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Sex-specific associations between insulin resistance and bone parameters in overweight and obese older adults

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Abstract

Objectives: To determine sex-specific associations between insulin resistance and bone parameters measured by peripheral quantitative computed tomography (pQCT) in overweight and obese community-dwelling older adults.

Study design: Cross-sectional study of 79 community-dwelling overweight and obese adults (mean±SD age 62.8±7.9 years; BMI 32.3±6.1 kg/m²; 58% women).

Main outcome measures: pQCT assessed distal radius and tibia trabecular volumetric bone mineral density (vBMD) and proximal radius and tibia cortical vBMD, periosteal circumference, endosteal circumference and stress-strain index (SSI). The Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) score was calculated from fasting glucose and insulin values. Lean mass was assessed using dual-energy X-ray absorptiometry (DXA). Total minutes of moderate and vigorous physical activity (MVPA) was calculated using the Active Australia Survey.

Results: Men and women in this cohort had no significant differences in fasting glucose and insulin concentrations, HOMA-IR and diabetes prevalence (all P>0.05). In women, HOMA-IR was positively correlated with proximal radius periosteal and endosteal circumference (r=0.331; P=0.034 and r=0.325; P=0.038, respectively). These associations became non-significant in multivariable regression analyses, however, HOMA-IR was negatively associated with proximal radius cortical vBMD (B=-4.79; 95% CI -8.66, -0.92) after adjusting for age, lean mass and MVPA. All associations between HOMA-IR and bone parameters became non-significant in a sensitivity analysis excluding individuals with

1 diabetes, or self-reported use of glucose-lowering medications. There were no associations
2 between HOMA-IR and bone parameters in men.

3 **Conclusions:** HOMA-IR was negatively associated with radial cortical vBMD in overweight
4 and obese older women, but not in men. Further studies are needed to clarify sex-specific
5 associations between insulin resistance and bone health in overweight and obese older adults.

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12 **Keywords:** Bone; Density; Microarchitecture; Geometry; Insulin Resistance.

13 **1.0 Introduction**

14 Insulin resistance is a hallmark of type 2 diabetes mellitus (T2DM). Individuals with
15 T2DM often have higher areal bone mineral density (aBMD) determined by dual-energy X-
16 ray absorptiometry (DXA), but increased fracture risk compared to non-diabetic individuals ¹.
17 This increased fracture risk is thought to arise through an increased falls risk ² and
18 interactions between features of insulin resistance and other aspects of bone health, such as
19 geometry and strength, which can predict fracture independently, and in some instances just
20 as accurately as aBMD ^{3,4}. Insulin resistance is positively associated with fat mass ⁵ and to
21 the best of our knowledge, there are no studies investigating associations with bone
22 parameters beyond aBMD in overweight and obese older adults.

23 Features of insulin resistance that may increase bone fragility include increased
24 advanced glycated end product (AGE) deposition within the bone collagen matrix, micro-
25 and macrovascular complications and a pro-inflammatory phenotype ^{6,7}. On the contrary,
26 hyperinsulinaemia is a feature of insulin resistance that appears to have osteo-anabolic effects
27 on bone ⁸ and has been associated with increased BMD in older adults ⁹. It is unclear how
28 these metabolic factors individually and collectively increase fracture risk in individuals with
29 insulin resistance.

30 Men and women have differences in lean mass, body fat percentage and distribution
31 and concentrations of sex-hormones ¹⁰. These sex differences influence bone health and
32 glucose metabolism ^{5,11,12}. Lean mass, which is generally greater in men, may play an
33 important role in mediating the association between insulin resistance and bone parameters.

1 This is because in addition to the positive effects lean mass has on bone through mechanical
2 loading ¹³, it is also involved in glucose clearance and metabolism ¹¹. Sex-specific
3 associations may therefore exist between insulin resistance and bone health.

4 Screening for fracture risk using DXA-determined aBMD is limited in overweight
5 and obese and T2DM populations. This is because the precision of this scanning modality is
6 affected by tissue depth (e.g. excess fat mass) ¹⁴. Also, DXA cannot distinguish between
7 trabecular and cortical bone, which may be disproportionately affected in insulin resistant
8 individuals ¹⁵. Three-dimensional imaging technology such as peripheral quantitative
9 computed tomography (pQCT) may be a more informative tool to understand the relationship
10 between insulin resistance and determinants of bone quality in these populations.

