.04) | 0.40 (0.99) | -0.09 (0.86) | -0.52 (0.70) | -1.00 (0.73) | -1.13 (0.72) | ***<0.001*** |
| Trabecular number | 1.44 (1.00) | 0.42 (0.95) | -0.11 (0.79) | -0.53 (0.69) | -1.14 (0.75) | -1.30 (0.79) | ***<0.001*** |
| Trabecular thickness | 0.90 (0.83) | 0.58 (0.80) | -0.10 (0.77) | -0.82 (0.64) | -1.38 (0.68) | -1.34 (0.60) | ***<0.001*** |
| Trabecular separation | 1.18 (0.76) | 0.56 (0.79) | -0.08 (0.73) | -0.84 (0.69) | -1.37 (0.80) | -1.10 (0.81) | ***<0.001*** |
|  |  |  |  |  |  |  |  |
| **DXA aBMD parameter** | **Underweight** | **Normal** | **Overweight** | **Class 1** | **Class 2/3** | **Morbid obesity** | **P-values for trend** |
| **(n=10)** | **(n=199)** | **(n=172)** | **(n=71)** | **(n=38)** | **(n=22)** |
| Whole body total aBMD | 1.66 (0.65) | 0.66 (0.72) | -0.20 (0.65) | -0.91 (0.54) | -1.65 (0.61) | -1.59 (0.57) | ***<0.001*** |
| Total hip aBMD | 1.22 (0.90) | 0.56 (0.80) | -0.13 (0.80) | -0.70 (0.68) | -1.31 (0.76) | -1.28 (0.62) | ***<0.001*** |
| Femoral neck aBMD | 1.41 (0.82) | 0.54 (0.78) | -0.16 (0.81) | -0.70 (0.70) | -1.31 (0.80) | -1.38 (0.65) | ***<0.001*** |
| Total lumbar spine aBMD | 1.35 (0.81) | 0.48 (0.84) | -0.12 (0.82) | -0.59 (0.76) | -1.25 (0.93) | -1.14 (0.82) | ***<0.001*** |
| BMI categories were defined as follows: Underweight (BMI<18.5); Normal (18.5≤BMI<25); Overweight (25≤BMI<30); Class 1 (30≤BMI<35); Class 2/3 (BM≥35)  Morbid obesity: Class 2/3 obese and hypertension/diabetes; this category was not used in the calculation of p-values for trend. Significant p-values (p<0.05) are highlighted in bold. | | | | | | | |

**Online Resource**

**Article title:** Adiposity and bone microarchitecture in the GLOW Study

**Journal:** Osteoporosis International

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| **eTable 1: Number of participants who had falls and fractures at certain sites according to BMI category** | | | | | | |
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| **Participant characteristic** | **Underweight** | **Normal** | **Overweight** | **Class 1** | **Class 2/3** | **Morbid obesity** |
| **(n=10)** | **(n=196)** | **(n=169)** | **(n=67)** | **(n=38)** | **(n=22)** |
| Fall | 8 (80.0%) | 119 (61.3%) | 120 (71.9%) | 50 (75.8%) | 28 (73.7%) | 13 (59.1%) |
|  |  |  |  |  |  |  |
| Fracture site |  |  |  |  |  |  |
| Clavicle | 0 (0.0%) | 1 (0.5%) | 1 (0.6%) | 1 (1.6%) | 0 (0.0%) | 0 (0.0%) |
| Upper arm | 0 (0.0%) | 6 (3.1%) | 4 (2.5%) | 2 (3.2%) | 2 (5.6%) | 2 (10.0%) |
| Wrist | 3 (30.0%) | 16 (8.2%) | 14 (8.7%) | 6 (9.4%) | 0 (0.0%) | 0 (0.0%) |
| Spine | 0 (0.0%) | 2 (1.0%) | 2 (1.2%) | 2 (3.2%) | 1 (2.9%) | 0 (0.0%) |
| Rib | 1 (10.0%) | 8 (4.1%) | 6 (3.8%) | 1 (1.6%) | 0 (0.0%) | 0 (0.0%) |
| Hip | 0 (0.0%) | 2 (1.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Pelvis | 0 (0.0%) | 0 (0.0%) | 1 (0.6%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Ankle | 0 (0.0%) | 4 (2.1%) | 8 (5.0%) | 5 (7.8%) | 2 (5.6%) | 0 (0.0%) |
| Upper leg | 0 (0.0%) | 2 (1.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Lower leg | 0 (0.0%) | 8 (4.2%) | 4 (2.5%) | 2 (3.2%) | 3 (8.3%) | 2 (10.0%) |
|  |  |  |  |  |  |  |
| Fracture (any site listed above) | 4 (44.4%) | 37 (19.5%) | 35 (22.0%) | 11 (17.5%) | 7 (20.6%) | 4 (20.0%) |
| BMI categories were defined as follows: Underweight (BMI<18.5); Normal (18.5≤BMI<25); Overweight (25≤BMI<30); Class 1 (30≤BMI<35); Class 2/3 (BM≥35)  Morbid obesity: Class 2/3 obese and hypertension/diabetes  At baseline and at the 1-, 2-, 3- and 5-year follow-up, participants were asked to report the number of times they had fallen during the last 12 months; the number of participants with at least one fall, based on the data at all time-points, is presented  The number of participants who experienced fractures at each site from age 45 years until the 5-year follow-up is presented  Overall differences in participant characteristics according to the following BMI categories were not statistically significant (p>0.05 for all associations): Underweight; Normal; Overweight; Class 1; Class 2/3 | | | | | | |