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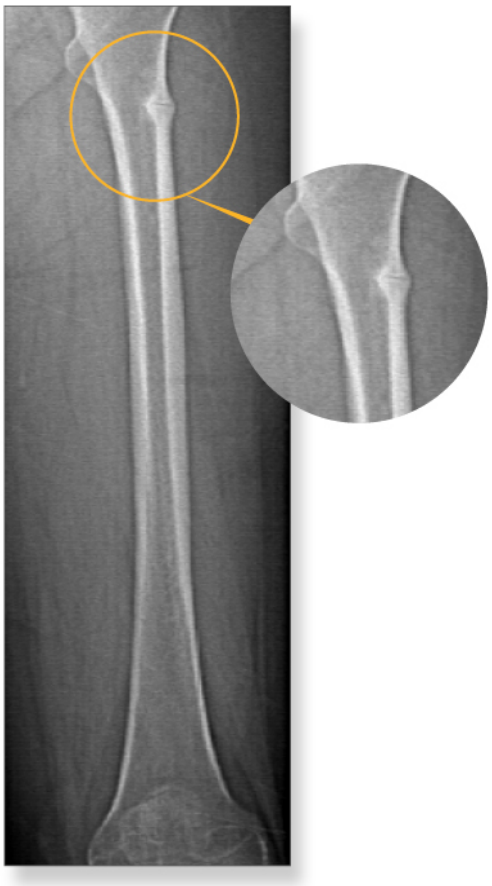

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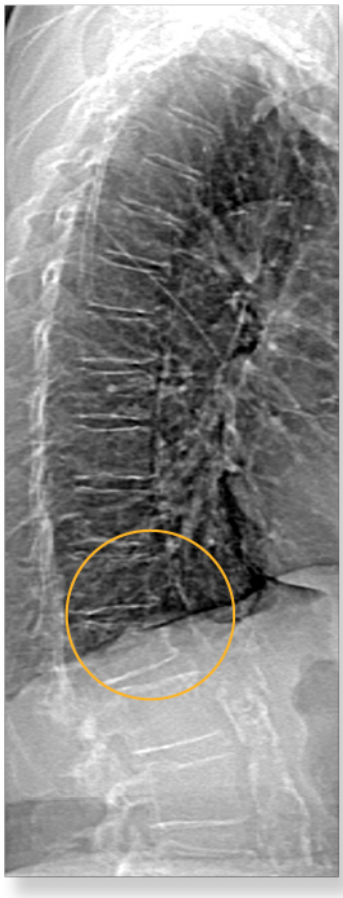

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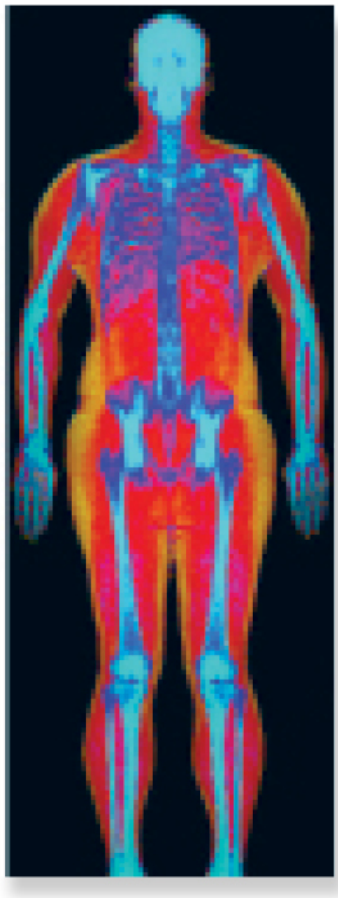

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RESEARCH ARTICLE

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Is There a Causal Relationship between Physical Activity and Bone Microarchitecture? A Study of Adult Female Twin Pairs

