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Calcaneal Quantitative Ultrasound Indicates Reduced Bone Status Among Physically Active Adult Forager-Horticulturalists

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Abstract

Sedentary lifestyle contributes to osteoporosis and fragility fracture risks among modern humans, but whether such risks are prevalent in physically active pre-industrial societies with lower life expectancies is unclear. Osteoporosis should be readily observable in pre-industrial societies if it was regularly experienced over human history. In this study of 142 older adult Tsimane forager-horticulturalists (mean age±SD=62.1±8.6, range=50-85, 51% female) we use calcaneal quantitative ultrasonography (qUS) to assess bone status, document prevalence of adults with reduced bone status, and identify factors (demographic, anthropometric, immunological, kinesthetic) associated with reduced bone status. Men (23%) are as likely as women (25%) to have reduced bone status, although age-related decline in qUS parameters is attenuated for men. Adiposity and fat-free mass positively co-vary with qUS parameters for women but not men. Leukocyte count is inversely associated with qUS parameters controlling for potential confounders; leukocyte count is positively correlated within adults over time, and adults with persistently low counts have higher adjusted qUS parameters (6-8%) than adults with a high count. Reduced bone status characteristic of osteoporosis is common among active Tsimane with minimal exposure to osteoporosis risk factors found in industrialized societies, but with energetic constraints and high pathogen burden.

Keywords

Osteoporosis; bone mineral density; anthropometrics; immune activation; physical activity

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1. Introduction

Osteoporosis is characterized by low bone mineral density (BMD) and bone strength, and for both sexes is linked to major morbidity and mortality secondary to fractures [1, 2]. Osteoporosis is under-diagnosed and under-treated, including in world regions with advanced clinical infrastructure, because it is asymptomatic until fracture occurs. In industrialized societies, osteoporosis risk factors include older age, female sex, history of adult fracture (including family history), low body mass, nutrient deficiency and physical inactivity [3]. In developing countries and pre-industrial societies, determinants and consequences of osteoporosis are poorly understood, although lower life expectancies may contribute to lower population prevalence of osteoporosis and absolute fracture risk due to mortality selection and young age structure [4, 5]. A recent study of rural agrarian Ecuadorians indicates a considerable prevalence of adults aged 50+ with reduced bone status (43% women, 18% men) [6], suggesting high osteoporosis risk despite a physically active lifestyle. *In vivo* studies in pre-industrial societies are necessary to understand the ecological and energetic constraints under which human bones evolved.

Modern human osteoporosis susceptibility may be due to a postcranial skeleton that is more gracile (i.e. lower bone mass for body size) than that of other hominoids and extinct hominins [7, 8]. Human thoracic vertebrae, which are commonly subject to fragility fracture, show reduced trabecular bone volume fraction and thinner vertebral shells compared to wild-shot apes after adjusting for body mass, with differences emerging in early adulthood [9]. Reductions in trabecular bone volume fraction of the metatarsal head [10], calcaneus [11], femoral head [12] and metacarpal head [13] have similarly been documented among modern humans compared to other extant apes. Within the genus *Homo*, earlier studies documented a decline in postcranial skeletal strength relative to body size throughout the Pleistocene [8, 14], but recent studies suggest this decline occurred in the later Pleistocene or Holocene [7, 15, 16]. Bio-mechanical correlates of habitual bipedality per se thus cannot fully account for modern human skeletal gracility.

One prominent hypothesis to explain skeletal gracility is that modern humans are less physically active than other hominoids and extinct hominins [7-9, 14, 17]. Transition from a mobile hunting and gathering subsistence regime toward sedentary agriculture, and increasing reliance on technology, caused reductions in activity and mechanical loading on bone, leading to skeletal gracilization. Comparisons of adult skeletal remains of hunter-gatherers and either full- or part-time agriculturalists reveal accelerated age-related decline in radial bone mineral content [18] and reduced femoral strength among agriculturalists [7, 19]. Differences in limb strength have also been found among Later Stone Age (ca. 10,000-2,000 BP) South African foragers and 19th century Andamanese foragers [20]; the former were mobile terrestrial foragers whereas the latter were terrestrially constrained but adept seafarers, using canoes for transport and food procurement. As expected if habitual subsistence activities (e.g. hunting in rugged vertical terrain vs. rowing) result in localized osteogenic responses, South Africans have relatively strong lower limbs and weaker upper limbs whereas Andamanese have weaker lower limbs and strong upper limbs. High activity level can thus result not only in stronger bones, but also localized redistribution of bone tissue in the direction of highest bending strains. These observations coupled with those from a separate clinical and kinesthetic literature [21-23] suggest that insufficient skeletal loading leads to reduced peak bone mass, accelerated rate of bone loss, and increased risks of osteoporosis and fragility fractures.

This paper explores whether physical activity level above the level characteristic of industrialized societies protects against age-related bone loss and fragility fracture risk. In paleo-pathological samples, fractures are common but usually result from excessive trauma rather than reduced bone strength, leading some to conclude that fragility fractures are rare in active pre-industrial societies, even among the elderly [24, 25]. Yet despite limitations of paleo-pathological studies (e.g. small and unrepresentative samples, imprecise age estimates), the archaeological record shows evidence of age-related bone loss, osteoporosis and fragility fractures [24, 26-29]. Studies of contemporary pre-industrial societies suggest that bone mass is not preserved in older adulthood [25, 30, 31], although direct evidence of fragility fractures is scant given logistical difficulties of bone imaging in remote geographical areas. Accelerated bone loss with age, which has also been documented among free-ranging chimpanzees [32], appears to be a basic feature of human aging, although most research among humans is done in industrialized societies.

