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Relationships between bone geometry, volumetric bone mineral density and bone microarchitecture of the distal radius and tibia with alcohol consumption ☆☆☆



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ABSTRACT

Purpose: Chronic heavy alcohol consumption is associated with bone density loss and increased fracture risk, while low levels of alcohol consumption have been reported as beneficial in some studies. However, studies relating alcohol consumption to bone geometry, volumetric bone mineral density (vBMD) and bone microarchitecture, as assessed by high-resolution peripheral quantitative computed tomography (HR-pQCT), are lacking.

Methods: Here we report an analysis from the Hertfordshire Cohort Study, in which we studied associations between HR-pQCT measures at the distal radius and tibia and alcohol consumption in 376 participants (198 men and 178 women) aged 72.1–81.4 years.

Results: A total of 30 (15.2%), 90 (45.5%) and 78 (39.4%) men drank minimal/none (<1 unit/week), low (≥ 1 unit/week and <11 units/week) and moderate/high (≥ 11 units/week) amounts of alcohol respectively. These figures were 74 (41.8%), 80 (45.2%) and 23 (13.0%) respectively in women for minimal/none (<1 unit/week), low (≥ 1 unit/week and <8 units/week) and moderate/high (≥ 8 units/week). At the distal radius, after adjustment for confounding factors (age, BMI, smoking status, dietary calcium intake, physical activity and socioeconomic status and years since menopause and HRT use for women), men that drank low alcohol had lower cortical thickness ($p = 0.038$), cortical vBMD ($p = 0.033$), and trabecular vBMD ($p = 0.028$) and higher trabecular separation ($p = 0.043$) than those that drank none/minimal alcohol. Similar differences were shown between minimal/none and moderate/high alcohol although these only reached statistical significance for the cortical parameters. Interestingly, after similar adjustment, women showed similar differences in the trabecular compartment between none/minimal alcohol and low alcohol at the distal tibia. However, women that drank moderate/high alcohol had significantly higher trabecular vBMD ($p = 0.007$), trabecular thickness ($p = 0.026$), and trabecular number ($p = 0.042$) and higher trabecular separation ($p = 0.026$) at the distal radius than those that drank low alcohol.

Conclusions: Our results suggest that alcohol consumption (low and moderate/high) may have a detrimental impact on bone health in men in both the cortical and trabecular compartments at the distal radius with similar results in women in the trabecular compartment between none/minimal alcohol and low alcohol at the distal tibia suggesting that avoidance of alcohol may be beneficial for bone health.

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Abbreviations: aBMD, areal bone mineral density; BMI, body mass index; Ct.area, cortical area; Ct.vBMD, cortical density; Ct.Po, cortical porosity; Ct.Th, cortical thickness; DXA, dual energy X-ray absorptiometry; HCS, Hertfordshire Cohort Study; HRpQCT, high-resolution peripheral quantitative computed tomography; pQCT, peripheral quantitative computed tomography; Tt.area, total cross-sectional area; Tb.vBMD, trabecular BMD; Tb.N, trabecular number; Tb.Th, trabecular thickness; Tb.Sp, trabecular separation; vBMD, volumetric bone mineral density.

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Introduction

There is increasing interest in how modifiable lifestyle factors may influence bone health. Among these, alcohol consumption is of particular interest, given rising alcohol consumption in most populations [1,2]. In a number of reports, decreased areal bone mineral density (aBMD) and increased fracture risk has been reported in individuals with chronic heavy alcohol consumption [3–5]; alcohol consumption was independently associated with the risk of both hip and wrist fractures, with a dose–response relationship, in a prospective cohort of 84,484 middle-age women [6]. Compared with abstainers, women consuming greater than or equal to 25 g alcohol/d (1.8 drinks or more per day) had a relative risk (RR) of 2.33 (95% CI = 1.18–4.57) for hip fractures and an RR of 1.38 (95% CI = 1.09–1.74) for wrist fractures [6]. Another study found an increased odds of vertebral fracture among men who consumed more than 0.3 drinks per day compared with abstainers (adjusted odds ratio 4.61 [1.19–17.90]) [7]. However, there have also been reports of a positive association between modest alcohol consumption and bone health; a systematic review of the literature with meta-analysis found that the association between alcohol consumption and hip fracture seemed to be J-shaped rather than linear [4–6,8–11]. Compared with abstainers, persons consuming more than 0.5 to 1.0 drinks per day had a lower hip fracture risk (RR 0.80 [95% CI = 0.71–0.91]), and persons consuming more than 2 drinks per day had a higher risk (RR 1.39 [95% CI = 1.08–1.79]). Alcohol consumption is included in fracture risk stratification tools, including FRAX®, but with a cut off of >2 drinks per day [12].

It is increasingly recognized that bone geometry, and bone microarchitecture contribute to bone strength and thus fracture risk [13], but there are few studies which have examined the relationships between alcohol consumption and measurements of volumetric BMD and bone geometry using peripheral quantitative computed tomography (pQCT) and no consistent relationships have been shown [14,15]. The aim of this study was therefore to explore the relationships between alcohol consumption and bone geometry, vBMD and bone microarchitecture assessed by HR-pQCT and aBMD assessed by DXA in a well phenotyped cohort of elderly men and women from the Hertfordshire Cohort Study (HCS).