11 The aim of the present study was to determine the sex-specific associations between
12 insulin resistance and trabecular and cortical bone parameters measured by pQCT in
13 overweight and obese community-dwelling older adults.

2.0 Materials and Methods

2.1 Study design and participants

Eighty-five overweight or obese (body mass index [BMI] $\geq 25 \text{ kg/m}^2$) community-dwelling men and women residing in Melbourne, Australia aged ≥ 50 years were recruited for this study. Six individuals were excluded from analyses due to self-reported use of anti-osteoporotic medication, hormone replacement therapy or corticosteroids. Thus, 79 individuals were included in our analyses. Participants responded to print and online advertisements and were English speaking, ambulant and had no self-reported diagnosis of progressive neurological or psychotic disorders, severe arthritis (awaiting a joint replacement), or life expectancy < 12 months. This study was conducted according to the principles of the Declaration of Helsinki and was approved by the Melbourne Health Human Research Ethics Committee (HREC 2013.294). Participants provided written informed consent and all testing was conducted at the Clinical Trials Unit at the Australian Institute for Musculoskeletal Science (AIMSS) between March 2014 and August 2016.

2.2 Questionnaire

A self-administered questionnaire included questions on demographics, chronic health conditions and weekly physical activity levels. Total minutes of weekly moderate and vigorous physical activity (MVPA) were calculated using the Active Australia Survey¹⁶.

2.3 Blood collection and analysis

A blood sample was collected after an overnight fast of at least 10 hours. Serum glucose, high-density lipoprotein (HDL) cholesterol, and triglycerides concentrations were analysed using the automated ADVIA 1650 Chemistry System (Siemens Healthcare Diagnostics Incorporation, Australia). Serum insulin concentration was analysed by a commercial solid-phase enzyme-labelled chemiluminescent immunoassay (IMMULITE 2000 Insulin, Siemens, Bayswater, Australia), with a sensitivity of $2 \mu\text{IU/mL}$. The Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) score was calculated from fasting glucose and insulin values¹⁷. One participant did not consent to blood collection, and two participants did not have glucose or insulin analysed.

2.4 Anthropometry

Weight (Seca 804 electronic scales, Seca, Hamburg, Germany) and height (Seca 222 wall-mounted stadiometer, Seca, Hamburg, Germany) were measured with footwear,

headwear and heavy items of clothing removed. Body mass index (BMI) was calculated as weight (kg)/ height (m²).

2.5 Bone parameters and body composition

A whole-body DXA (Hologic Discovery W, Hologic, Bedford MA, USA) determined aBMD (without the head), total body fat and lean mass (kg), and regional lean and fat mass, including visceral fat area (cm²). The DXA was calibrated daily using the manufacturer's phantom.

The pQCT system (Stratec XCT3000, Stratec, Germany) acquired single 2.5-mm transverse scans at 4% and 66% of the radial and tibial length, with a voxel size of 0.5mm and scan speed of 20mm/sec. Radial length was measured from the distal end of the ulna styloid to the tip of the olecranon; tibial length was measured from the prominence of the medial malleolus to the tibial plateau. The scan sites were determined using a planar scout view of the distal radius or tibia and the reference lines were placed to bisect the medial border of the distal radial joint surface and being parallel to the distal joint surface of the tibia¹⁸. The non-dominant arm and dominant limb were used for all scans.

All images were analysed using the manufacturer's software (version 6.2). Scans with movement artefacts were excluded from analysis (n=2). Trabecular bone was identified at the distal radius and tibia using the manufacturer's default setting which concentrically separates the outer 55% of bone area and defines the inner 45% as trabecular bone. The trabecular bone compartment is actually larger than 45% in this region, however, due to pQCT resolution limitations the border between cortical and trabecular bone in this region cannot be easily distinguished. As such, defining the inner 45% of this region as trabecular bone is thought to be conservative and offers a margin of safety ensuring cortical bone is not included in the trabecular region of interest¹⁹. Cortical bone was identified at the proximal radius and tibia using the default threshold of 710mg/cm³¹⁸. At this threshold, partially occupied voxels in the cortical compartment that are included in the analysis are approximately equal to the number excluded, thereby reducing error that may arise from a partial volume effect. Importantly, the use of these default settings allows for comparability with other studies using the same analysis methodology. After applying these thresholds, the following bone mass and geometry indicators were ascertained: distal trabecular and proximal cortical volumetric bone mineral density (vBMD) (mg/cm³), proximal periosteal and endosteal circumference (mm) and polar stress-strain index (SSI; 66%; a measurement of bone strength calculated using cortical vBMD and the section modulus)²⁰. The pQCT was calibrated on all data collection

