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Adiposity without obesity: Associations with osteoporosis, sarcopenia and falls in The Healthy Ageing Initiative cohort study

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What is already known about this subject?

- Higher body mass index (BMI) is generally associated with higher bone and lean mass
- Obesity defined by BMI does not necessarily reflect adiposity

What are the new findings in your manuscript?

- A substantial proportion (68%) of older adults have normal BMI but high adiposity
- Older adults with normal BMI but high adiposity may have poor bone and muscle health

How might your results change the direction of research or the focus of clinical practice?

- Clinical fracture prediction tools should consider body composition rather than, or in addition to, body mass.

Abstract

Objective: Obesity is commonly defined by body mass index (BMI) rather than adiposity, which may have differential effects on musculoskeletal health. We compared musculoskeletal outcomes in older adults with normal adiposity and BMI (NA-NBMI), high adiposity but normal BMI (HA-NBMI), and those with high adiposity and BMI (HA-HBMI).

Methods: In 3,411 70-year-olds, obesity was defined as BMI ≥30kg/m² and adiposity as body fat percentage ≥25% (men) or ≥35% (women) from dual-energy X-ray absorptiometry

(DXA). Bone parameters were measured by DXA and peripheral quantitative computed tomography. Sarcopenia was defined as low hand grip strength with or without low appendicular lean mass. Falls were self-reported 6 and 12 months later.

Results: Prevalence of NA-NBMI, HA-NBMI and HA-HBMI were 14.2%, 68.1% and 17.7%, respectively. Compared with HA-HBMI, HA-NBMI had increased likelihood for sarcopenia (adjusted odds ratio: 3.99; 95% CI: 1.41-11.32) and osteoporosis (2.91; 2.35-3.61), but similar likelihood of falls (P>0.05). HA-NBMI had lower values for a number of bone geometry parameters, and also grip strength, than both NA-NBMI and HA-HBMI (all P<0.05).

Conclusions: High adiposity without high BMI is more common than BMI-defined obesity in older Swedish adults, but does not provide similar protection from osteoporosis and sarcopenia.

Introduction

The World Health Organization defines obesity as abnormal or excessive fat accumulation that may impair health and, while noting that body mass index (BMI) may not accurately represent body fatness, recommends the BMI as the most useful population-level measure of obesity (1). High BMI may be appropriate for defining obesity in clinical settings given it is consistently associated with poor cardiometabolic health and increased mortality (2). However, associations with musculoskeletal outcomes differ because higher BMI is generally associated with greater bone (3) and muscle (4) mass, and reduced fracture rates (5).

There is a high prevalence of older adults with high adiposity but normal BMI (6). High adiposity may compromise muscle quality (7) and does not appear to provide any benefit for bone health given lean mass, not fat mass, is positively associated with BMD (8). Indeed, higher adiposity itself is associated with increased hip fracture risk (9), and in the presence of low lean mass, which is likely to be common in those with high adiposity but normal BMI, we have demonstrated observed lower BMD and increased incident fractures (10, 11).

It has been postulated that the health burden of obesity will continue to increase due to disabling conditions (12), including sarcopenia, osteoporosis and falls. There is consequently an urgent need to determine appropriate methods to identify individuals with obesity who are at increased risk for these fracture-related risk factors. We aimed to compare

measures of osteoporosis, sarcopenia and incident falls over 12 months between older Swedish adults with normal adiposity (defined by dual-energy X-ray absorptiometry; DXA) and normal BMI (NA-NBMI), high adiposity and normal BMI (HA-NBMI), and those with high adiposity and high BMI (HA-HBMI).

Methods

Study design and participants

The Healthy Ageing Initiative (HAI) is an ongoing observational study of 70-year-old adults in Umeå, northern Sweden (13). Its objectives are to investigate traditional and novel risk factors for cardiovascular disease and injurious falls and fractures in 70-year-old men and women. Only two eligibility criteria apply: individuals must be 70 years of age at the time of testing and residing in the Umeå municipal area. Potentially eligible individuals were identified from population registers and sent written information about the study. Individuals were subsequently contacted by telephone and invited to participate with a study participation rate of 69.5%. The study was approved by the Umeå University Research Ethics Committee and complied with the World Medical Association's Declaration of Helsinki. All participants provided written informed consent. The current analysis included the first 3,413 participants with complete data for body composition, BMI, sarcopenia and osteoporosis at baseline. Participants attended a hospital near Umeå University for baseline clinic measurements including a questionnaire assessing demographics, lifestyle and medical history (comorbidities and medication use; although bone- and muscle-related conditions and medications were not obtained), as well as assessments described below. Immediately following the baseline clinic, participants wore a triaxial accelerometer (GT3X+; Actigraph, Pensacola, FL, USA) for seven days as described previously (14). Percentage of time spent performing moderate-to-vigorous physical activity (MVPA) was classified using cut-points proposed by Freedson et al (15).