There are several reasons why reduced bone status characteristic of osteoporosis might be expected even among active foragers with minimal exposure to osteoporosis risk factors found in industrialized societies (e.g. glucocorticoid therapy) and lower life expectancies. First, energetic limitation, due to high energy expenditure relative to consumption, results in lower body mass, which reduces skeletal loading. Energetic limitation may also be associated with micro-nutrient deficiency, particularly of bone-forming minerals, which contributes to lower bone mass [21]. Low body mass is associated with increased fracture risk even after adjusting for BMD [33]; BMD alone explains roughly 75% of the variance in bone strength (i.e. the ability to withstand an applied load) [34]. The greatest voluntary skeletal loads come from muscle contractions [22, 23], but adipose tissue also increases loading and indirectly facilitates bone mineral acquisition and maintenance via endocrine mechanisms (e.g. aromatization of adrenal androgens to estrogen) [35-38]. Positive associations between fat-free or fat mass and BMD are stronger among adults with low visceral fat stores [39], which is typical of active, energy-limited foragers.

Second, greater immune activation due to high pathogen exposure may result in reduced bone status among active foragers. Among Tsimane forager-horticulturalists, the population studied here, high pathogen burden increases immune activation throughout life [40]. Pathogen burden is associated with elevated levels of inflammatory biomarkers (e.g. interleukin-6) that stimulate osteoclastic bone resorption and inhibit osteoblast function in humans and other species [41-44]. Intestinal parasites are also common among Tsimane (>70% prevalence of helminth infection), and can impact mineral absorption efficiency [45], with potential downstream consequences for bone mineralization. Bone is normally a sterile area, but the most prevalent skeletal diseases are due to pathogenic actions on bone including destruction of non-cellular bone components by liberation of acids and proteases (as in the case of dental caries, which are common among Tsimane), promotion of cellular processes stimulating bone degradation (e.g. inflammation), and inhibition of bone matrix synthesis [46]. Despite recognition that morbidity inhibits growth [47, 48], and despite recognition that mediators of immune function regulate osteoblast and osteoclast activity [49, 50], effects of pathogen burden and immune activation on bone properties have not been well-characterized among humans.

1.1. Study goals and hypotheses

In vivo study of bone properties in active pre-industrial societies provides an opportunity to examine energetic and ecological factors that are often invisible to bio-archaeological inquiry, and to examine whether high physical activity level protects against age-related bone loss. Here we use calcaneal quantitative ultrasonography (qUS) to assess bone status, and we assess how qUS parameters are affected by variation in demographics, anthropometrics, immune activation and physical activity among older adults (mean age ±SD=62.1±8.6, range=50-85).

We first report prevalence of adults with reduced bone status, and then identify factors associated with reduced bone status. We examine age-related decline (rate and overall magnitude) in qUS parameters, and the relative influence of adiposity and fat-free mass in affecting qUS parameters. We test whether effects of aging and anthropometrics on qUS parameters are stronger for women than men given declines in sex steroid hormone concentrations around menopause. Women are expected to have lower qUS parameters than men even after controlling for anthropometrics and other factors (e.g. physical inactivity) which may vary by sex and independently affect bone status. We also test whether degree of physical limitation, an indicator of physical inactivity, is inversely associated with qUS parameters. We further test whether immune activation, as indicated by leukocyte (WBC) count, is inversely associated with qUS parameters. Finally, we examine whether WBC count is correlated within adults over time (at two time points). Bone remodeling cycles occur over several months [51], and we expect the inverse association between immune activation and qUS parameters to be stronger when immune activation is persistently high or low.

2. Materials and Methods

2.1. Study population

Tsimane forager-horticulturalists of lowland Bolivia are semi-sedentary and live in >90 villages, nearly all of which lack running water and electricity. Tsimane have relatively short life expectancy (life expectancy at birth, at age 15, and at age 45: e_0=42 years, e_{15}=57, and e_{45}=66, respectively) [52]. Their diet consists of cultigens grown in small swiddens (66% of calories; mostly rice, plantains, sweet manioc and corn), lean meat from hunting (17%), freshwater fish (7%), and fruits and nuts gathered from the forest (6%) [53]. Few Tsimane rear cattle (<5% of families), most cattle owners maintain small herds (<3 head) and do not process milk for consumption. Market foods (e.g. pasta, sugar) and domesticated animals (e.g. cattle, chicken, pig) each provide 2% of the daily calories, and eggs provide <0.5% of calories. Relative to Western dietary standards calcium intake is low (~320 mg/day, unpublished data), but intake of other bone-forming minerals is ample (magnesium: ~450 mg/day; zinc: ~11 mg/day) or high (phosphorus: ~1,300 mg/day). Despite a lean diet and high fertility (total fertility rate=9 births per woman) with prolonged on-demand breastfeeding, Tsimane women's breast-milk concentration of long-chain polyunsaturated fatty acids is high relative to American women, and does not decline with parity or age [53]. Higher parity and older age are, however, each associated with reduced bone status [31].