Materials and methods

Study participants

The HCS is a population-based UK cohort designed to examine the relationships between growth in infancy and the subsequent risk of adult diseases, such as osteoporosis. Study design and recruitment have been described in detail previously [16]. HCS participants were generally comparable with those in the nationally representative Health Survey for England [16]. In brief, in conjunction with the National Health Service Central Registry and the Hertfordshire Family Health Service Association, we traced men and women who were born between 1931 and 1939 in Hertfordshire and still lived there during the period 1998–2003. A nurse-administered questionnaire and clinic visit were done at this time. In 2004–2005, 642 men and women from the geographical area of East Hertfordshire took part in a follow-up clinic visit which included a nurse-administered questionnaire. Of these, 376 (59%) agreed to a HR-pQCT scan in 2011–2012. The East and North Hertfordshire Ethical Committees granted ethical approval for the study and all participants gave written informed consent in accordance with the Declaration of Helsinki [17].

Demographic and clinical assessment

Height was measured to the nearest 0.1 cm using a wall-mounted SECA stadiometer on the day of scanning, and weight using electronic scales (make, model) to the nearest 0.1 kg. Body mass index (BMI)

was calculated as weight/height² (kg/m²). Data related to alcohol consumption and smoker status were available from the 2004–2005 follow-up. Details regarding physical activity, dietary calcium intake, and socioeconomic status, age at menopause and HRT use were available from the nurse-administered questionnaire assessed in 1998–2003 [16].

Physical activity was calculated as a standardized score ranging from 0 to 100 derived from frequency of gardening, housework, climbing stairs and carrying loads in a typical week [18]. Higher scores indicated greater levels of activity. Dietary calcium intake was assessed using a food frequency questionnaire [19]. Socioeconomic status was determined using own current or most recent occupation of the participant in men and single women, and of the husband in ever-married women based on the Office of Population Censuses and Surveys Standard Occupational Classification Scheme for occupation and social class. Assessment of smoking habits included questions concerning smoker status (never, ex or current).

Alcohol consumption was categorized into bands because of concerns that there may be J-shaped relationships between alcohol consumption and bone parameters [3]. Questions were asked about the quantity of alcohol consumed at the point of questionnaire administration in 2004–2005. Those that drank <1 units of alcohol per week were defined as minimal alcohol. Those that drank more alcohol than this were subdivided into those that drank under half of the maximum recommended amount of alcohol (<11 units in men, <8 units in women), hereafter defined as low alcohol, and those that drank more than half of the maximum recommended amount of alcohol (≥11 units in men, ≥8 units in women), hereafter defined as moderate–high alcohol [20].

Dual-energy X-ray absorptiometry

Dual-energy X-ray absorptiometry (DXA) was performed at time of HR-pQCT in 2011–2012. Bone area (cm²), BMC (g) and aBMD (g/cm²) at the non-dominant hip were measured using DXA (Lunar Prodigy Advanced Scanner, GE Medical Systems, UK). Positioning for all scans was completed in accordance with the manufacturer's instructions.

High-resolution peripheral quantitative computed tomography

Each participant had measurements of the non-dominant distal radius and distal tibia using HR-pQCT (XtremeCT, Scanco Medical AG, Switzerland) except when it had previously been fractured in which case the dominant side was scanned. This allowed acquisition of a stack of parallel CT slices using a two-dimensional detector array. A total of 110 slices were obtained which represented a volume of bone 9 mm in axial length with a nominal resolution (voxel size) of 82 μm. The scanned limb was immobilized during the examination in a carbon fiber cast. Antero-posterior 2D scout views were performed to determine the region to be scanned. All scans were acquired by one of two trained technicians using standard positioning techniques. These were in keeping with the manufacturer's guidelines and as described by Boutroy et al. [21]. Each scan was assessed for motion artefact, and if present a second scan was performed. The quality of the measurements was assessed by using a 5-point scale recommended by the manufacturer (1, excellent; 2, good; 3, acceptable; 4, poor; 5, unacceptable). Only examinations with quality grades 1 through 4 were included in the study.

Image analysis was carried out using the standard manufacturer's method which has been described in detail previously [22,23]. In brief, we used a semi-automated, hand-drawn contouring system to delineate the periosteal surface. A threshold-based algorithm then separated cortical from trabecular compartments. The threshold used to discriminate cortical from trabecular bone was set to one-third of the apparent cortical bone density value. Standard morphologic analysis produced total (Tt.vBMD, g/cm³) and trabecular BMD (Tb.vBMD, g/cm³).

Trabecular number (Tb.N, per mm) was determined using the ridge-extraction method [24]. Trabecular thickness (Tb.Th, μm) and separation (Tb.Sp, μm) were calculated from trabecular density and trabecular number according to standard morphologic relationships [25]. Each measure has been validated against micro-CT imaging [26].

Further analysis was performed using an automated segmentation algorithm [27]. Assessments were made of total cross-sectional area (Tt.area, mm^2), cortical area (Ct.area, mm^2), and cortical density (Ct.vBMD, g/cm^3). Cortical density was determined as the average mineral density in the region of auto-segmentation cortical bone mask. Using Image Processing Language (IPL, Version 6.1, ScancoMedical), cortical porosity (Ct.Po, %) was derived from the number of void voxels in each thresholded cortex image divided by the number of voxels in the cortex. Cortical thickness (Ct.Th, μm) was determined from the threshold cortex image using a distance transform after removal of intracortical pores [28].