Anthropometric, body composition and bone measurements

At baseline, height and weight were assessed by stadiometer (Holtain Limited, Crymych, Dyfed, UK) and scales (Avery Berkel HL 120, Smethwick, West Midlands, UK), respectively, and body mass index (BMI; kg/m^2) was calculated. A DXA whole-body scan was used to estimate total body fat percentage and visceral fat mass using a Lunar iDXA with

encore version 16.0 software (GE Healthcare Lunar, Madison, WI, USA). Appendicular lean mass (ALM) was also estimated from whole-body DXA scans.

Areal BMD (aBMD; g/cm^2) was measured via DXA scans at the lumbar spine (L1–L4), and non-dominant total hip and femoral neck. T-scores were estimated for lumbar spine and total hip using the US NHANES reference ranges. Each morning prior to measurements, the standard "block" phantom was scanned, and each week a phantom in water bath was scanned for precision. Coefficients of variation (CVs) for in-vivo measurements of the iDXA are 0.4% for the lumbar spine and 1.4% for the femoral neck (16). All DXA scans were assessed post-scanning for quality. Regions of Interest were adjusted according to the manufacturer's guidelines and all technicians underwent necessary education and were certified by the manufacturer in accordance with the International Society of Clinical Densitometry criteria.

A peripheral quantitative computed tomography (pQCT) device (XCT-2000; Stratec Medizintechnik, Pforzheim, Germany) was used to measure total, cortical and trabecular vBMD (mg/cm^3) and area (mm^2), cortical thickness (mm), periosteal and endosteal circumferences (mm), and stress-strain index (SSI polar; mm^3) of the non-dominant tibia and radius. Slice thickness was 2.0 mm and voxel size was 0.5 mm. Total and trabecular vBMD and area were measured at scan sites in the metaphysis located at 4% (distal site) of total tibial bone length in the distal–proximal direction, and cortical vBMD, area, thickness, periosteal and endosteal circumferences, and SSI polar were measured at diaphyseal scan sites located at 66% (proximal site) of total bone length. Calf muscle cross-sectional area (CSA; mm^2) and density (mg/cm^3; density of tissue within the muscle compartment after removal of subcutaneous fat and bone areas) were determined from the pQCT scan performed at the proximal tibia, which is the region with the largest outer calf diameter with small variability across individuals (17). All pQCT measurements were repeated in the event of motion artefacts. Acquisition and analysis of scans was performed using the manufacturer's software (version 6.2). A standard phantom was scanned each study morning and a cone phantom was scanned each month. Reported CVs for the Stratec XCT-2000 pQCT device are 1.6% for trabecular density and 0.3% for cortical density (18). Both DXA and pQCT instruments remained in control throughout the study period.

Physical function measurements

Hand grip strength of the non-dominant hand was assessed using an isokinetic hand dynamometer (Jamar; Patterson Medical, Warrenville, IL, USA). Participants maintained a

90° angle at the elbow joint and kept the elbow in close proximity to the waist while squeezing the dynamometer as forcefully as possible. The best of two attempts was recorded. The Timed Up-and-Go (TUG) test assessed physical performance; participants were asked to rise unaided from an armchair and walk forward 3 meters, then to turn around and return to a seated position in the chair. Research nurses provided instructions and measured TUG time using a stopwatch.

12-month incident falls

Six and 12 months after the baseline clinical appointment, participants were contacted by a research nurse by telephone to determine incident falls since the appointment.(19) Participants were asked whether they had experienced any low energy falls in the past six months, where the participant had unexpectedly come to rest on the ground by him/herself. Individuals who reported one fall over 12 months were classified as "single fallers", and individuals who reported 2 or more falls were classified as "multiple fallers" (20).

Definitions for obesity, sarcopenia and osteoporosis

Obesity was defined using the World Health Organization BMI cut-point of ≥ 30kg/m^2). Although reference values for body composition assessed by DXA are available (21), there are no consensus definitions for high adiposity defined by body fat percentage. We used sex-specific cut-off points for total body fat percentage of ≥25% for men and ≥35% for women as these have been most commonly utilised in the literature to date (6). Participants were classified into the following groups according to adiposity and obesity cut-points: normal adiposity and normal BMI (NA-NBMI); high adiposity and normal BMI (HA-NBMI); and high adiposity and high BMI (HA-HBMI).