Tsimane display relatively high physical activity levels (PALs) typical of other subsistence populations [54]. Women's PAL is in the “moderate to active” range (PAL=1.73–1.85) and remains constant throughout adulthood. Men's PAL is considered “vigorously active” (PAL=2.02-2.15), and declines by 10-20% from the peak (achieved in the late 20s) to older adulthood (age 60+). PALs among adults residing near the closest market town of San Borja are not substantially different than among adults residing in remote riverine or forest villages [54].

Tobacco consumption is minimal among Tsimane (for women in the present sample: mean ±SD pack-years=0.10±0.54; for men: 0.63±1.15). While 14% of women and 66% of men report occasional tobacco use (often from tobacco grown in home gardens), 97% of women and 77% of men have smoked <1 pack-year. Cigarette smoking (pack-years, or whether any history of smoking is reported) does not predict any qUS parameter and is thus omitted from multivariate analyses.

2.2. Participants

One hundred and forty-two adults aged 50+ (51% female) participated (see ESM for additional sample details). No participant reported ever using dietary supplements or hormonal contraception with consistency. All female participants were post-menopausal; during medical exams conducted in villages by Tsimane Health and Life History Project (THLHP) physicians, no woman was pregnant, lactating, or had experienced a menstrual cycle in the past year. Mean number of years since menopause±SD is 12.1±7.9. Number of years since menopause does not predict any qUS parameter after controlling for age, and is thus omitted from multivariate analyses.

For all protocols institutional (UNM and UCSB) IRB approval was granted, as was informed consent at three levels: (1) Tsimane government that oversees research projects, (2) village leadership, and (3) study participants.

2.3. Calcaneal quantitative ultrasonography (qUS)

Using a gel-based Sahara Clinical Bone Sonometer (Hologic, Waltham, MA, USA), qUS measurements of the right heel were obtained in 34 villages as part of the THLHP's population-level aging study (see ESM and [31] for additional details). The sonometer generates multiple measures including speed of sound (SOS, m/s), which reflects ultrasound wave velocity through the calcaneus for a given heel width. Another measure is broadband ultrasound attenuation (BUA, dB/MHz). Bone attenuates high frequency sound waves more than low frequency waves, and BUA reflects wave attenuation through the calcaneus in a frequency range (0.2–0.6 MHz) where attenuation is linearly associated with frequency. BUA is the slope of a linear regression of wave attenuation versus frequency within this range; the slope is less steep for osteoporotic bone [34]. SOS is largely influenced by trabecular separation, and BUA by both trabecular separation and connectivity [55]. The sonometer also generates a derived measure, the quantitative ultrasound index (QUI), sometimes referred to as “stiffness”. Compared to BUA or SOS, QUI is more strongly correlated to calcaneal BMD obtained from dual-energy X-ray absorptiometry (DXA). QUI is derived from a linear combination of SOS and BUA: QUI=0.41*(SOS+BUA) – 571. For SOS, BUA and QUI, lower values indicate lower bone mineral content per surface area. The sonometer also estimates BMD (g/cm^2) from a linear combination of SOS and BUA (estimated BMD=0.002592*(SOS+BUA) – 3.687) [56]. Because qUS does not directly measure BMD, in this paper we do not report BMD values; however, qUS BMD estimates are used here to calculate T-scores (see section 2.5).

During qUS measurement participants were asked if they ever experienced a skeletal fracture and for each fracture, year of fracture, skeletal site, cause, and whether radiographic confirmation was obtained from a San Borja physician. Participants were also asked if they fell in the past year, and if so how many times.

2.4. Demographics, anthropometrics, immune activation and physical limitation

Birth years were assigned based on a combination of methods described elsewhere (see [52] and ESM for additional details).

During medical exams, height was measured using a Seca Road Rod 214 stadiometer. Weight was measured using a Tanita Ironman InnerScan model BC-1500. This scale also measured impedance and generated estimates of adiposity and fat-free mass using proprietary prediction equations based on age, sex, height and weight (see ESM for additional details).

To measure immune activation, morning fasting blood specimens were collected by a trained biotechnician during annual medical exams. Immediately after sample collection WBC counts were conducted using a QBC Autoread Plus Dry Hematology System (Drucker Diagnostics, Port Matilda, PA). Participants contributed blood samples at two time points; mean number of years±SD between WBC count measures is 2.4±1.6 (mode=1).

To assess degree of physical limitation, adults performed a modified battery of mild exercises originally used in the MacArthur Studies of Successful Aging (see ESM for additional details). Eleven measures were summed to create a “disability score” (mean ±SD=13.1±5.4, range=5.2-23.8). As expected if disability score indicates degree of physical limitation and inactivity over the long-term, participants who reported no longer being able to carry heavy loads (e.g. a *quintal* of rice, ~45 kg) scored higher than participants reporting continued ability based on systematic questioning during medical exams.