days using the manufacturer's phantom, which had a coefficient of variation (CV) of 0.2% for the duration of this study. The short-term intra-individual CV for radial trabecular and tibial cortical vBMD were 0.9 and 0.2%, respectively.

2.6 Statistical analyses

Continuous data were assessed for normality and non-parametric tests were used as appropriate. Sex-specific interactions were observed, as such participants were stratified by sex for further analyses. Independent samples t-tests and Mann-Whitney U tests compared continuous variables, and Chi-square tests compared categorical variables between groups stratified by sex. Spearman correlations examined associations between HOMA-IR with tibial and radial bone parameters. Additionally, Spearman correlations examined associations between MVPA and lean mass with tibial and radial bone parameters in men and women respectively. Multivariable linear regression analyses explored associations between HOMA-IR and tibial and radial bone parameters in men and women. Model 1 was adjusted for age, Model 2 was adjusted for Model 1 plus lean mass and Model 3 was adjusted for Model 2 plus MVPA. A sensitivity analysis explored associations between HOMA-IR and bone parameters in men and women without self-reported diabetes or use of glucose-lowering medications. Variance Inflation Factors were examined to inspect for multicollinearity in all models and tolerance was set at 10. P-values <0.05 or 95% confidence intervals (CI) not including the null point were considered statistically significant. All analyses were performed in SPSS Statistics 25 (IBM, USA).

3.0 Results

In total, 79 adults (mean $\pm$ SD; age 62.8 ± 7.9 years; 58% women) were studied. The median BMI was 30.2 (IQR; 27.30, 36.05) kg/m^2 and 51.8% of participants were obese (BMI $\geq 30 \text{ kg/m}^2$). Table 1 presents descriptive characteristics according to sex. Men had significantly higher lean mass and MVPA compared to women. There were no significant differences in HOMA-IR, fasting glucose and insulin concentrations, and prevalence of self-reported diabetes between men and women.

Associations between HOMA-IR and bone parameters at the radius and tibia in men and women are shown in Table 2. In women, HOMA-IR was negatively correlated with proximal radius cortical density and proximal tibial endosteal circumference. HOMA-IR was

also positively correlated with proximal radius periosteal and endosteal circumference. There were no associations between HOMA-IR and bone parameters in men.

Table 3 presents associations between lean mass and MVPA with tibial and radial bone parameters in men and women. In women, lean mass was positively correlated with proximal radius and tibia periosteal circumference and SSI polar, proximal radius endosteal circumference and distal tibia trabecular density. In men, lean mass was positively correlated with proximal tibia and radius periosteal circumference and SSI polar. MVPA was negatively associated with distal trabecular density in women. There were no associations between MVPA and bone parameters in men.

Multivariable linear regression analyses exploring associations between HOMA-IR and radial and tibial bone parameters in men and women are shown in Table 4. In women, HOMA-IR was negatively associated with proximal radius cortical density in all models. HOMA-IR was positively associated with distal tibia trabecular density in Model 1, however, after further adjustment in Models 2 and 3, the association was attenuated. In men, there were no associations between HOMA-IR and bone parameters in multivariable regression models. There were no associations between HOMA-IR and whole-body aBMD in men and women at the radius and tibia (data not shown).

Table 5 presents a sensitivity analysis exploring associations between HOMA-IR and bone parameters in 29 men and 33 women (individuals with self-reported diabetes or use of glucose-lowering medications were excluded). There were no associations between HOMA-IR and bone parameters in men and women. There were also no associations between HOMA-IR and whole-body aBMD in men and women at the radius and tibia (data not shown).

4.0 Discussion

This cross-sectional study of community-dwelling, overweight and obese older adults demonstrated that inverse associations exist between HOMA-IR and proximal radius cortical vBMD in women, but not men. These associations remained significant after adjustment for age, lean mass and MVPA, suggesting that insulin resistance may have independent, negative, sex-specific associations with structural aspects of bone health in overweight and obese older adults.