Sarcopenia was defined according to the European Working Group on Sarcopenia in Older People's revised definition (EWGSOP2), which categorises probable sarcopenia as low muscle strength only, and confirmed sarcopenia as low muscle strength and low lean mass (22). Low muscle strength was defined as hand grip strength <27kg (men) or <16 kg (women), while low lean mass was defined as ALM <20.0 kg (men) or <15.0 kg (women) (22).

Osteoporosis was defined as a T-score at the lumbar spine or total hip of ≤-2.5 SD, and osteopenia was defined as a T-score between -1.0 and -2.5 (23).

Statistical Analyses

All statistical analyses were performed using SPSS Version 25 (IBM Corp, Armonk, NY, USA). We initially generated sex-stratified scatter plots to explore the distribution of participants with and without high adiposity (high body fat percentage) and obesity (high BMI). We compared differences in participant characteristics at baseline between NA-NBMI, HA-NMBI and HA-HBMI groups using one-way ANOVA (continuous variables) and Chi-square tests (categorical variables) with Bonferroni post-hoc tests to determine between-group differences. These analyses were stratified by sex. Sex-stratified Pearson correlations were also used to explore associations between body composition variables.

Generalised linear models were used to compare differences in body composition and bone parameters between groups (linear model; normal probability distribution; identity link function). Given that prior analyses indicated similar relationships between body composition and outcomes of interests these analyses were not performed separately for men and women, but were adjusted for sex, as well as self-reported smoking and diabetes status, use of blood pressure medication, and mean percentage of time spent in MVPA. The NA-NBMI group was set as the referent group in the primary analyses, and post-hoc analyses with the HA-HBMI group set as referent were performed in order to allow comparisons of outcomes between HA-NBMI and HA-HBMI.

Chi-square tests with Bonferroni post-hoc tests compared the proportion of participants in each group who met criteria for probable or confirmed sarcopenia, osteopenia or osteoporosis, and who had a single or multiple incident falls. Finally, ordinal logistic regression models compared likelihood of probable or confirmed sarcopenia, osteopenia or osteoporosis, and single or multiple incident falls between groups. Each variable in the ordinal regression models had three levels (1: no sarcopenia, 2: probable sarcopenia and 3: confirmed sarcopenia; 1: no osteopenia/osteoporosis, 2: osteopenia, 3: osteoporosis; 1: no falls, 2: single fall, 3: multiple falls). As per previous analyses, the models included sex, smoking and diabetes status, use of blood pressure medication, and percentage MVPA as covariates, and the NA-NBMI group was set as the referent group in the primary analyses with post-hoc analyses setting the HA-HBMI group as referent.

For all analyses, P-values <0.05 or 95% confidence intervals (95% CI) not including the null point were considered statistically significant.

Results

A total of 3,413 participants had complete data at baseline. Figure 1 reports the classification of participants by adiposity and obesity status. Only two participants with high BMI had normal adiposity and were excluded from analyses. Amongst the remaining 3,411 participants, 14.2% of participants had normal adiposity and normal BMI (NA-NBMI), 17.7% had high adiposity and high BMI (HA-HBMI), while the largest group (68.1%) comprised those with high adiposity and normal BMI (HA-NBMI). As demonstrated in Table 1, the proportions of men and women were similar across NA-NBMI, HA-NBMI, and HA-HBMI. For both men and women, the prevalence of diabetes was greater, timed up-and-go time was slower, and MVPA time was lower, in HA-HBMI compared to the other groups. In women only, hand grip strength was lower in HA-NBMI compared to the other groups, whereas for men, HA-NMBI had lower hand grip strength than NA-NBMI only. Means for BMI, body fat percentage, visceral fat mass, ALM and total hip aBMD were significantly higher in HA-HBMI compared with the other groups.

BMI and body fat percentage were strongly positively correlated in both women (r=0.81; P<0.001) and men (r=0.76; P<0.001). Table 2 reports Pearson correlations for BMI and body fat percentage with other body composition measures. BMI and body fat percentage had similar strong positive correlations with visceral fat mass, and weak negative correlations with calf muscle density. BMI was more strongly positively correlated than body fat percentage with ALM in both men and women. BMI was also more strongly positively correlated that body fat percentage with calf muscle CSA in men. In women, BMI was weakly positively correlated with calf muscle CSA whereas body fat percentage had no significant association.