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ABSTRACT

The reasons for the association between physical activity (PA) and bone microarchitecture traits are unclear. We examined whether these associations were consistent with causation and/or with shared familial factors using a cross-sectional study of 47 dizygotic and 93 monozygotic female twin pairs aged 31–77 years. Images of the nondominant distal tibia were obtained using high-resolutionperipheral quantitative computed tomography. The bone microarchitecture was assessed using StrAx1.0 software. Based on a self-completed questionnaire, a PA index was calculated as a weighted sum of weekly hours of light (walking, light gardening), moderate (social tennis, golf, hiking), and vigorous activity (competitive active sports) = light + 2 * moderate + 3 * vigorous. We applied Inference about Causation through Examination of FAmiliaL CONfounding (ICE FALCON) to test whether cross-pair cross-trait associations changed after adjustment for within-individual associations. Within-individual distal tibia cortical cross-sectional area (CSA) and cortical thickness were positively associated with PA (regression coefficients [β] = 0.20 and 0.22), while the porosity of the inner transitional zone was negatively associated with PA ($\beta = -0.17$), all $p < 0.05$. Trabecular volumetric bone mineral density (vBMD) and trabecular thickness were positively associated with PA ($\beta = 0.13$ and 0.14), and medullary CSA was negatively associated with PA ($\beta = -0.22$), all $p \leq 0.01$. Cross-pair cross-trait associations of cortical thickness, cortical CSA, and medullary CSA with PA attenuated after adjustment for the within-individual association ($p = 0.048$, $p = 0.062$, and $p = 0.028$ for changes). In conclusion, increasing PA was associated with thicker cortices, larger cortical area, lower porosity of the inner transitional zone, thicker trabeculae, and smaller medullary cavities. The attenuation of cross-pair cross-trait associations after accounting for the within-individual associations was consistent with PA having a causal effect on the improved cortical and trabecular microarchitecture of adult females, in addition to shared familial factors. © 2023 The Authors. *Journal of Bone and Mineral Research* published by Wiley Periodicals LLC on behalf of American Society for Bone and Mineral Research (ASBMR).

KEY WORDS: CORTICAL BONE; HIGH-RESOLUTION PERIPHERAL QUANTITATIVE COMPUTED TOMOGRAPHY; ICE FALCON; OSTEOPOROSIS; PHYSICAL ACTIVITY

Introduction

The risk of fragility fractures decreases by 11%–40% with increasing levels of physical activity (PA) for adults over the age of 40 years.[1] In the Tromsø Study, the most active women and men over 55 years had a 20%–40% lower risk of fractures on the weight-bearing skeleton than sedentary individuals.[2] This could be due to improvements in bone structure, bone

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mass, muscle strength, balance, and reduced risk of falling. Unloading the skeleton, for instance because of limb immobilization, prolonged bed rest, or spinal cord injury, causes bone loss.[3] However, the association of PA with bone mineral density (BMD) and bone microarchitecture depends on activity type, intensity, duration, and loading.[3]

From a cross-sectional study of 15 female tennis players with a mean age of 20 years, the racquet arm had thicker cortices and thicker trabeculae at the distal radius compared with the nonracquet arm.[4] Similarly, a prospective study of 91 female recruits with a mean age of 22 years found increased cortical and trabecular thickness at the distal tibia as a response to 8 weeks of basic combat training.[5] Few studies on the association of PA with bone microarchitecture have included females over 40 years of age and used high-resolution peripheral quantitative computed tomography (HR-pQCT). The mechanisms behind the effect of PA on bone structure for women around menopause are therefore unclear. Knowledge on these associations is needed for optimal fracture prevention for women, as menopause is the single most important factor associated with bone loss and fracture risk.[6]

The aim of this study was to investigate potential reasons for the association of PA with bone microarchitecture at the distal tibia and examine whether the relationship of PA with bone microarchitecture was consistent with causation, shared familial factors, or a mixture of both causation and shared familial factors.

Material and Methods

Subjects

During the period 2008–2011, 324 female twin pairs (199 monozygotic [MZ] and 125 dizygotic [DZ]) aged 27–77 years were included in a baseline study in Melbourne, Australia (Fig. 1).[7-10] They were invited to a follow-up after 3.1 years (range 1.5–4.5) from 2011 to 2013.[11,12] At follow-up, they answered a questionnaire, which included information on weekly hours of PA, and underwent a total body scan. Women who had been treated with hormone replacement therapy and those with movement artifacts on the HR-pQCT scans were excluded, leaving 194 twin pairs for the follow-up visit. In addition, 54 pairs were excluded because of missing total body scans, missing measurements of co-twin, or missing information about PA for at least one of the twins. This left 140 twin pairs (47 DZ and 93 MZ) aged 31–77 years included in the analysis. All participants provided written informed consent, and the study was approved by the Austin Health Human Research Ethics Committee (H2008/03151).