Our findings show negative associations between HOMA-IR and radial bone parameters in women, but not men. Similar observations were not observed at the tibia. Reasons for this may be multifaceted, but likely attributable to weight-bearing effects or benefits of ambulatory activity in the latter region. Edelstein and Barrett-Connor previously

demonstrated that lean mass and fat mass are better markers of BMD at axial weight-bearing sites than at non-weight-bearing radial sites²¹. However, despite these measures of body size being better markers of BMD at weight-bearing sites, they still influence BMD at the radius, albeit to a lesser degree. Additionally, higher MVPA levels relative to women may also contribute to the lack of association between HOMA-IR and bone parameters in men. Interestingly, we reported an inverse association between MVPA and distal tibia trabecular vBMD in women, which may appear counter-intuitive. However, it should be noted that this association was not body weight-adjusted and therefore women that were more active may have had a lower body weight, which is associated with lower BMD. Also, higher intensity physical activity does not necessarily result in generation of impacts and muscle loading that are required to induce osteogenesis, which could contribute to inconsistent associations with BMD²². Although adjustment for self-reported MVPA did not influence the observed associations in multivariable models, it is possible that other objective assessments of physical activity may have revealed different associations. Following adjustment for age, lean mass and MVPA, the association between HOMA-IR and proximal radius cortical vBMD remained in women. This suggests that insulin resistance may negatively affect cortical, but not trabecular, vBMD in the radius of overweight and obese older women. Early identification of compromised bone structure is particularly important in this site given that the wrist has been reported to have the highest 3-year cumulative incidence of fracture (2.2%) in older women when compared with nine other skeletal sites including hip, pelvis, upper and lower leg, spine, clavicle, rib, upper-arm/shoulder and ankle²³. Mechanisms behind this disproportionate bone loss are presently unclear and require further investigation.

Several studies have demonstrated that individuals with T2DM have normal or increased trabecular bone, yet compromised cortical bone compared with controls^{15,24,25}. Compromised cortical bone structure includes cortical porosity, which can be quantified using advanced imaging modalities such as high-resolution pQCT (HR-pQCT)²⁵. However, HR-pQCT has limited availability in a research setting due to high costs. Thus, in a clinical setting standard pQCT may be a practical complementary assessment to DXA scans. This may increase reliability of bone health assessments in T2DM/insulin resistant populations, and also in obese populations where DXA scans become less reliable¹⁴. Cortical porosity is a risk factor for fragility fractures; Bala et al. reported that cortical porosity at the ultradistal radius of osteopenic post-menopausal women was associated with a 4-fold increased risk of forearm fracture²⁶. Patsch et al. also demonstrated that in post-menopausal women with T2DM, those that sustained fragility fractures had significantly greater cortical porosity (4.7-

fold at the distal radius) compared with individuals with T2DM that did not sustain fragility fractures²⁷. Interestingly, high bone turnover is often associated with cortical porosity in normal individuals²⁸, however, individuals with T2DM and insulin resistance often have low bone turnover^{29,30}. This suggests that other factors may compromise radial cortical vBMD in overweight and obese older women and further studies are required in order to characterise them.

The lower lean mass and higher proportion of women with severe insulin resistance in this study compared with men may also explain the sex-specific associations between HOMA-IR and radial cortical vBMD in this cohort. Lean mass is often a better predictor of BMD than fat mass¹². Gjesdal et al. demonstrated that in older men and women, BMD increases per unit of lean mass were larger than BMD increases per unit of fat mass³¹. This suggests that mechanical loading applied to bone via muscle contraction may be more important for BMD than body mass-related forces alone. It is possible that the lack of association between HOMA-IR and bone parameters in men was due to the greater lean mass ameliorating the detrimental effects of insulin resistance on bone. In this cohort, men and women had similar HOMA-IR values, which were considered to be in the normal range³². However, the value of the 75th percentile reported for HOMA-IR was greater in women compared with men (6 versus 2.8). The notion that women with a higher degree of insulin resistance were driving the association between radial cortical vBMD and HOMA-IR was confirmed through our sensitivity analysis presented in Table 5. This table demonstrated that after exclusion of individuals with self-reported diabetes or use of glucose-lowering medications, all associations between HOMA-IR and radial cortical vBMD became non-significant. Lastly, a recent study by Viljakainen et al.³³ utilised similar methodology to our study and reported that in adolescent males, HOMA-IR was positively correlated with various bone structural parameters and to a greater degree than in adolescent women. The different associations reported in these studies may be due to a disparity in sex hormone concentrations between the populations, adolescents likely having a shorter exposure to an adverse metabolic state, or not having reached peak bone mass.