A calibration phantom (Scanco Medical AG, Bruttisellen, Switzerland) was used which included 5 cylinders containing a mixture of hydroxyapatite and resin. The mineral concentrations of these cylinders were 0, 100, 200, 400 and 800 mgHA/cm^3 . The value of 0 mgHA/cm^3 equates to a soft tissue background devoid of mineral. Quality control testing was performed on a weekly basis and quality assurance on a daily basis. Short term precision values (% CV) for cortical and trabecular BMD have been shown to range from 0.3 to 1.2 [29]. The effective dose to the subject during each scan was $<3 \mu\text{Sv}$.

Statistical methods

Statistical analyses were performed using STATA version 13.1. Variables were assessed for normality and transformed if necessary. Descriptive statistics for continuous variables are expressed as mean, standard deviation; and categorical variables as frequency and percentage.

Differences in continuous variables were assessed using Student's *t*-tests (for two groups) or one-way ANOVA (for multiple groups) and in categorical variables using Pearson's χ^2 test. Statistical significance was defined as a *p*-value of ≤ 0.05 .

HR-pQCT measures were described separately for men and women. Primary analysis used linear regression to examine the associations between alcohol consumption (minimal/none, low and moderate/high) and HR-pQCT bone parameters in the distal radius and in the distal tibia. This analysis was undertaken with and without adjustment for a priori confounders: age, BMI, smoking status, dietary calcium intake, physical activity and socioeconomic status, years since menopause and HRT use for women. The second analysis used linear regression to examine separately the associations between several DXA parameters at femoral neck and total hip: bone area, BMC and aBMD in men and women with alcohol consumption. This analysis was also undertaken with and without adjustment for age, BMI, smoking status, dietary calcium intake, physical activity and socioeconomic status, years since menopause and HRT use for women.

Results

Characteristics of study participants

The mean age of participants was 76.5 and 76.1 years in women and men, respectively (Table 1). On average, men were taller and heavier than women but BMI did not differ significantly by sex. Information on smoking status, alcohol consumption, social class and time since menopause was not available within the dataset on 2, 1, 8 and 3 individuals respectively. Rates of smoking were higher in men than women ($p < 0.001$); 58.6% of men ($n = 116$) and only 34.7% of women ($n = 61$) were current or ex-smokers. Alcohol consumption was also greater in men ($p < 0.001$) with 39.4% ($n = 78$) in the moderate/high alcohol consumption category (≥ 11 units/week) whereas this figure was only

13% in women (≥ 8 units/week) ($n = 23$). The mean daily dietary calcium intake was 1137 mg and 1225 mg in women and men, respectively ($p = 0.012$). Physical activity score was also higher in men than women. Women had gone through the menopause a mean of 28.1 years previously. Social class did not differ significantly by sex.

A total of 30 (15.2%), 90 (45.5%) and 78 (39.4%) men drank minimal/none, low and moderate/high amounts of alcohol respectively. These figures were 74 (41.8%), 80 (45.2%) and 23 (13.0%) respectively in women (Table 1). Characteristics of study participants were compared among men and women by alcohol consumption (Table 2). Rates of smoking (ever smoked) were higher in women with moderate/high alcohol consumption ($p = 0.033$). Body mass index was also higher in men with moderate/high alcohol consumption than those with low ($p = 0.013$).

Bone geometry, volumetric bone mineral density and microarchitecture at the distal radius: relationship with alcohol consumption

After adjustment for confounding factors (age, BMI, smoking status, dietary calcium intake, physical activity and socioeconomic status), men that drank low alcohol had lower Ct.Th ($\beta = -0.437$, $[-0.849, -0.025]$ *z*-score; $p = 0.038$), Ct.vBMD ($\beta = -0.438$, $[-0.839, -0.037]$ *z*-score; $p = 0.033$), and Tb.vBMD ($\beta = -0.412$, $[-0.777, -0.046]$ *z*-score; $p = 0.028$) and higher Tb.Sp ($\beta = 0.361$, $[0.011, 0.711]$ *z*-score; $p = 0.043$) than those that drank none/minimal alcohol (Table 3, Fig. 1). Moreover, men that drank moderate–high alcohol had lower Ct.Th ($\beta = -0.374$, $[-0.741, -0.007]$ *z*-score; $p = 0.046$), and Ct.vBMD ($\beta = -0.559$, $[-0.944, -0.175]$ *z*-score; $p = 0.005$) than those that drank none/minimal alcohol (Table 3, Fig. 1).

Regarding trabecular parameters, women that drank low amounts of alcohol had significantly lower Tb.vBMD ($\beta = -0.368$, $[-0.673, -0.064]$ *z*-score; $p = 0.018$) and tended to have lower Tb.Th, Tb.N and higher Tb.Sp than those that drank none/minimal alcohol (Table 4, Fig. 1) whereas women that drank moderate/high alcohol had significantly higher Tb.vBMD ($\beta = 0.548$, $[0.153, 0.943]$ *z*-score; $p = 0.007$), Tb.Th ($\beta = 0.536$, $[0.066, 1.007]$ *z*-score; $p = 0.026$), Tb.N ($\beta = 0.460$, $[0.016, 0.903]$ *z*-score; $p = 0.042$) and lower Tb.Sp ($\beta = -0.482$, $[-0.905, -0.058]$; $p = 0.026$) than those that drank low alcohol (Table 4, Fig. 1).