Bone microarchitecture

During follow-up in 2011–2013, images of the distal tibia were obtained using HR-pQCT (XtremeCT, Scanco Medical AG, Brüttisellen, Switzerland, isotropic resolution of 82 μm).[13,14] The scanning was performed on the same side as the nondominant hand. If the participants had a fracture or osteosynthesis material on the nondominant side, the opposite side was scanned. The region of interest was confined at a standardized distance of 22.5 mm from a reference line at the endplate of the distal tibia. Of the 110 slices obtained, the 49 most proximal slices were chosen since the cortex is thicker in this region, allowing an accurate assessment of the cortical porosity.[9] Cortical and trabecular bone microarchitecture was quantified using StrAx1.0 software, which segments the bone into a compact-appearing cortex,

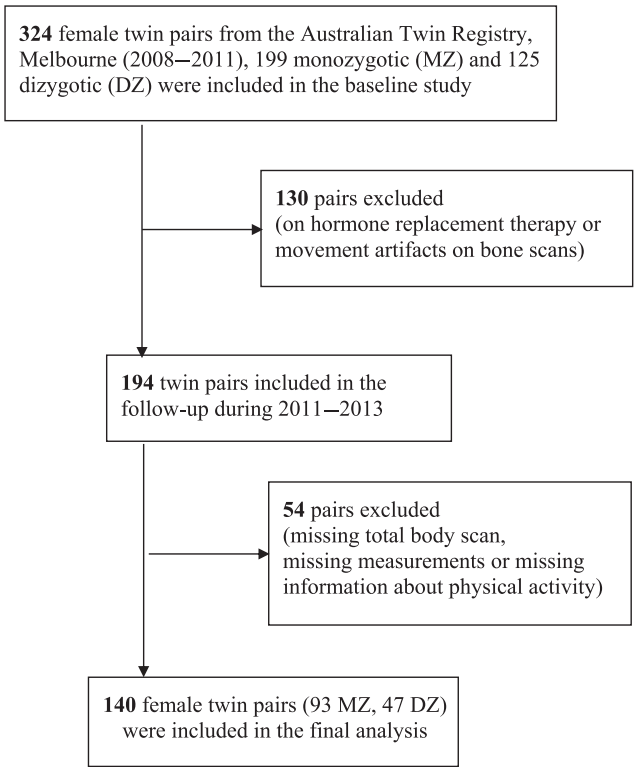

Fig. 1. Participants in a cross-sectional twin study in 2011–2013.

outer and inner transitional zones (TZs), and a trabecular compartment.[15] StrAx1.0 software is density-based, in contrast to Scanco, which is threshold-based.[15] Scanco quantifies the porosity of the compact cortex and includes only totally empty voxels and pores larger than 100 μm in diameter. In contrary, StrAx1.0 includes both the compact cortex and the TZs.[16] StrAx1.0 automatically selects the attenuation profile curves with two plateaus corresponding to the compact-appearing cortex and the trabecular compartment. The S-shaped curve between these two plateaus represents the TZ.[15] Moreover, StrAx1.0 quantifies porosity as a fraction of void regardless of the size of the pores, and it accounts for the partial volume effect by including partially empty voxels, resulting in high porosity values. Studies using Scanco yield lower values of porosity compared to studies using StrAx1.0, and it has been reported that Scanco underestimates porosity by 3%–11%.[17,18]

The following parameters were obtained after processing the images: total bone cross-sectional area (CSA), total volumetric BMD (vBMD), total bone mineral content (BMC), cortical CSA, cortical thickness, porosity of total cortex, compact cortex, outer- and inner TZs, cortical vBMD, cortical BMC, medullary CSA, trabecular thickness, trabecular number, trabecular separation, trabecular vBMD, and trabecular BMC.