Age-associated reductions in sex hormones are another factor that may influence the sex-specific inverse association between HOMA-IR and radial cortical vBMD. Sex hormones play an important role in maintaining musculoskeletal health, and deficiencies in these hormones are more pronounced in older woman than in older men¹⁰. Riggs et al. demonstrated that older women experience greater radial cortical density declines than older men, and this was predominantly attributed to acute estrogen deficiency experienced post-

menopause³⁴. The median age of menopause in Australia is 51³⁵ and 98% of women in this cohort were above this age, with the median being 63 years. Therefore, it is reasonable to suspect that most of the women in this cohort were post-menopausal and as such, previous acute loss of sex hormones may potentially have influenced the association between HOMA-IR and radial cortical vBMD. Evidently, men may be protected against these declines and the effects of insulin resistance as they experience reductions in sex-hormone concentrations (particularly estrogen) at a slower rate compared with women¹⁰.

In women, associations between HOMA-IR and periosteal and endosteal circumference at the proximal radius became non-significant following adjusting for confounders. Previous literature has demonstrated that individuals with T2DM have smaller bone CSA and thinner cortices compared with controls^{1,15,36} and inverse associations between insulin resistance and bone size have been demonstrated in non-diabetic post-menopausal women³⁷. Smaller bone CSA may be a result of impaired bone turnover, failure to adapt to mechanical load or adipokine secretion^{38,39}. Individuals within our cohort were overweight and obese; therefore the increased weight-bearing forces they experience may influence bone size more than insulin resistance, mitigating the detrimental influence of HOMA-IR on bone that has been previously observed^{36,37}. Bone CSA is important; periosteal apposition has the capacity to partially offset age-related cortical thinning, which occurs through endocortical resorption⁴⁰. Also, as bone size increases as a result of periosteal apposition, corresponding increases in bone strength are also observed⁴¹. These changes in bone area appear to influence fracture risk more than cortical vBMD. Ahlborg et al. demonstrated that in older women, relative risk of forearm fracture decreases by -1.5 (0.9 to -2.6) compared with -3.6 (-1.6 to -7.9) with every SD increase in cortical vBMD and section modulus (a surrogate measure of bone strength heavily influenced by bone CSA), respectively⁴².

SSI and bone material strength have been reported to be lower in older adults with T2DM^{30,36}, but we observed no associations with HOMA-IR in our cohort. SSI at peripheral sites demonstrates similar non-vertebral fracture predictive ability as femoral neck aBMD⁴. Since our cohort was not recruited based on diabetes status, our participants may have lacked many of the comorbidities associated with T2DM that may impact bone strength.

This study had a cross-sectional design, which limits comments on causation. The use of a one-off sample of blood to measure HOMA-IR also has limitations including decreased reliability and accuracy in individuals with diabetes and/or those taking glucose-lowering medications. Also, due to the pulsatile secretion of insulin, a single fasting blood sample may

not accurately reflect systemic insulin concentrations. Additionally, the cohort constituted of a relatively small sample of generally healthy community-dwelling older adults. As such, it is likely the findings cannot be generalised to the wider older adult population, although obesity in this Australian cohort (47%) was consistent with that of 49% reported in the 2012 Australian Diabetes, Obesity and Lifestyle Study⁴³. Future studies would be improved by utilising gold-standard measures of insulin resistance such as hyperinsulinaemic-euglycaemic clamps, objective assessments of physical activity and advanced imaging modalities such as HR-pQCT, which may provide greater insight into bone microarchitecture and strength⁴⁴. Lastly, the effects of bone remodelling, including osteocalcin, and sex steroids should be explored further as their relationship with insulin resistance and bone in overweight and obese individuals remains unclear.

In conclusion, HOMA-IR was negatively associated with radial cortical vBMD in overweight and obese older women, but not men. Further studies are needed to clarify sex-specific associations of insulin resistance and bone health in overweight and obese older adults.