Table 1
Characteristics of study participants.

Variables	Men (<i>n</i> = 198)	Women (<i>n</i> = 178)	<i>P</i> -value
Age, year	76.1 (2.5)	76.5 (2.6)	0.185
Body weight, kg	82.4 (12.1)	71.0 (12.7)	<0.001
Body height, cm	173.4 (6.6)	159.9 (5.7)	<0.001
BMI (kg/m^2)	27.4 (3.8)	27.8 (4.7)	0.379
Daily calcium intake (mg)	1225 (298)	1137 (381)	0.012
Physical activity score	65.7 (13.6)	62.1 (13.7)	0.012
Time since menopause (years)	NA	28.1 (6.7)	NA
Social status ^a			
I–IIINM	84 (44.2)	77 (43.3)	
IIIM–V	106 (55.8)	101 (56.7)	0.854
Smoker status			
Never	82 (41.4)	115 (65.3)	
Ex	102 (51.5)	52 (29.6)	
Current	14 (7.1)	9 (5.1)	<0.001
Alcohol consumption ^b			
Minimal/none	30 (15.2)	74 (41.8)	
Low	90 (45.5)	80 (45.2)	
Moderate/high	78 (39.4)	23 (13.0)	<0.001

BMI: body mass index.

Bold data mean results statistically significant.

^a I–IIINM (I to III non-manual), IIIM–V (III manual to V).

^b Minimal/none, <1 unit/week; low alcohol consumption, ≥ 1 unit/week and <8 units/week in women or <11 units/week in men; moderate–high alcohol consumption, ≥ 8 units/week in women or ≥ 11 units/week in men.

Table 2
Characteristics of study participants by alcohol consumption.

Variables	Men (n = 198)			P
	None/minimal ^a (n = 30)	Low ^a (n = 90)	Moderate/high ^a (n = 78)	
Age, year	75.9 (2.5)	76.2 (2.5)	76.1 (2.6)	0.783
BMI (kg/m ²)	27.7 (4.2)	26.7 (3.3)	28.1 (4.0)	0.046
Daily calcium intake (mg)	1216 (307)	1256 (274)	1193 (322)	0.394
Physical activity score	65.2 (15.1)	64.5 (13.0)	67.2 (13.7)	0.430
Social status ^b (I–IIINM)	14 (48.3)	41 (47.7)	29 (38.7)	0.461
Ever smoked	17 (56.7)	46 (51.1)	53 (67.9)	0.085

Variables	Women (n = 178)			P
	None/minimal ^a (n = 74)	Low ^a (n = 80)	Moderate/high ^a (n = 23)	
Age, year	76.1 (2.6)	76.4 (2.6)	77.6 (2.6)	0.073
BMI (kg/m ²)	28.0 (4.5)	27.9 (5.1)	26.6 (4.3)	0.453
Daily calcium intake (mg)	1117 (297)	1156 (457)	1139 (351)	0.823
Physical activity score	62.3 (13.7)	62.1 (14.1)	60.9 (12.2)	0.909
Social status ^b (I–IIINM)	30 (40.5)	37 (46.3)	10 (43.5)	0.775
Ever smoked	20 (27.0)	29 (36.2)	13 (56.5)	0.033

BMI: body mass index.

Bold data mean results statistically significant.

^a Minimal/none, <1 unit/week; low alcohol consumption, ≥1 unit/week and <8 units/week in women or <11 units/week in men; moderate–high alcohol consumption, ≥8 units/week in women or ≥11 units/week in men.

^b I–IIINM (I to III non-manual) versus IIIM–V (III manual to V).

Interestingly, men that drank low amounts of alcohol had higher radial Tt.area ($\beta = 0.304$, [0.004, 0.604] z-score; $p = 0.047$) and Tb.area ($\beta = 0.388$, [0.044, 0.732] z-score; $p = 0.027$) and tended to have a lower Ct.area ($\beta = -0.280$, [-0.586, 0.026] z-score; $p = 0.072$) than those that drank minimal/none alcohol (Table 3, Fig. 1). However, after adjustment for confounding factors, this remained significant only for Tb.area ($\beta = 0.362$, [0.015, 0.708] z-score; $p = 0.041$). In women, consumption of alcohol was not found to be independently associated with bone size at the distal radius. This was when comparing low to minimal/none, high/moderate to minimal/none and high/moderate to low (Table 4, Fig. 1).

Bone geometry, volumetric bone mineral density and microarchitecture at the distal tibia: relationship with alcohol consumption

After adjustment for confounding factors, women that drank low amounts of alcohol had lower Tb.vBMD ($\beta = -0.351$, [-0.682, -0.021] z-score; $p = 0.037$), Tb.N ($\beta = -0.338$, [-0.640, -0.037] z-score; $p = 0.028$) and higher Tb.Sp ($\beta = 0.351$, [0.048, 0.653] z-score; $p = 0.023$) than those that drank none/minimal alcohol (Supplementary material: Table S1) whereas Ct.area and Ct.Th in men that drank low amounts of alcohol were lower than those that drank none/minimal alcohol ($\beta = -0.349$, [-0.662, -0.036] z-score; $p = 0.029$) and ($\beta = -0.489$, [-0.866, -0.112] z-score; $p = 0.011$) respectively (Supplementary material: Table S2).