Other variables

Height and weight were measured for calculation of body mass index (BMI), and lean body mass was quantified using dual-energy X-ray absorptiometry (Lunar, Madison, WI, USA). Based on self-reported questionnaires, a PA index was calculated by adding weekly hours of leisure-time light (walking, lawn bowls,

light gardening), moderate (social tennis, golf, hiking), and vigorous activity (competitive active sports), giving the hours with moderate and vigorous PA double and triple weight: index = hours of light PA + 2 * (hours of moderate PA) + 3 * (hours of vigorous PA) (Data S1). One hour of light activity is expected to have a weaker effect on bone microarchitecture than 1 h of vigorous activity, which is not accounted for by adding all hours into a total. By giving the moderate and vigorous activity double and triple weight, the intensity is to some extent taken into consideration. This approach was previously used in analyses of PA data from the Tromsø Study.[19,20]

Statistical methods

Initial exploratory analysis indicated that most bone traits had a nonlinear relationship with potential confounders. Standardized residuals were created by running a semiparametric additive regression model for each bone trait against potential confounders age, height, BMI, total tibia CSA, and lean body mass. The absolute value of correlations between potential confounders ranged from $r = 0.00$ to 0.65. Age was included in every model while other potential confounders were taken into account if significant nonlinear or linear relationships were identified. The predictor PA was log transformed and standardized to achieve approximate normality. Outliers in PA were removed by visual inspection of differences between twins. Outliers in the standardized residuals of bone traits were defined as values where the absolute value of the distance from the upper or lower quartile, divided by the interquartile range, was greater than or equal to two, depending on whether the values were at or beyond the upper or lower quartile.

Summary statistics for age, height, weight, BMI, lean body mass, PA, and bone traits at the distal tibia were presented by mean and SD for MZ and DZ twins. The characteristics of MZ and DZ twins were compared using linear regression with zygosity as the binary predictor and the generalized estimating equation (GEE) method,[21] which takes into account correlations within twin pairs.

The within-individual association between the residuals of each bone trait (outcome) and PA (predictor) was also assessed using the GEE method.[9] Bone traits that were significantly associated with PA were further assessed to determine whether there was evidence for a causal relationship underlying the association between the measures or confounding from shared familial factors (genetic or environmental) using the Inference about Causation from Examination of FAmiliaL CONfounding (ICE FALCON) approach.[12,22] This approach allows for further insight into the relationship between PA and bone traits than the within-individual association alone because it uses family data to allow for decomposition of the association into causal and familial contributions. ICE FALCON examines the cross-pair cross-trait association. That is, if the cross-pair cross-trait association attenuates toward zero while adjusting for the within-individual association, the result is consistent with the predictor having a causal effect on the outcome; otherwise, the association is due to familial confounding. In practice, we tested for changes in regression

Table 1. Characteristics of Participants and Distal Tibia Bone Traits, and Comparison of Dizygotic (DZ) and Monozygotic (MZ) Twins Using Generalized Estimating Equations