After multivariable adjustment (Table 3) in generalised linear models, ALM, visceral fat mass and calf muscle CSA were significantly greater, but calf muscle density was significantly lower and TUG time was slowest, in HA-HBMI compared with other groups. Hand grip strength was significantly lower in HA-NBMI compared with NA-NBMI and HA-HBMI.

Table 4 presents findings from generalised linear models comparing bone parameters between groups. DXA aBMD and T-scores were consistently significantly higher in HA-NBMI compared with NA-NBMI, but HA-HBMI values were significantly greater compared with both groups. Similar patterns were observed for pQCT vBMD parameters including total and trabecular vBMD (distal radius and tibia), and total vBMD at the proximal tibia. HA-

NBMI had significantly lower total and trabecular bone area at the distal radius compared with other groups, and at the distal tibia compared with HA-HBMI. At the proximal radius, HA-NBMI had lower cortical area, cortical thickness and SSI compared with HA-HBMI, and lower periosteal and endosteal circumferences than both groups. At the proximal tibia, HA-NBMI had lower values for all parameters except cortical vBMD and SSI compared with HA-HBMI, and had lower values for SSI and endosteal circumference compared with NA-NBMI.

A total of 1,412 (41.4%) participants met criteria for osteopenia and a further 442 (13.0%) met criteria for osteoporosis. Low numbers of participants had probable or confirmed sarcopenia, specifically 34 (1.0%) and 32 (0.9%), respectively. A total of 2,538 (74.4%) participants provided complete falls records at 12 months; 266 (10.5%) participants reported a single fall and a further 36 (1.4%) reported more than one fall and were classified as multiple fallers. Figure 2 demonstrates that there were no differences in the prevalence of probable or confirmed sarcopenia but both NA-NBMI (44.8% and 27.5%, respectively) and HA-NBMI (43.7% and 12.4%, respectively) had significantly higher prevalence of osteopenia and osteoporosis compared with HA-HBMI (29.9% and 3.6%, respectively). There were significantly more NA-NBMI participants (91.5%) who experienced no incident falls compared with HA-HBMI (85.2%).

After adjustment for confounders in multivariable ordinal regression models (Table 5), likelihood for probable and confirmed sarcopenia was approximately 72% higher for HA-NBMI compared with NA-NBMI and although this difference was not significant, the difference between HA-NBMI and HA-HBMI was significant (odds ratio: 3.99; 95% CI: 1.41-11.32). The odds ratio for osteopenia and osteoporosis in HA-NBMI compared with HA-HBMI was also significantly increased (2.91; 2.35-3.61). The likelihood of single and multiple falls was almost two-fold higher for HA-HBMI compared with NA-NBMI and this was significant. Odds for single and multiple falls were increased by 50% in HA-NBMI compared with NA-NBMI and this approached significance (P=0.055).

Discussion

This prospective study demonstrated that the majority of community-dwelling older adults without obesity according to BMI classifications have high adiposity, and that these individuals have a greater likelihood for osteoporosis and sarcopenia than those with BMI-defined obesity. High adiposity in the absence of BMI-defined obesity may therefore offer

little protection against age-related bone and muscle declines, and further studies are required to determine whether this results in increased fracture risk.

BMI cut-points appear to have excellent specificity for identifying individuals without high adiposity (24), as demonstrated in the present study where only two participants with high BMI did not have high adiposity. However, over two-thirds of participants in this study demonstrated high levels of adiposity despite having normal BMI, highlighting the relatively poor sensitivity of BMI cut-points. A systematic review and meta-analysis including almost 32,000 participants similarly reported that BMI cut-offs for obesity fail to identify half of the people with excess body fat percentage (6). These individuals may represent a segment of the population with low muscle mass relative to body size. Indeed, while the HA-NBMI group had mean values for BMI and body fat percentage that were generally 3-4 kg/m^2 and 10-11% higher than those of the NA-NBMI group, respectively, in multivariable analyses their ALM was <0.4 kg higher, and calf muscle CSA did not differ. Both ALM and calf muscle CSA were significantly lower in HA-NBMI compared with HA-HBMI. HA-NBMI also had significantly lower calf muscle density than NA-NBMI, and this is consistent with evidence that individuals with greater overall adiposity tend to demonstrate greater muscle fat infiltration (7). Furthermore, HA-NBMI had significantly lower hand grip strength than both the NA-NBMI and HA-HBMI groups. We previously observed that older adults with sarcopenic obesity demonstrate poorer hand grip strength than those with obesity alone and those with neither sarcopenia nor obesity (10), suggesting that low muscle mass in the presence of high adiposity significantly compromises muscle strength.