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Role of the funding body

The funding bodies had no role in the study design, conduct analysis or interpretation of data, or the decision to publish.

Author Contributions

DS and PRE conceived and designed the study. JM, DS, CSL and LM were involved in participant recruitment, data collection and data entry. BdC contributed to statistical analyses and manuscript preparation. DS accepts responsibility for integrity of the data. All authors have read and approved the manuscript.

Conflicts of Interest

None.

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Table 1. Descriptive characteristics stratified by sex.

	Men (N=36)	Women (N=43)	P-value
Age (y) median (IQR)	60.5 (55, 67.3)	63 (56, 65)	0.745
Weight (kg) median (IQR)	91.8 (83.8, 102.2)	80.3 (69.1, 92.9)	0.002
Height (m)	173.0 ± 5.9	158.0 ± 6.3	<0.001
BMI (kg/m²) median (IQR)	29.9 (27.5, 34.7)	32.6 (28.4, 39.2)	0.184
Obese (%)	18 (50)	26 (60)	0.870
Lean Mass (kg)	59.9 ± 7.4	43.8 ± 11.5	<0.001
Visceral Adipose Tissue (mm²)	232.9 ± 82.2	179.5 ± 73.4	0.003
MVPA (mins) median (IQR)	120.0 (0.0, 300.0)	10.0 (0.0, 60.0)	0.004
Self-reported Diabetes (%)	7 (19)	10 (23)	0.169
Glucose (mmol/L) median (IQR)	5.7 (5.3, 6.3)	5.7 (5.1, 7)	0.767
Insulin (mmol/L) median (IQR)	7.0 (5, 10.8)	7.0 (4.8, 18.3)	0.550
HOMA-IR (units) median (IQR)	1.9 (1.3, 2.8)	1.7 (1, 6)	0.779
Radial bone parameters			
Distal Trabecular Density (mg/cm³)	212.1 ± 36.8	172.8 ± 35.1	<0.001
Proximal Cortical Density (mg/cm³)	1082.7 ± 46.4	1062.6 ± 57.9	0.099
Proximal Periosteal Circumference (mm)	53.6 ± 7	45.5 ± 5.6	<0.001
Proximal Endosteal Circumference (mm)	39.9 ± 8.4	35.8 ± 7.4	0.022
Proximal SSI Polar (mm³)	401.2 ± 88.9	225.8 ± 45.4	<0.001
Tibial bone parameters			
Distal Trabecular Density (mg/cm³)	247.8 ± 34.4	228.2 ± 46.3	0.037
Proximal Cortical Density (mg/cm³)	1059.9 ± 35.1	1037.8 ± 39.4	0.011
Proximal Periosteal Circumference (mm)	99.1 ± 6.3	87.7 ± 6	<0.001
Proximal Endosteal Circumference (mm)	73.2 ± 8.9	67.8 ± 7.4	0.005
Proximal SSI Polar (mm³)	3062.5 ± 419.1	1950.8 ± 391.6	<0.001

All data are mean $\pm$ SD or frequency (%) unless otherwise specified. MVPA; Moderate and vigorous physical activity.

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Table 2. Spearman's correlation coefficients (P-values) for HOMA-IR with tibial and radial bone parameters in men and women.

		Distal Trabecular Density (mg/cm ³)	Proximal Cortical Density (mg/cm ³)	Proximal Periosteal Circumference (mm)	Proximal Endosteal Circumference (mm)	Proximal SSI Polar (mm ³)
Radial bone parameters						
HOMA-IR (units)	Women	0.043 (0.787)	-0.405 (0.009)	0.331 (0.034)	0.325 (0.038)	0.176 (0.270)
	Men	-0.292 (0.084)	-0.119 (0.491)	0.185 (0.281)	0.188 (0.273)	0.116 (0.500)
Tibial bone parameters						
HOMA-IR (units)	Women	0.179 (0.276) N=39	0.231 (0.147)	-0.237 (0.136)	-0.322 (0.040)	0.086 (0.594)
	Men	-0.030 (0.863)	-0.028 (0.869)	0.018 (0.916)	0.032 (0.855)	0.093 (0.591)

Table 3. Spearman's correlation coefficients (P-values) for moderate and vigorous physical activity (MVPA) and lean mass with tibial and radial bone parameters in men and women.