2.5. Data analysis

The World Health Organization (WHO) defines osteoporosis using a DXA-derived T-score of -2.5 at the spine, femoral neck or total hip (T-scores between -1.0 and -2.5 indicate low bone mass, and scores above -1.0 are considered normal). T-scores represent the difference in one's BMD from the mean in a young adult (aged 20–29) population, expressed in SD units. Here T-scores are calculated as follows: $T = (P\text{-}YA)/SD_{YA}$, where P is one's estimated BMD, YA is the Tsimane young adult reference group mean estimated BMD specific to each sex, and SD_{YA} is the standard deviation of the Tsimane young adult mean (see ESM for additional details on Tsimane young adult reference data). We use a calcaneal qUS-specific T-score threshold of -1.8 to identify individuals with reduced bone status (following [56], where it is suggested that the WHO threshold of T = -2.5 for diagnosing osteoporosis requires modification when utilizing qUS).

Mann-Whitney *U*, chi-square and Kruskal-Wallis tests are used to compare study variables across groups (e.g. T-score group). To compare sexes we examine effect sizes in sex-specific multivariate analyses, we include sex as a main effect in analyses of the pooled sample, and we include interaction effects of sex and other predictors hypothesized to affect qUS parameters. We report results for SOS, BUA, and QUI because some qUS parameters may be more strongly associated with certain micro-architectural bone properties. Most participants received one ultrasound but a random subset (7%, n=10) received two since they received two medical exams during the study period (one per year). These repeated measures are included in analyses to avoid unnecessarily reducing sample sizes, and because parameter estimates from multivariate analyses are directly comparable to those omitting repeated measures. Generalized estimating equations (GEE) analyses are used to model effects of predictors on qUS parameters. The GEE method accounts for the correlated structure of a dependent variable arising from repeated measures over time, controlling for each individual [57]. For continuous outcomes (SOS, BUA, QUI) parameter estimates are reported as standardized betas unless otherwise noted. To model the probability of having reduced bone status, parameter estimates are reported as odds ratios (ORs) or predicted probabilities unless otherwise noted. There is no standard absolute goodness-of-fit measure with the GEE method.

3. Results

3.1. Sample characteristics

Means (±SDs) by sex and T-score group indicating bone status are shown in Table 1. Twenty-four percent of adults (25% women, 23% men) are classified as having reduced bone status. Older age and shorter stature are risk factors for both sexes, but only among women is reduced body mass – particularly reduced adiposity – associated with reduced bone status. Higher disability score is also associated with reduced bone status, particularly for women. Thirteen percent of adults (n=19) reported any fracture in adulthood (age 18+), and prior adult fracture is associated with reduced bone status. Descriptive statistics on fracture histories and variables used in subsequent regressions are available in ESM (Tables S1-S2, Figure S1), as is predicted absolute fracture risk (5-year and 10-year) using the Garvan Fracture Risk Calculator (Table S3). Twenty-three percent of adults (n=32) reported falling in the past year (often while carrying water or working in horticultural fields; mean number of times±SD among those who fell=1.3±0.7), but recent falling is not associated with any qUS parameter.

3.2. qUS parameters by age

3.2.1. Women—qUS parameters decline linearly with age (Figure S2), and show similar significant age-related declines (BUA: Std. β_{Age}= -0.535, 95% CI: -0.703 - -0.367, p<0.001; SOS: Std. β_{Age}= -0.530, 95% CI: -0.722 - -0.338, p<0.001; QUI: Std. β_{Age}= -0.565, 95% CI:

-0.742 - -0.387, p<0.001). From age 50 to 85 fitted BUA values decline by 48%, QUI by 40%, and SOS by 3%. For women aged 65, 75 and 85 respective predicted probabilities of having reduced bone status are 0.27, 0.67 and 0.92 (OR per year=1.18, 95% CI: 1.08-1.29, p<0.001).

3.2.2. Men—Weak age-related declines are evident for BUA (Std. β_{Age}= -0.179, 95% CI: -0.431-0.073, p=0.163), SOS (Std. β_{Age}= -0.194, 95% CI: -0.405-0.017, p=0.072), and QUI (Std. β_{Age}= -0.199, 95% CI: -0.419-0.021, p=0.077) (Figure S2). From age 50 to 85 fitted BUA values decline by 15%, QUI by 14%, and SOS by 1%. For men aged 65, 75 and 85 respective predicted probabilities of having reduced bone status are 0.25, 0.40 and 0.57 (OR per year= 1.07, 95% CI: 1.01-1.14, p=0.026).

3.2.3. Women vs. men—Controlling for age, men have higher BUA (Std. β_{Male}= 0.371, 95% CI: 0.073-0.669, p=0.015), QUI (Std. β_{Male}= 0.307, 95% CI: 0.010-0.603, p=0.043), and SOS (Std. β_{Male}= 0.239, 95% CI: -0.061-0.539, p=0.118) although the latter effect is not significant. For each qUS parameter age-related decline is greater for women, as indicated by a significant age*sex interaction (Table S4). While sex does not predict probability of having reduced bone status (age-adjusted OR_{Male}= 0.85, 95% CI: 0.36-2.00, p=0.712), women experience higher risk than men with age (age*sex interaction p=0.067, see Table S4D).