DXA measurements: relationship with alcohol consumption

Regarding DXA analyses, men that drank moderate/high alcohol had higher aBMD and BMC at the total hip than those that drank low alcohol ($\beta = 0.048$, [0.002, 0.093] g/cm²; $p = 0.041$ and $\beta = 2.004$, [0.136, 3.872] g; $p = 0.036$ respectively). After adjustment for confounding factors, these were no longer statistically significant. No associations were found at either skeletal site, between alcohol consumption or any of the DXA parameters in women.

Discussion

In this study, we utilized HR-pQCT to investigate geometric, volumetric and microstructural parameters at the distal radius and tibia in relation to alcohol consumption in participants of a community-based cohort of elderly men and women from Hertfordshire. At the distal radius, we found that, compared with men who drank none/minimal alcohol, men with low or moderate/high alcohol consumption had lower Ct.Th, Ct.vBMD, and Tb.vBMD and higher Tb.Sp than their teetotal counterparts, and similar results were shown at the distal tibia in women with low alcohol consumption compared to minimal/none alcohol for Tb.vBMD, Tb.N and Tb.Sp. Interestingly, women that drank moderate/high alcohol had significantly higher Tb.vBMD, Tb.Th, Tb.N and lower Tb.Sp than those that drank low alcohol at the distal radius.

There are very few studies that have completed similar analyses. Although associations between alcohol consumption and both cortical and trabecular vBMD have been previously assessed by pQCT [14,15], without significant relationships being identified, this is the first study to examine relationships with bone microarchitecture. A study by Barbour KE and colleagues [14] evaluated the impact of demographic, anthropometric, lifestyle, and medical factors on vBMD assessed by pQCT in 1172 men aged 69 to 97 years (MrOS). Alcohol consumption as a continuous variable was not associated with Ct.vBMD or Tb.vBMD at the distal radius and tibia [14]. In another study, the extent of alcohol consumption in a group of 258 healthy men (aged 40–63) did not differentiate trabecular, cortical or total BMC values at the distal radius [15]. However, there are also several animal studies on alcohol and bone microarchitecture that corroborate our findings [30,31].

Our results suggest that alcohol consumption (low and moderate/high) may have a detrimental impact on bone health in men in both the cortical and trabecular compartments at the distal radius with similar results in women in the trabecular compartment at the distal tibia. The exact mechanisms by which alcohol might adversely affect bone health have not been fully elucidated. It has been suggested in human, animal and cell culture studies that alcohol has a dose-dependent toxic influence on osteoblast activity [32]. The effect of long-term alcohol consumption on bone remodeling likely involves a complex uncoupling of formation and resorption with a decreased bone formation rather than increased bone resorption [32]. Data from experimental studies indicate that osteocalcin (a marker of bone formation) increases after abstinence [33] and decreases after alcohol administration [34].

Consequently, results from this study showing higher trabecular density, number and thickness and lower trabecular separation in women with moderate/high alcohol consumption compared to low alcohol consumption may be contrary to what one might expect and cannot be explained purely by confounders such as smoking (Table 2). Indeed, rates of smoking were higher in women with moderate/high alcohol consumption in comparison with others groups which, if anything, would be expected to cause the opposite effect. Clearly, these results should be interpreted with caution due to the small number of women ($n = 23$) in the moderate/high alcohol consumption group.

However, differences have been shown to exist in the pattern of bone density loss in men and women. Specifically, women with greater alcohol consumption had lower rates of bone density loss whereas men with the greatest alcohol consumption had the highest rates of bone density loss [35–37]. Biologically, the beneficial effects of alcohol consumption in women could be partially explained by elevations in circulating estradiol levels but these effects have mainly been demonstrated in women on hormonal replacement therapy [38,39].

Interestingly, prior to adjustment, higher aBMD was found in men that drank moderate/high alcohol than those that drank low alcohol. This difference was fully attenuated after adjustment for confounders. It is known that DXA measurements are influenced by body

Table 3
Regression analysis of radial bone microarchitecture comparing men with low alcohol consumption and moderate–high alcohol consumption to those with minimal alcohol consumption and men with moderate–high alcohol consumption to those with low alcohol consumption.