Conversely, we also observed in the present study that the HA-NBMI group had faster TUG time than HA-HBMI, despite being slower than NA-NBMI. BMI-defined obesity is associated with physical frailty (25) but it is unclear why physical performance, and not muscle strength, may be better in HA-NBMI compared with HA-HBMI. It is possible the relationship is explained by the greater overall body size of the HA-HBMI group which may reduce mobility (26), and/or the significantly greater adiposity of skeletal muscle in the lower-limbs observed for HA-HBMI compared with HA-NBMI. In agreement, we and others have reported that greater lower-limb muscle density, indicating lower fat infiltration muscle, is consistently associated with better physical performance, but inconsistently associated with muscle strength (7, 27). Furthermore, the HA-NBMI group demonstrated significantly higher MVPA than the HA-HBMI group and we have reported in this cohort that higher MVPA time is more strongly associated with better TUG performance than muscle strength (28).

Despite generally having greater aBMD and vBMD values than the NA-NBMI group, HA-NBMI also generally had lower BMD values compared with HA-HBMI, and demonstrated significantly lower values than NA-NBMI, HA-HBMI or both, for pQCT-derived bone geometric parameters including total, trabecular and cortical area, cortical thickness, stress-strain index and periosteal and endosteal circumferences. The finding that these geometric parameters were lower in HA-NBMI participants, despite having higher aBMD as assessed by DXA, supports the need for use of other imaging modalities to more completely assess bone health in individuals with high adiposity (29). There is evidence that volumetric BMD and architectural parameters predict fractures in older adults independently of DXA aBMD (30). Estimate errors associated with increasing overlying fat are smaller and more uniform for QCT vBMD than for DXA aBMD (31), and pQCT measurements may also be less influenced by arterfact (such as sclerotic lesions in the lumbar spine), although there was generally concordance in differences in aBMD and vBMD between groups in our study.

High BMI has been associated with greater vBMD, cortical area, thickness, periosteal, and endosteal circumference and SSI (32) and this was generally observed in the present study where the HA-HBMI group demonstrated the highest values for total and trabecular vBMD, and cortical area and thickness at the tibia and radius. We also previously reported higher aBMD, and tibial cortical area, thickness and SSI in older adults with obesity compared with non-obese counterparts according to BMI, but no differences in these parameters when obesity was defined by body fat percentage (33). High BMI, but not high adiposity, appears to be beneficial for bone health in older adults due to the aforementioned greater muscle mass and associated mechanical loading in those with high BMI compared with those with high adiposity but normal BMI. This concept is supported by evidence that fat mass is not a strong predictor of bone size or geometry, whereas bone and skeletal muscle are a functional unit where bone cross-sectional properties respond to muscle mass and strength to maintain mechanical integrity (34). In support, our previous data indicate that older adults with sarcopenic obesity (low lean mass with high adiposity) have lower BMD and increased incident fractures compared with those with obesity and normal lean mass (10, 11). Thus, the BMD- and fracture-protective effects of high BMI may be observed primarily in individuals with high muscle mass, and those with high relative adiposity may receive little protective benefit.

Indeed, amongst risk factors for fracture explored in the present study, the protection from osteoporosis was significantly lower for HA-NBMI compared with HA-HBMI, and HA-NBMI four-fold higher odds for sarcopenia. HA-HBMI was the only group with

significantly increased risk for incident falls which is somewhat surprising given their concurrent lower likelihood for sarcopenia. Obesity defined by BMI has been associated with increased falls risk previously (35, 36), and the association may be explained by factors such as poor postural stability and centre of mass displacement (37). The finding may also be related to the poorer muscle quality of the HA-HMIB group described above; we have reported in this cohort that low calf muscle density is associated with increased risk of incident falls (38), and others have also observed lower muscle density in older fallers (39, 40). Nonetheless, the increased likelihood of falls for HA-NBMI compared with NA-NBMI approached significance, and there was no difference compared with HA-HBMI. This observation, coupled with an increased likelihood of sarcopenia and reduced protection from osteoporosis, suggests that older adults with high adiposity but normal BMI may be at the greatest risk for incident fractures. Further prospective studies are needed to confirm whether incident fracture rates are increased in this population.