3.3. qUS parameters by anthropometrics

3.3.1. Women—qUS parameters are positively associated with weight but not height controlling for age (Table S5). In stepwise models, height is not a significant predictor of any qUS parameter controlling for adiposity and fat-free mass. BUA is associated with adiposity (Std. $\beta_{\%\ body\ fat}$= 0.221, 95% CI: 0.043-0.399, p=0.015, controlling for age and fat-free mass) and fat-free mass (Std. $\beta_{Fat\text{-}free\ mass}$= 0.194, 95% CI: 0.010-0.378, p=0.038, controlling for age and percent body fat). Adiposity but not fat-free mass predicts SOS (Std. $\beta_{\%\ body\ fat}$= 0.333, 95% CI: 0.131-0.534, p=0.001, controlling for age) and QUI (Std. $\beta_{\%\ body\ fat}$= 0.318, 95% CI: 0.139-0.497, p<0.001). While the effect of age on qUS parameters is attenuated after inclusion of anthropometric variables (compared to bivariate analyses in section 3.2.1), age remains the strongest predictor, with effect sizes ranging from 0.42-0.53 SDs (Table S5). Age and adiposity significantly predict probability of having reduced bone status; for women aged 65, 75 and 85 with adiposity 1.5 SDs below (vs. above) the mean of 24.8%, respective predicted probabilities are 0.59 (0.08), 0.90 (0.35), and 0.98 (0.77).

3.3.2. Men—Neither BUA, SOS, QUI, nor probability of having reduced bone status is significantly associated with any anthropometric variable (Table S5). Moreover, no qUS parameter is associated with the ratio of fat-free to fat mass for either sex.

3.3.3. Women vs. men—SOS and QUI positively co-vary with adiposity for women but not men, as indicated by a significant sex*percent body fat interaction controlling for age and age*sex (Table S5, Figure S3). Probability of having reduced bone status is inversely associated with adiposity for women but not men (sex*percent body fat interaction p=0.044, using controls in Table S5: Model C3). No significant sex*fat-free mass interaction was found for any qUS parameter.

3.4. qUS parameters by degree of immune activation and physical limitation

qUS parameters are inversely associated with WBC count controlling for potential confounders (Table 2). Across the range of observed WBC counts (4,500-16,400 cells/μL), fitted BUA values for women (men) decline by 18% (17%), QUI declines by 16% (15%), and SOS declines by 1% (1%) after controlling for significant predictors in Table S5: Model 3 (also see Figure S4). We tested for a WBC count*age interaction but found no significant effect.

Disability score is weakly associated with qUS parameters in the predicted negative direction (Table 2). While disability score is more strongly correlated with qUS parameters for women than men (Tables 1 and S2), no significant sex*disability score interaction was found for any qUS parameter. WBC count is not positively associated with disability score for either sex (Table S2), and no significant WBC count*disability score interaction was found for any qUS parameter.

Figure 1 presents the relative contribution of predictors in affecting qUS parameters (only main effects are shown). Age is consistently the strongest predictor; adiposity and WBC count are the only other predictors with significant effects across all qUS parameters.

3.5. Immune activation within adults over time, and comparison of qUS parameters across immune activation groups

WBC count during medical exams at the time of qUS measurement is moderately correlated with WBC count from the previous medical exam (partial r=0.462, $p<0.001$, controlling for time [in years] between measures). Using a cut-off of >10,000 cells/μL to indicate high WBC count (http://www.nlm.nih.gov/medlineplus/ency/article/003643.htm), 50% of adults have lower counts at both time points while 12% have repeated high counts (38% have either a lower count at time 1 and a high count at time 2, or vice versa). Comparing adults with repeated lower counts to other adults (i.e. those with at least one high count), BUA of the former group is 8% higher than the latter (marginal mean=58.23 vs. 53.57 dB/MHz, $p=0.016$, controlling for age, sex, percent body fat, fat-free mass, age*sex, sex*percent body fat, and time between WBC count measures), QUI of the former group is 6% higher than the latter (marginal mean=72.63 vs. 68.52, $p=0.043$, same controls minus fat-free mass), and SOS of the former group is 0.34% higher than the latter (marginal mean=1512 vs. 1506 m/s, $p=0.128$). Inclusion of disability score does not yield a significant parameter estimate or attenuate the difference in qUS parameters across immune activation groups.

4. Discussion

Among physically active Tsimane forager-horticulturalists, calcaneal qUS indicates reduced bone status for 24% of adults aged 50+. Most population prevalence data are not directly comparable to the current study (because DXA-derived BMD of the spine, femoral neck or total hip is used to diagnose osteoporosis in other populations), but the Tsimane prevalence of reduced bone status is within the range of age-matched Americans with osteoporosis (9%)

and low bone mass (49%) [58]. A recent study comparing calcaneal qUS parameters of Tsimane and American women aged 15-75 found lower values among Tsimane throughout adulthood even after adjusting for reduced Tsimane body mass [31]. Calcaneal BUA also shows greater annual decline for older Tsimane adults (both sexes) compared to older Chinese [59], Dutch [60] and Germans [61]. These population-level differences are apparent despite the fact that Tsimane habitually engage in physically intensive subsistence activities (often without protective footwear, thus increasing ground reaction forces and bone loading), and have lower life expectancy [52, 54]. Together, these results are not consistent with the hypothesis, often supported in studies of industrialized populations [21], that higher activity levels during childhood and early adulthood lead to higher peak bone mass (all else equal), which in turn protects against later age-related bone loss. Future studies of bone structure that standardize methods are needed for valid population-level comparisons, and to permit direct hypothesis tests.