		Distal Trabecular Density (mg/cm ³)	Proximal Cortical Density (mg/cm ³)	Proximal Periosteal Circumference (mm)	Proximal Endosteal Circumference (mm)	Proximal SSI Polar (mm ³)
Radial bone parameters						
Lean mass (kg)	Women	0.198 (0.203)	-0.119 (0.446)	0.505 (0.001)	0.409 (0.006)	0.529 (<0.001)
	Men	0.062 (0.721)	-0.301 (0.075)	0.425 (0.010)	0.306 (0.069)	0.459 (0.005)
MVPA (mins)	Women	-0.172 (0.269)	-0.016 (0.918)	-0.097 (0.535)	-0.076 (0.630)	-0.118 (0.450)
	Men	0.320 (0.057)	0.117 (0.497)	-0.150 (0.384)	-0.183 (0.285)	-0.160 (0.351)
Tibial bone parameters						
Lean mass (kg)	Women	0.341 (0.029) N=39	0.112 (0.474)	0.513 (<0.001)	0.268 (0.083)	0.665 (<0.001)
	Men	0.155 (0.367)	-0.116 (0.501)	0.377 (0.024)	0.219 (0.200)	0.456 (0.005)

MVPA (mins)	Women	-0.402 (0.009) N=39	-0.240 (0.122)	0.182 (0.241)	0.297 (0.053)	-0.114 (0.465)
	Men	0.093 (0.589)	-0.182 (0.289)	0.123 (0.473)	0.106 (0.539)	0.066 (0.702)

MVPA; Moderate and vigorous physical activity.

Table 4. Multivariable linear regression exploring associations between HOMA-IR and radial and tibial bone parameters in men and women.

			Distal Trabecular Density (mg/cm ³)	Proximal Cortical Density (mg/cm ³)	Proximal Periosteal Circumference (mm)	Proximal Endosteal Circumference (mm)	Proximal SSI Polar (mm ³)
Radial bone parameters							
Women	HOMA-IR (units)	Model 1	0.84 (-1.53, 3.21)	-5.11 (-8.61, -1.61)*	0.35 (-0.04, 0.75)	0.47 (-0.05, 0.98)	1.56 (-1.7, 4.81)
		Model 2	0.42 (-2.12, 2.96)	-4.72 (-8.50, -0.94)*	0.13 (-0.24, 0.50)	0.23 (-0.28, 0.74)	-0.35 (-3.39, 2.68)
		Model 3	0.40 (-2.20, 3.00)	-4.79 (-8.66, -0.92)*	0.15 (-0.23, 0.53)	0.26 (-0.26, 0.78)	-0.08 (-3.14, 2.97)
Men	HOMA-IR (units)	Model 1	-1.18 (-5.11, 2.75)	-0.37 (-5.26, 4.53)	0.09 (-0.67, 0.84)	0.12 (-0.78, 1.03)	3.21 (-6.00, 12.42)
		Model 2	-1.33 (-5.35, 2.70)	0.30 (-4.46, 5.05)	-0.05 (-0.75, 0.65)	0.003 (-0.88, 0.88)	1.34 (-6.91, 9.60)
		Model 3	-0.82 (-4.96, 3.31)	0.20 (-4.77, 5.17)	-0.09 (-0.82, 0.63)	-0.07 (-0.99, 0.84)	1.96 (-6.62, 10.54)
Tibial bone parameters							
Women	HOMA-IR (units)	Model 1	3.16 (0.07, 6.25) N=39*	1.07 (-1.55, 3.69)	-0.03 (-0.44, 0.39)	-0.20 (-0.68, 0.27)	16.57 (-11.26, 44.40)
		Model 2	2.23 (-1.05, 5.51) N=39	1.09 (-1.76, 3.93)	-0.32 (-0.68, 0.04)	-0.44 (-0.91, 0.03)	-4.16 (-27.18, 18.85)
		Model 3	2.18 (-1.19, 5.55) N=39	1.11 (-1.81, 4.03)	-0.29 (-0.65, 0.07)	-0.41 (-0.88, 0.07)	-2.38 (-25.64, 20.87)
Men	HOMA-IR (units)	Model 1	-0.94 (-4.64, 2.76)	-0.75 (-4.53, 3.03)	-0.08 (-0.75, 0.60)	0.07 (-0.89, 1.03)	-6.01 (-50.97, 38.94)
		Model 2	-1.21 (-4.95, 2.52)	-0.57 (-4.43, 3.29)	-0.19 (-0.82, 0.44)	-0.02 (-0.98, 0.94)	-15.04 (-55.46, 25.37)
		Model 3	-1.21 (-5.12, 2.70)	-1.06 (-5.03, 2.91)	-0.12 (-0.78, 0.53)	0.08 (-0.91, 1.07)	-10.41 (-52.05, 31.24)