There are several limitations to this study. The sarcopenia- and osteoporosis-related outcomes were only assessed at baseline and so causality in their relationships with obesity and adiposity cannot be conferred, and it also unclear whether these associations translate to fracture outcomes. Nevertheless, fracture predictors appear to be similar for older individuals with and without obesity, so the fracture risk factors observed in this study may be expected to increase fracture risk similarly for those with high adiposity as those with normal adiposity (41). Although DXA and pQCT have high precision and standard scanning acquisition and analysis protocols were followed by all technicians, we do not have data on precision of these measurements in our hands, and artefact including sclerotic lesions and tissue asymmetry may have influenced estimates. We also did not collect data on bone diseases or bone-active medications that may affect BMD and bone architecture. We utilised adiposity cut-points of 25% for men and 35% for women and these cut-points may not be appropriate for identifying high adiposity in non-Caucasian populations. The use of different cut-points to define adiposity would clearly influence its observed prevalence associations with fracture-related risk factors. Finally, this cohort exclusively consists of community-dwelling 70-year-old Swedish men and women who are generally healthy and may not be generalisable to other older adult populations. Indeed, the proportion of participants with sarcopenia (<2%) was low which may be related to the high levels of physical activity that we have previously reported in this study (42). However, other studies in similar populations have reported sarcopenia prevalence according to the EWGSOP2 definition of 0.4% to 7.4% (43, 44), and our estimate falls within this range. The number of participants with incidence falls over 12 months

(<12%) was also low and this may be due to the good physical function generally observed as well as the fact that only falls resulting in coming to rest at ground level were recorded (45).

In conclusion, community-dwelling older adults with higher relative adiposity but normal BMI may have poorer bone geometry and muscle strength than those with normal adiposity and those with BMI-defined obesity. Further research is required to determine whether these associations translate to differences in incidence of fractures, but it is possible that clinical fracture prediction tools should consider body composition rather than, or in addition to, body mass.

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Figure Legends

Figure 1. Scatterplots for total body fat percentage and BMI in women (A) and men (B) with classification of participants by adiposity and obesity status.

Figure 2. Proportion of participants with sarcopenia, osteoporosis and incident falls by adiposity and obesity categories. *indicates significantly different to HA-HBMI; #indicatesd significantly different to HA-NBMI and HA-HBMI.

Table 1. Participant characteristics according to adiposity and obesity categories.

	Women (N=1692)			Men (N=1719)		
	NA-NBMI (N=268; 15.8%)	HA-NBMI (N=1116; 66.0%)	HA-HBMI (N=308; 18.2%)	NA-NBMI (N=216; 12.6%)	HA-NBMI (N=1206; 70.2%)	HA-HBMI (N=297; 17.3%)
Age (years)	70.0±0.1	70.0±0.1	70.0±0.1	70.0±0.1	70.0±0.1	70.0±0.1
Current smoker (%)*	9.3	**5.4**	7.5	7.4	5.1	4.7
Diabetes (%)*	4.2	4.6*	**14.1**	2.4	**9.2***	**24.5**
Stroke (%)*	3.0	2.3	2.9	4.3	3.9*	7.8
BMI (kg/m^2)	21.3±1.9	**25.4±2.4***	**33.9±3.8**	22.6±1.9	**26.0±2.3***	**33.0±3.0**
Total fat mass (%)	30.9±3.5	**41.8±3.8***	**49.1±3.5**	21.4±3.1	**32.2±4.1***	**39.6±4.4**
Visceral fat mass (kg)	0.38±0.23	**0.99±0.48***	**1.93±0.65**	0.73±0.33	**1.86±0.72***	**3.37±1.01**
ALM (kg)	16.4±2.1	16.7±2.0*	**20.0±2.4**	23.9±2.7	24.2±2.9*	**27.5±3.2**
Total hip aBMD (g/cm^2)	0.81±0.12	**0.87±0.11***	**0.95±0.12**	0.96±0.13	**1.01±0.13***	**1.06±0.15**
Hand grip strength (kg)	26.6±5.1	**25.1±4.5***	26.3±4.7	44.7±7.0	**43.1±7.6**	43.5±7.8
Timed up-and-go (s)	9.4±2.2	**9.8±2.5***	**11.2±3.4**	9.2±1.6	**9.9±2.1***	**10.9±2.8**
MVPA time (%)	5.3±3.5	**3.8±2.7***	**2.3±2.1**	5.4±3.3	**4.4±3.2***	**3.0±2.6**

All data are mean±SD, except *proportions. Bold values are significantly different to NA-NMBI (P<0.05); * indicates HA-NBMI is significantly different to HA-HBMI (P<0.05; Bonferroni post-hoc tests). Abbreviations: NA-NBMI; normal adiposity and normal BMI, HA-NMBI; high adiposity and normal BMI, HA-HBMI; high adiposity and high BMI, BMI; body mass index, ALM; appendicular lean mass, MVPA; moderate/vigorous physical activity.