Tsimane men (23%) are as likely as women (25%) to have reduced bone status (Table 1), although age-related decline in qUS parameters is attenuated for men (Table 2; Figures S2-S4). Lower peak bone mass attained by women in early adulthood, maternal depletion of mineral reserves given high fertility and prolonged on-demand breastfeeding [31], and declining sex steroid hormone concentrations accompanying menopause all likely contribute to reduced bone status and greater age-related decline in qUS parameters among Tsimane women.

Adiposity and fat-free mass are positively associated with calcaneal BUA (Table 2; Figure 1), an indicator of trabecular separation and connectivity [55], but only among Tsimane women (Table S5). In energy-limited settings greater adiposity reflects improved nutritional status, and can attenuate rate of bone loss via endocrine mechanisms [62], although here we do not consider effects of hormonal mediators on qUS parameters. Fat-free mass in part reflects physical activity level and associated effects on bone of muscle contractions, which aside from trauma represent the greatest skeletal loads [22, 23]. The relative contribution of adiposity and fat-free mass to BMD in older adulthood is currently debated, with some suggesting that adiposity is more important [38], others suggesting fat-free mass [22, 23, 36] and others assigning similar weight to both tissues [35, 37, 39]. Heterogeneity in previous findings may result from lack of a gold standard in separating effects of fat and muscle tissues (which are collinear but may co-vary in different ways by sex, see Table S2), and from differences across studies in bone strength indices used and skeletal sites measured. For Tsimane women, main effect sizes for adiposity and fat-free mass on BUA are similar (0.22 and 0.19, respectively, see Table S5: Model A2), but only adiposity is associated with SOS and QUI. Reduction in bone status is thus consistently attenuated with greater adiposity among post-menopausal women in this energy-limited and high fertility setting. The fact that neither adiposity nor fat-free mass predicts any qUS parameter among Tsimane men is surprising, and further research is needed to understand sex differences in bone mineral acquisition and maintenance.

WBC count, an indicator of immune activation, is inversely associated with all qUS parameters. This finding is consistent with previous findings linking infection or inflammation to reduced bone mineral status in nonhuman animal models, human clinical samples, population-based studies in industrialized societies, and paleo-pathological samples [41-44, 63]. The few relevant studies in contemporary pre-industrial societies have focused on children and rely on small sample sizes, interview data rather than biomarkers to assess infectious status, and few predictors of bone strength beyond infectious status [47, 48]. The current study is the first to link greater immune activation to reduced bone status *in vivo* among adults in a pre-industrial society. High infectious burden and immune activation, which are often invisible to bio-archaeological inquiry [64], may not only reduce peak bone mass earlier in life (as morbidity often inhibits growth), but may also accelerate rate of bone loss later in life, and increase risks of osteoporosis and fragility fractures. Mechanisms through which greater immune activation may induce net bone resorption are unclear and require further study. WBCs are produced in the bone marrow, and bone marrow monocytes are osteoclast precursors [50]. Aside from long-lived memory lymphocytes, WBCs have short lifespans (a few hours to weeks). Because bone remodeling cycles occur over several months, we expected the inverse association between immune activation and qUS parameters to be stronger when immune activation was persistently high or low. As expected, adults with lower WBC counts at multiple time points had higher adjusted BUA (8%) and QUI (6%) than adults with at least one high count.

Disability score, an indicator of physical limitation and inactivity, does not significantly predict any qUS parameter, nor does it affect associations between other predictors and qUS parameters. While greater physical activity maintains bone structure through various pathways (e.g. by increasing bending strains and bone strength in the direction of movement), BMD gains in response to exercise training in older adulthood are actually small and dependent on adequate nutrition [65]. Limited nutrient availability, including low dietary calcium intake (see section 2.1), may constrain osteogenic responses to high activity although here we lack direct measures of activity level, ground reaction forces, nutrient intake, and cross-sectional bone geometry. Cortical bone of the appendicular skeleton undergoes endosteal resorption and marrow cavity expansion at a faster rate than periosteal apposition (leading to net bone loss with age), but some hypothesize that rate of periosteal expansion is accelerated (attenuating rate of loss) among active foragers due to habitually greater skeletal loading [14, 17, 19, 24]. This could compensate for age-related bone loss by maintaining favorable geometric bone properties and structural resistance to loading and fragility fracture, even with lower bone mass, although this hypothesis has not yet been tested *in vivo* among foragers [24].

4.1. Limitations

First, we use qUS to assess bone status and lack DXA-derived BMD measures which are preferred for diagnostic purposes. Moreover, lacking imaging data (e.g. from quantitative computed tomography) we cannot distinguish between trabecular and cortical bone properties, or examine micro-architecture that can affect bone strength independently of BMD. Second, the study design is cross-sectional which limits our ability to document age-related change in qUS parameters, or establish that hypothesized predictors cause reduced bone status. Third, we use bioelectrical impedance analysis (BIA) to estimate body composition (e.g. fat-free mass) and lack DXA-derived measures; BIA cannot distinguish between intra- and extra-cellular water content and is prone to greater measurement variability due to hydration status (for which we lack data). Fourth, we utilize an indirect measure of physical inactivity, which may partly account for the weak association between inactivity and qUS parameters. We also lack data on strain frequency and intensity which are useful for determining whether certain activities (e.g. carrying heavy loads, running) are more likely to induce osteogenic responses. Fifth, we lack individual-level data on nutrient intake and alcohol use, which may affect associations reported here. Sixth, given our focus on older adults we are unable to determine whether results generalize to younger adults. Lastly, despite an active lifestyle and lack of public health infrastructure, Tsimane are not pure hunter-gatherers and may differ in important ways from ancestral human populations in terms of residential mobility, diet and disease exposures. Yet no population represents the range of experiences across different environments that shaped the evolution of our species over the millennia in which global climates and ecologies fluctuated.