Variables	Low alcohol consumption ^b vs. minimal/none ^a				Moderate–high alcohol consumption ^c vs. minimal/none ^a				Moderate–high alcohol consumption ^c vs. low alcohol consumption ^b			
	β (95% CI)	<i>P</i> -value	β (95% CI)*	<i>P</i> -value*	β (95% CI)	<i>P</i> -value	β (95% CI)*	<i>P</i> -value*	β (95% CI)	<i>P</i> -value	β (95% CI)*	<i>P</i> -value*
Tt.area z-score	0.304 (0.004, 0.604)	0.047	0.275 (−0.028, 0.579)	0.075	0.225 (−0.041, 0.491)	0.096	0.209 (−0.071, 0.489)	0.141	−0.079 (−0.292, 0.135)	0.467	−0.101 (−0.331, 0.129)	0.385
Ct.area z-score	−0.280 (−0.586, 0.026)	0.072	−0.0277 (−0.571, 0.017)	0.065	−0.169 (−0.472, 0.134)	0.273	−0.238 (−0.543, 0.066)	0.123	0.112 (−0.103, 0.327)	0.306	0.054 (−0.170, 0.278)	0.635
Tb.area z-score	0.388 (0.044, 0.732)	0.027	0.362 (0.015, 0.708)	0.041	0.284 (−0.032, 0.600)	0.077	0.272 (−0.063, 0.608)	0.111	−0.104 (−0.344, 0.137)	0.395	−0.119 (−0.377, 0.139)	0.364
Tb.vBMD z-score	−0.387 (−0.751, −0.023)	0.037	−0.412 (−0.777, −0.046)	0.028	−0.232 (−0.602, 0.138)	0.217	−0.248 (−0.622, 0.127)	0.193	0.155 (−0.106, 0.416)	0.243	0.167 (−0.103, 0.436)	0.223
Tb.N z-score	−0.276 (−0.615, 0.063)	0.109	−0.287 (−0.632, 0.058)	0.103	−0.013 (−0.403, 0.376)	0.946	−0.094 (−0.464, 0.277)	0.617	0.263 (−0.002, 0.528)	0.052	0.218 (−0.044, 0.481)	0.103
Tb.Th z-score	−0.343 (−0.740, 0.053)	0.089	−0.374 (−0.782, 0.033)	0.071	−0.270 (−0.663, 0.123)	0.176	−0.261 (−0.669, 0.146)	0.206	0.074 (−0.201, 0.349)	0.597	0.101 (−0.187, 0.390)	0.488
Tb.Sp z-score	0.344 (−0.003, 0.692)	0.052	0.361 (0.011, 0.711)	0.043	0.105 (−0.277, 0.488)	0.586	0.163 (−0.211, 0.537)	0.388	−0.239 (−0.500, 0.022)	0.073	−0.215 (−0.478, 0.048)	0.108
Ct.vBMD z-score	−0.423 (−0.817, −0.030)	0.035	−0.438 (−0.839, 0.037)	0.033	−0.597 (−0.972, −0.222)	0.002	−0.559 (−0.944, −0.175)	0.005	−0.173 (−0.454, 0.107)	0.224	−0.127 (−0.423, 0.169)	0.400
Ct.Th z-score	−0.456 (−0.880, −0.031)	0.036	−0.437 (−0.849, −0.025)	0.038	−0.323 (−0.685, 0.039)	0.080	−0.374 (−0.741, −0.007)	0.046	0.133 (−0.157, 0.422)	0.367	0.077 (−0.225, 0.380)	0.614
Ct.Po z-score	−0.052 (−0.443, 0.339)	0.792	−0.056 (−0.455, 0.343)	0.780	0.366 (−0.021, 0.753)	0.064	0.240 (−0.142, 0.622)	0.215	0.418 (0.133, 0.703)	0.004	0.324 (0.036, 0.613)	0.028

Abbreviations: Tt.area: total area; Ct.area: cortical area; Tb.area: trabecular area; Tb.vBMD: trabecular volumetric bone mineral density; Tb.N: trabecular number; Tb.Th: trabecular thickness; Tb.Sp: trabecular separation; Ct.vBMD: cortical volumetric bone mineral density; Ct.Th: cortical thickness; Ct.Po: cortical porosity.

Bold data mean results statistically significant.

^a Minimal/none, <1 unit/week.

^b Low alcohol consumption, ≥ 1 unit/week and <8 units/week in women or <11 units/week in men.

^c Moderate–high alcohol consumption, ≥ 8 units/week in women or ≥ 11 units/week in men.

* Adjusted for age, body mass index, smoking status, calcium intake, physical activity, and social class.