Table 2. Pearson correlation coefficients (P-values) for associations between body composition measures in men and women.

	Women		Men	
	BMI	Body fat percentage	BMI	Body fat percentage
ALM	**0.682 (<0.001)**	**0.345 (<0.001)**	**0.583 (<0.001)**	**0.160 (<0.001)**
Visceral fat mass	**0.765 (<0.001)**	**0.739 (<0.001)**	**0.800 (<0.001)**	**0.802 (<0.001)**
Calf muscle CSA	**0.299 (<0.001)**	-0.001 (0.982)	**0.429 (<0.001)**	**0.071 (0.007)**
Calf muscle density	**-0.294 (<0.001)**	**-0.269 (<0.001)**	**-0.296 (<0.001)**	**-0.310 (<0.001)**

Abbreviations. ALM; appendicular lean mass, CSA; cross-sectional area, BMI; body mass index. Bold values indicate significant correlations (P<0.05).

Table 3. Generalised linear models expressing differences in sarcopenia-related parameters according to adiposity and obesity categories.

	NA-NBMI	HA-NBMI	HA-HBMI
ALM (kg)	REF	**0.37 (0.10, 0.63)***	**3.71 (3.37, 4.04)**
Visceral fat mass (kg)	REF	**0.75 (0.69, 0.82)***	**1.87 (1.79, 1.95)**
Calf muscle CSA (cm^2)	REF	5.51 (-4.71, 15.72)*	**69.20 (55.68, 82.73)**
Calf muscle density (mg/cm^3)	REF	**-1.39 (-1.84, -0.95)***	**-3.56 (-4.15, -3.00)**
Hand grip strength (kg)	REF	**-1.32 (-1.97, -0.68)***	0.15 (-0.81, 0.84)
Timed up-and-go (s)	REF	**0.29 (0.06, 0.53)***	**1.17 (0.87, 1.48)**

Data are B-coefficients (95% CI). All analyses adjusted for sex, smoking and diabetes status, use of blood pressure medication, and MVPA (%).

*Bold values are significantly different to NA-NMBI (P<0.05); * indicates HA-NBMI is significantly different to HA-HBMI (P<0.05).*

Table 4. Generalised linear models expressing differences in osteoporosis-related parameters according to adiposity and obesity categories.

	NA-NBMI	HA-NBMI	HA-HBMI
DXA			
Lumbar spine			
L1-L4 aBMD (g/cm^2)	REF	**0.06 (0.04, 0.08)***	**0.15 (0.12, 0.17)**
L1-L4 T-score	REF	**0.49 (0.34, 0.64)***	**1.20 (1.00, 1.40)**
Left hip			
Femoral neck aBMD (g/cm^2)	REF	**0.04 (0.02, 0.05)***	**0.08 (0.06, 0.09)**
Total hip aBMD (g/cm^2)	REF	**0.05 (0.04, 0.06)***	**0.12 (0.10, 0.13)**
Total hip T-score	REF	**0.39 (0.29, 0.48)***	**0.89 (0.76, 1.01)**
pQCT - Radius			
4% site			
Total area (mm^2)	REF	**-12.38 (-19.53, -5.24)***	-1.82 (-11.00, 7.36)
Total vBMD (mg/cm^3)	REF	**10.32 (5.00, 15.63)***	**18.09 (11.26, 24.93)**
Trabecular area (mm^2)	REF	**-5.57 (-8.79, -2.36)***	-0.82 (-4.95, 3.32)
Trabecular vBMD (mg/cm^3)	REF	**5.97 (1.86, 10.07)***	**11.92 (6.64, 17.19)**
66% site			