4.2. Conclusion

Reduced bone status characteristic of osteoporosis is relatively common among Tsimane older adults with minimal exposure to osteoporosis risk factors found in industrialized societies. Despite showing relatively high physical activity levels typical of other subsistence populations, energetic limitation and greater immune activation contribute to reduced bone status among Tsimane. Future research that explores whether and how these factors affect bone micro-architecture and fracture risk, and how they interact with age, sex, and physical activity level in determining bone strength is likely to reveal novel insights.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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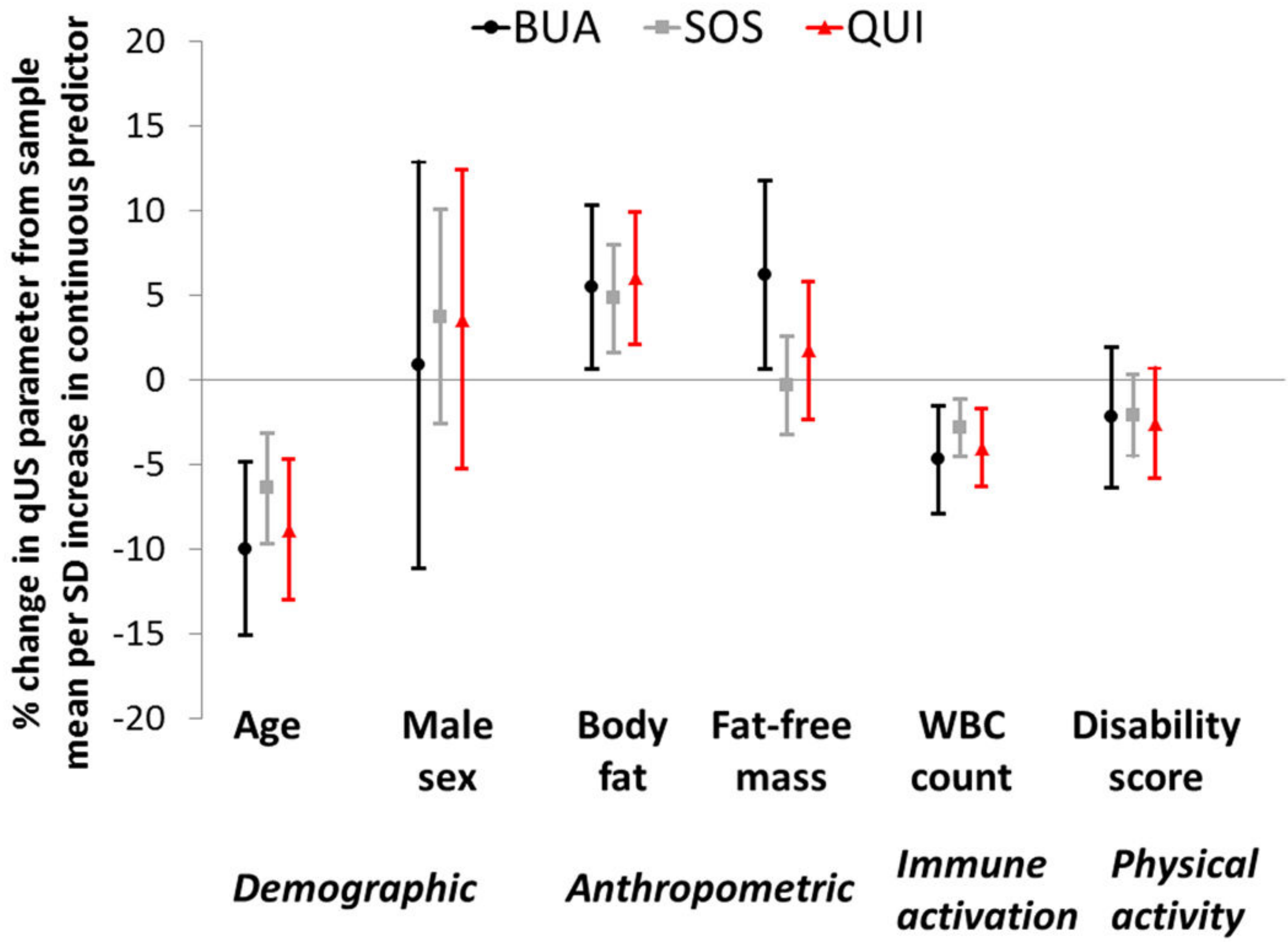

Figure 1.