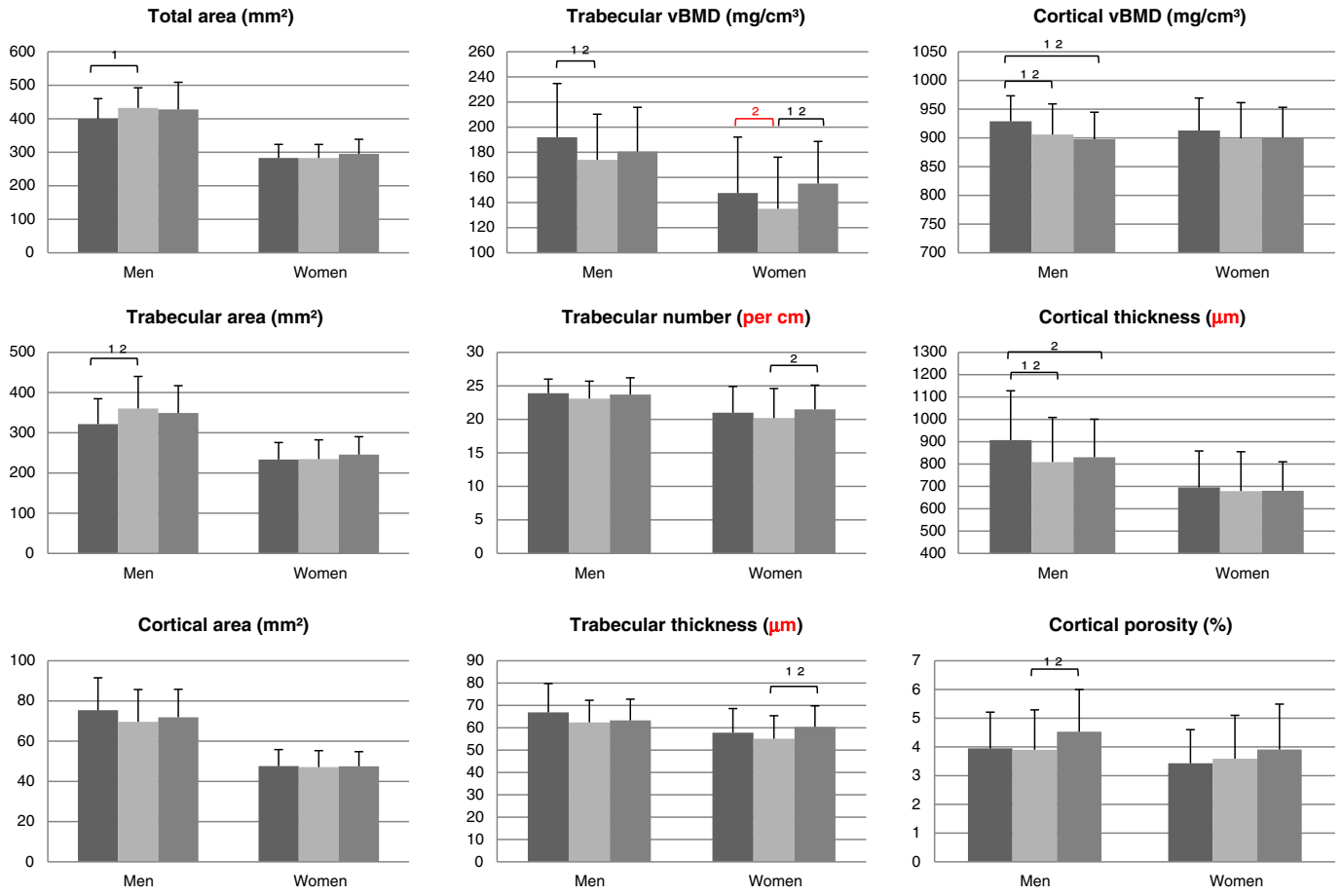


Fig. 1. Comparative analysis of bone geometry, vBMD and microarchitecture at the distal radius in men and women on alcohol consumption. ¹ indicates significant differences between alcohol consumption categories without adjustment and ² with adjustment by age, BMI, smoking status, calcium intake, physical activity, social class, years since menopause and HRT use for women. Dark grey: minimal/none, <1 unit/week; light grey: low alcohol consumption, ≥1 unit/week and <8 units/week in women or <11 units/week in men; medium grey: moderate–high alcohol consumption, ≥8 units/week in women or ≥11 units/week in men.

composition, including adiposity, and as men in the moderate/high alcohol group also had a significantly greater BMI, this might explain the unadjusted relationship. Furthermore, this highlights one of the benefits of using vBMD over aBMD when assessing differences in bone health between groups.

The strengths of our study include a well phenotyped cohort of elderly men and women allowing adjustment for multiple potential confounders. Furthermore, most of the variables (such as alcohol consumption and smoking status) were collected by trained research nurses, resulting in a lower risk of misclassification. The study also has some potential limitations. Firstly, based on the observational nature of this study design, causality cannot be established because we are unable to determine temporal relationships between the variables. Moreover, this study design did not allow us to check in a longitudinal way for individual changes on alcohol consumption bands. Indeed, individuals classified as none/moderate alcohol consumption may be at higher risk of fracture (and poorer bone microarchitecture), due to poorer health status that led them to stop drinking alcohol. Secondly, the relationships between alcohol consumption and bone parameters have been evaluated in a cohort of elderly men and women. These results cannot therefore be extrapolated to younger women and men in whom moderate alcohol consumption may be associated with better bone health [40]. Thirdly, our study did not include laboratory assessments, so we could not investigate how bone metabolism in participants might have been affected by lower 25-OH vitamin D levels, altered renal function and their relationships with bone density and microarchitecture. Fourthly, another limitation has been to consider alcohol as a single type of beverage. Indeed, several studies suggest

that the effect of beer, wine and spirits on bone parameters may differ significantly. It is likely that it is not only the total amount of absorbed alcohol, but also the associated components that have their role in bone physiology (e.g. silicon appears to mediate the association of beer, but not that of wine or liquor, with BMD) [41,42]. Finally, HR-pQCT data is restricted to the peripheral skeleton and does not provide a direct measure of bone quality at axial regions such as hip and vertebrae which are both common sites of fragility fracture.

In summary, this study shows that men who drank low or moderate/high alcohol had lower cortical thickness, cortical volumetric bone mineral density, and trabecular volumetric bone mineral density and higher trabecular separation at the distal radius than abstainers, with similar results seen in women between none/minimal alcohol and low alcohol for trabecular parameters at the distal tibia. Surprisingly, women that drank moderate/high alcohol had significantly higher trabecular parameters than those that drank low alcohol at the distal radius. Further research is needed to characterize age- and gender differences in the effect of alcohol on bone health. Better delineation of the potential mechanisms, presumably acting on cortical and trabecular remodelling, is required to improve our understanding of the pathogenesis of bone fragility in individuals that consume alcohol.