Total area (mm^2)	REF	**-3.28 (-6.43, -0.13)***	**5.12 (1.08, 9.17)**
Total vBMD (mg/cm^3)	REF	**16.14 (5.34, 26.94)**	**22.23 (8.35, 36.11)**
Cortical area (mm^2)	REF	0.107 (-1.49, 1.70)*	**5.18 (3.13, 7.23)**
Cortical vBMD (mg/cm^3)	REF	-0.67 (-5.74, 4.40)	-4.19 (-10.71, 2.33)
Cortical thickness (mm)	REF	0.03 (-0.01, 0.08)*	**0.12 (0.06, 0.18)**
SSI Polar (mm^3)	REF	-8.95 (-18.23, 0.34)*	**13.43 (1.51, 25.36)**
Periosteal circumference (mm)	REF	**-0.51 (-0.94, -0.08)***	**0.72 (0.17, 1.27)**
Endosteal circumference (mm)	REF	**-0.71 (-1.24, -0.17)***	-0.05 (-0.74, 0.64)
pQCT – Tibia			
4% site			
Total area (mm^2)	REF	-17.99 (-34.87, 4.90)*	15.92 (-10.16, 41.99)
Total vBMD (mg/cm^3)	REF	**11.08 (6.61, 15.54)***	**22.92 (17.07, 28.78)**
Trabecular area (mm^2)	REF	-6.74 (-15.69, 2.02)*	7.17 (-4.57, 18.90)
Trabecular vBMD (mg/cm^3)	REF	**10.59 (6.35, 14.83)***	**20.33 (14.77, 25.90)**
66% site			
Total area (mm^2)	REF	-8.42 (-19.48, 2.63)*	7.28 (-7.22, 21.77)
Total vBMD (mg/cm^3)	REF	**13.51 (3.93, 23.10)***	**27.64 (15.06, 40.21)**
Cortical area (mm^2)	REF	3.41 (-1.72, 8.53)*	**19.20 (12.48, 25.92)**
Cortical vBMD (mg/cm^3)	REF	-1.23 (-5.30, 2.84)	-2.96 (-8.30, 2.38)
Cortical thickness (mm)	REF	**0.08 (0.01, 0.16)***	**0.26 (0.16, 0.36)**
SSI Polar (mm^3)	REF	**-60.99 (-114.40, -7.59)**	-24.26 (-94.30, 45.78)

Periosteal circumference (mm)	REF	-0.61 (-1.41, 0.20)*	0.41 (-0.65, 1.47)
Endosteal circumference (mm)	REF	**-1.13 (-2.13, -1.40)**	-1.22 (-2.53, 0.08)

Data are B-coefficients (95% CI). All analyses adjusted for sex, smoking and diabetes status, use of blood pressure medication, and MVPA (%).

*Bold values are significantly different to NA-NMBI (P<0.05); * indicates HA-NBMI is significantly different to HA-HBMI (P<0.05).*

Abbreviations: NA-NBMI; normal adiposity and normal BMI, HA-NMBI; high adiposity and normal BMI, HA-HBMI; high adiposity and high BMI, aBMD; areal bone mineral density, vBMD; volumetric bone mineral density, SSI; stress-strain index, MVPA; moderate/vigorous physical activity.

Table 5. Ordinal regression models expressing odds ratios (95% CI) for probable and confirmed sarcopenia, osteopenia and osteoporosis, and single and multiple falls, according to adiposity and obesity categories.

	NA-NBMI	HA-NBMI	HA-HBMI
Probable and confirmed sarcopenia	REF	1.72 (0.67, 4.44)*	0.43 (0.11, 1.68)
Osteopenia and osteoporosis	REF	**0.45 (0.37, 0.55)***	**0.15 (0.11, 0.20)**
Single and multiple falls	REF	1.50 (0.99, 2.28)	**1.98 (1.20, 3.26)**

*All analyses adjusted for sex, smoking and diabetes status, use of blood pressure medication, and MVPA (%). Bold values are significantly different to NA-NMBI (P<0.05); * indicates HA-NBMI is significantly different to HA-HBMI (P<0.05). Abbreviations: NA-NBMI; normal adiposity and normal BMI, HA-NMBI; high adiposity and normal BMI, HA-HBMI; high adiposity and high BMI, MVPA; moderate/vigorous physical activity.*
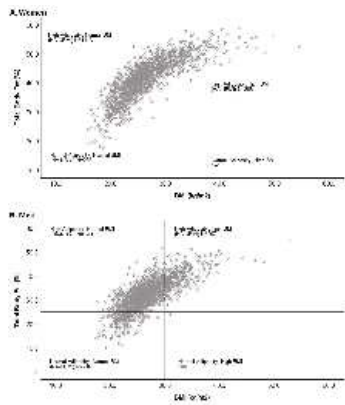
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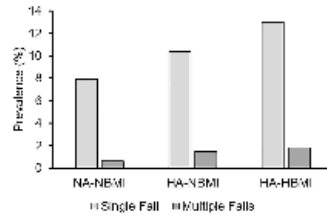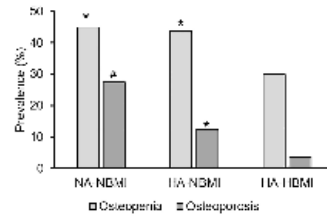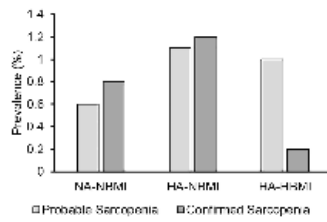
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