Percent change (95% CI) in qUS parameters from the pooled sample mean as a function of hypothesized predictors. Estimates are derived from GEE analyses including effects of age, sex, percent body fat, fat-free mass, leukocyte (WBC) count, disability score, time between exercise battery performance and qUS measurement, and age*sex and sex*percent body fat interactions. Effects on SOS are re-scaled (multiplied by 10) given the small change from mean.

Table 1

Sample means (±SDs) by sex and T-score group indicating bone status among Tsimane aged 50+ (n=142)

	FEMALE			*MALE*		
	T-score group			**T-score group**		
Variable	**Higher bone status (n=54)**	**Low bone status (n=18)**	**HvL**	**Higher bone status (n=54)**	**Low bone status (n=16)**	**HvL**
Age (years)	59.7 ± 6.3	69.8 ± 9.9	***	60.9 ± 8.3	66.3 ± 9.5	*
Height (cm)	149.8 ± 3.8	148.0 ± 5.9	*	160.3 ± 4.8	157.2 ± 4.1	*
Weight (kg)	53.8 ± 7.5	45.4 ± 8.3	***	60.3 ± 7.7	59.3 ± 7.6	NS
BMI (kg/m^2)	24.0 ± 3.0	20.7 ± 3.3	**	23.5 ± 3.0	24.1 ± 3.4	NS
Body fat (%)	26.4 ± 6.7	21.0 ± 7.9	**	17.8 ± 6.8	20.9 ± 6.9	NS
Fat mass (kg)	14.6 ± 5.4	9.8 ± 4.8	***	11.1 ± 5.5	12.7 ± 5.8	NS
Fat-free mass (kg)	39.3 ± 3.6	35.5 ± 5.8	**	49.2 ± 4.8	46.7 ± 4.6	^
WBC count (cells/μL) at qUS measurement	9076 ± 2177	9785 ± 2431	NS	9710 ± 2509	10186 ± 2682	NS
Disability score[a]	12.3 ± 4.1	17.6 ± 5.3	***	11.9 ± 5.3	15.9 ± 7.4	^
Ever fractured bone as adult[b] (%)	4	22	*	13	38	*
BUA (dB/MHz)	60.0 ± 11.0	37.2 ± 5.4	***	64.6 ± 10.7	44.3 ± 8.2	***
SOS (m/s)	1516 ± 19	1485 ± 11	***	1522 ± 18	1489 ± 10	***
QUI	75.1 ± 11.4	53.1 ± 4.8	***	79.5 ± 10.9	57.6 ± 4.5	***

[a]Higher score indicates greater degree of physical limitation.

[b]Based on self-report; 1/6 women who fractured a bone received radiographic confirmation from a San Borja physician (the remainder did not visit a physician); 6/13 men who fractured a bone received radiographic confirmation.

For 10 individuals with repeated qUS measures the average value on a given variable was used to calculate means and determine T-score group. HvL indicates higher (T-score > -1.8) vs. low (≤ -1.8) bone status.

Abbreviations: NS, not significant; BMI, body mass index; WBC, white blood cell; qUS, quantitative ultrasonography; BUA, broadband ultrasound attenuation; SOS, speed of sound; QUI, quantitative ultrasound index.

^ p≤0.1

* p≤0.05

** p≤0.01

*** p≤0.001; p-values are from a Mann-Whitney U or χ^2 test

Table 2

GEE analyses of the effect of hypothesized predictors on qUS parameters (intercepts not shown). Model 1 includes demographic, anthropometric and immune activation variables. Model 2 includes disability score and omits fat-free mass if non-significant.

	A) BUA				*B) SOS*				*C) QUI*			
	Model 1		**Model 2**		**Model 1**		**Model 2**		**Model 1**		**Model 2**	
Variable	**Std. β**	**P**	**Std. β**	**P**	**Std. β**	**P**	**Std. β**	**P**	**Std. β**	**P**	**Std. β**	**P**
Demographic												
Age (years)	-0.438	<0.001	-0.404	<0.001	-0.502	<0.001	-0.433	<0.001	-0.505	<0.001	-0.477	<0.001
Sex (male)	0.142	0.563	0.035	0.888	0.444	0.059	0.225	0.132	0.347	0.145	0.311	0.034
Age*Sex	0.322	0.024	0.357	0.035	0.315	0.030	0.393	0.013	0.336	0.015	0.412	0.010
Anthropometric												
Body fat (%)	0.226	0.018	0.221	0.027	0.340	0.002	0.330	0.003	0.313	0.002	0.315	0.001
Sex*Body fat	-0.217	0.143	-0.287	0.044	-0.387	0.023	-0.424	0.004	-0.340	0.032	-0.412	0.003
Fat-free mass (kg)	0.254	0.017	0.252	0.028	-0.023	0.827	-----	-----	0.088	0.404	-----	-----
Immune activation												
WBC count at qUS measurement (cells/μL)	-0.166	0.015	-0.191	0.004	-0.171	0.006	-0.192	0.001	-0.179	0.004	-0.209	<0.001
Physical activity												
Disability score	-----	-----	-0.090	0.297	-----	-----	-0.143	0.085	-----	-----	-0.134	0.113

Time (in years) between exercise battery performance and qUS measurement is also controlled in model 2 (not shown).

Abbreviations: WBC, white blood cell; qUS, quantitative ultrasonography; BUA, broadband ultrasound attenuation; SOS, speed of sound; QUI, quantitative ultrasound index.