Conflict of interest statement

Professor Cooper has received consultancy fees/honoraria from Servier; Eli Lilly; Merck; Amgen; Alliance; Novartis; Medtronic; GSK; Roche.

Table 4
Regression analysis of radial bone microarchitecture comparing women with low alcohol consumption and moderate–high alcohol consumption to those with minimal alcohol consumption and women with moderate–high alcohol consumption to those with low alcohol consumption.

Variables	Low alcohol consumption ^b vs. minimal/none ^a				Moderate–high alcohol consumption ^c vs. minimal/none ^a				Moderate–high alcohol consumption ^c vs. low alcohol consumption ^b			
	β (95% CI)	P-value	β (95% CI)*	P-value*	β (95% CI)	P-value	β (95% CI)*	P-value*	β (95% CI)	P-value	β (95% CI)*	P-value*
Tt.area z-score	−0.040 (−0.249, 0.169)	0.706	−0.067 (−0.286, 0.151)	0.542	0.161 (−0.135, 0.458)	0.283	0.129 (−0.200, 0.458)	0.437	0.201 (−0.112, 0.514)	0.205	0.181 (−0.149, 0.510)	0.279
Ct.area z-score	−0.054 (−0.275, 0.167)	0.630	−0.004 (−0.224, 0.216)	0.972	0.020 (−0.284, 0.324)	0.897	0.061 (−0.265, 0.387)	0.711	0.074 (−0.244, 0.392)	0.646	0.144 (−0.177, 0.464)	0.375
Tb.area z-score	−0.006 (−0.226, 0.215)	0.960	−0.044 (−0.276, 0.187)	0.705	0.158 (−0.154, 0.470)	0.317	0.118 (−0.229, 0.464)	0.502	0.164 (−0.166, 0.493)	0.327	0.136 (−0.210, 0.482)	0.437
Tb.vBMD z-score	−0.299 (−0.602, 0.005)	0.054	−0.368 (−0.673, 0.064)	0.018	0.142 (−0.306, 0.590)	0.531	0.150 (−0.305, 0.606)	0.514	0.441 (0.031, 0.850)	0.035	0.548 (0.153, 0.943)	0.007
Tb.N z-score	−0.159 (−0.475, 0.157)	0.321	−0.244 (−0.547, 0.059)	0.113	0.150 (−0.299, 0.599)	0.510	0.127 (−0.316, 0.570)	0.570	0.309 (−0.166, 0.784)	0.200	0.460 (0.016, 0.903)	0.042
Tb.Th z-score	−0.248 (−0.563, 0.067)	0.122	−0.282 (−0.616, 0.051)	0.096	0.245 (−0.216, 0.706)	0.294	0.300 (−0.176, 0.777)	0.214	0.493 (0.051, 0.935)	0.029	0.536 (0.066, 1.007)	0.026
Tb.Sp z-score	0.211 (−0.099, 0.521)	0.182	0.296 (−0.003, 0.595)	0.053	−0.127 (−0.573, 0.320)	0.575	−0.112 (−0.556, 0.331)	0.615	−0.337 (−0.792, 0.118)	0.145	−0.482 (−0.905, 0.058)	0.026
Ct.vBMD z-score	−0.234 (−0.582, 0.114)	0.186	−0.177 (−0.544, 0.190)	0.342	−0.248 (−0.730, 0.234)	0.310	−0.270 (−0.819, 0.278)	0.330	−0.014 (−0.380, 0.463)	0.956	0.062 (−0.466, 0.589)	0.817
Ct.Th z-score	−0.107 (−0.403, 0.190)	0.479	−0.040 (−0.347, 0.268)	0.800	−0.065 (−0.470, 0.339)	0.750	−0.044 (−0.494, 0.406)	0.847	0.041 (−0.380, 0.463)	0.846	0.126 (−0.309, 0.561)	0.566
Ct.Po z-score	0.076 (−0.247, 0.399)	0.642	0.044 (−0.303, 0.391)	0.801	0.320 (−0.122, 0.763)	0.154	0.253 (−0.236, 0.741)	0.306	0.244 (−0.255, 0.743)	0.334	0.200 (−0.324, 0.723)	0.450

Abbreviations: Tt.area: total area; Ct.area: cortical area; Tb.area: trabecular area; Tb.vBMD: trabecular volumetric bone mineral density; Tb.N: trabecular number; Tb.Th: trabecular thickness; Tb.Sp: trabecular separation; Ct.vBMD: cortical volumetric bone mineral density; Ct.Th: cortical thickness; Ct.Po: cortical porosity.

Bold data mean results statistically significant.

^a Minimal/none, <1 unit/week.

^b Low alcohol consumption, ≥ 1 unit/week and <8 units/week in women or <11 units/week in men.

^c Moderate–high alcohol consumption, ≥ 8 units/week in women or ≥ 11 units/week in men.

* Adjusted for age, body mass index, smoking status, calcium intake, physical activity, social class, years since menopause and HRT use.

Julien Paccou, Mark Edwards, Kate Ward, Karen Jameson, Charlotte Moss, Nicholas Harvey, and Elaine Dennison declare that they have no conflict of interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.bone.2015.05.002>.

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