Data are regression coefficients (95% confidence interval) HOMA-IR (units). Model 1 adjusted for age. Model 2 adjusted for Model 1 plus lean mass. Model 3 adjusted for Model 2 plus MVPA. *P<0.05.

Table 5. Sensitivity analysis exploring associations between HOMA-IR and bone parameters in men and women excluding individuals with self-reported diabetes or use of glucose-lowering medications.

			Distal Trabecular Density (mg/cm ³)	Proximal Cortical Density (mg/cm ³)	Proximal Periosteal Circumference (mm)	Proximal Endosteal Circumference (mm)	Proximal SSI Polar (mm ³)
Radial bone parameters							
Women N=33	HOMA-IR (units)	Model 1	-1.25 (-5.41, 2.91)	-3.15 (-8.91, 2.62)	0.12 (-0.57, 0.82)	0.21 (-0.73, 1.15)	-2.32 (-8.11, 3.48)
		Model 2	-1.21 (-5.47, 3.05)	-2.96 (-8.81, 2.89)	0.06 (-0.60, 0.71)	0.15 (-0.77, 1.06)	-3.14 (-7.80, 1.53)
		Model 3	-1.41 (-5.82, 3.00)	-3.31 (-9.35, 2.73)	0.12 (-0.55, 0.79)	0.24 (-0.70, 1.17)	-2.28 (-6.81, 2.24)
Men N=29	HOMA-IR (units)	Model 1	-6.37 (-18.78, 6.04)	-7.41 (-22.31, 7.49)	1.95 (-0.24, 4.14)	2.39 (-0.20, 4.97)	-5.87 (-33.45, 21.71)
		Model 2	-11.47 (-24.65, 1.71)	-1.79 (-17.79, 14.20)	0.52 (-1.55, 2.59)	1.06 (-1.58, 3.70)	-24.17 (-50.05, 1.71)
		Model 3	-9.71 (-22.43, 3.02)	-1.77 (-18.32, 14.78)	0.44 (-1.69, 2.57)	0.93 (-1.78, 3.63)	-23.66 (-50.40, 3.08)
Tibial bone parameters							
Women N=33	HOMA-IR (units)	Model 1	0.33 (-5.58, 6.25) N=31	1.43 (-3.77, 6.63)	-0.37 (-1.03, 0.29)	-0.42 (-1.24, 0.40)	0.77 (-44.91, 46.45)
		Model 2	-0.02 (-6.02, 5.98) N=31	1.21 (-4.02, 6.45)	-0.42 (-1.06, 0.21)	-0.43 (-1.27, 0.40)	-3.42 (-46.26, 39.42)
		Model 3	-0.11 (-6.35, 6.13) N=31	1.45 (-3.98, 6.88)	-0.36 (-1.01, 0.29)	-0.38 (-1.24, 0.48)	1.19 (-42.39, 44.76)
Men N=29	HOMA-IR (units)	Model 1	1.97 (-9.75, 13.68)	-2.69 (-14.03, 8.65)	0.93 (-1.18, 3.05)	0.57 (-2.43, 3.57)	53.25 (-86.25, 192.75)
		Model 2	-0.81 (-13.80, 12.19)	-2.72 (-15.56, 10.12)	-0.16 (-2.31, 1.99)	-0.45 (-3.70, 2.80)	-32.94 (-167.75, 101.87)

		Model 3	0.34 (-12.72, 13.40)	-4.47 (-16.83, 7.90)	0.04 (-2.11, 2.20)	-0.10 (-3.32, 3.12)	-30.22 (-169.50, 109.06)
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Data are regression coefficients (95% confidence interval) HOMA-IR (units). Model 1 adjusted for age. Model 2 adjusted for Model 1 plus lean mass. Model 3 adjusted for Model 2 plus MVPA.

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