	All women ($n = 280$)		DZ ($n = 94$)		MZ ($n = 186$)		
	Mean	SD	Mean	SD	Mean	SD	*p*
Age (years)	50.9	8.11	50.5	6.30	51.2	8.89	0.62
Height (m)	1.62	0.06	1.64	0.06	1.62	0.05	0.013
Weight (kg)	69.7	15.1	71.0	15.2	69.0	15.1	0.39
Body mass index (kg/m^2)	26.4	5.37	26.4	5.15	26.4	5.49	0.99
Lean body mass (kg)	39.9	5.04	40.3	4.82	39.6	5.14	0.37
Physical activity index	9.23	8.47	9.51	8.82	9.08	8.31	0.49
Distal tibia bone trait							
Total bone CSA (mm^2)	612	98.4	625	105	605	94.4	0.70
Total vBMD (mg HA/cm^3)	312	53.2	311	56.5	313	51.6	0.97
Total BMC (mg HA)	752	111	768	122	744	104	0.98
Cortical CSA (mm^2)	207	20.4	208	18.6	207	21.2	0.38
Cortical thickness (mm)	2.42	0.24	2.41	0.23	2.43	0.25	0.54
Total cortex porosity (%)	61.2	5.30	61.6	5.80	61.0	5.03	0.28
Compact cortex porosity (%)	42.4	6.09	42.5	6.14	42.4	6.08	0.46
Outer TZ porosity (%)	43.4	5.11	43.3	4.91	43.4	5.22	0.43
Inner TZ porosity (%)	85.7	2.55	85.5	3.03	85.8	2.27	0.45
Cortical vBMD (mg HA/cm^3)	653	67.0	648	73.5	656	63.5	0.31
Cortical BMC (mg HA)	545	77.4	544	77.7	545	77.4	0.36
Medullary CSA (mm^2)	404	88.7	416	95.1	398	85.0	0.58
Trabecular thickness (mm)	0.20	0.01	0.20	0.01	0.20	0.01	0.64
Trabecular number (1/mm)	2.31	0.50	2.35	0.51	2.29	0.50	0.88
Trabecular separation (mm)	1.47	0.27	1.44	0.27	1.49	0.26	0.34
Trabecular vBMD (mg HA/cm^3)	128	31.5	133	34.5	125	29.6	0.26
Trabecular BMC (mg HA)	207	69.0	221	77.9	200	62.9	0.39

Note: The analyses of bone traits were all adjusted for age, as well as height, body mass index, lean body mass, and distal tibia total CSA whenever these covariates were significant.

Abbreviations: BMC = bone mineral content; CSA = cross-sectional area; HA = hydroxyapatite; TZ = transitional zone; vBMD = volumetric bone mineral density.

Table 2. Within-Individual Associations of Distal Tibia Bone Traits with Physical Activity Using Generalized Estimating Equations

Distal tibia bone trait	n[a]	Estimate	SE	p
Total bone CSA (mm^2)	280	0.082	0.065	0.205
Total vBMD (mg HA/cm^3)	280	0.204	0.051	<0.001
Total BMC (mg HA)	278	0.209	0.050	<0.001
Cortical CSA (mm^2)	278	0.204	0.052	<0.001
Cortical thickness (mm)	280	0.220	0.054	<0.001
Total cortex porosity (%)	280	−0.089	0.051	0.081
Compact cortex porosity (%)	274	−0.075	0.053	0.155
Outer TZ porosity (%)	272	−0.093	0.049	0.058
Inner TZ porosity (%)	278	−0.170	0.051	0.001
Cortical vBMD (mg HA/cm^3)	280	0.090	0.050	0.075
Cortical BMC (mg HA)	280	0.213	0.052	<0.001
Medullary CSA (mm^2)	280	−0.223	0.055	<0.001
Trabecular thickness (mm)	276	0.134	0.049	0.007
Trabecular number (1/mm)	280	0.048	0.059	0.420
Trabecular separation (mm)	278	−0.094	0.054	0.080
Trabecular vBMD (mg HA/cm^3)	270	0.135	0.049	0.006
Trabecular BMC (mg HA)	272	0.091	0.049	0.061

Note: The analyses were adjusted for age, as well as height, body mass index, lean body mass, and distal tibia total CSA whenever these covariates were significant.

Abbreviations: BMC = bone mineral content; CSA = cross-sectional area; Estimate = regression coefficient; HA = hydroxyapatite; SE = standard error; TZ = transitional zone; vBMD = volumetric bone mineral density.

[a]The number of participants varied because of exclusion of outliers.

coefficients (β) of the cross-pair cross-trait association from before and after adjustment for the within-individual association. ICE FALCON analyses were conducted using the R (https://www.R-project.org/) package geepack[23] and our own written program, semiparametric additive regression models using the R SemiPar package,[24] while STATA (http://www.stata.com) was used for descriptive and within-individual analyses.

Results

The characteristics and bone traits at the distal tibia for the MZ and DZ female twins are presented in Table 1. The mean age was 50.9 years (SD = 8.1), ranging from 31 to 77 years. DZ twins were slightly taller than MZ twins (1.64 versus 1.62 m, $p = 0.013$). The other characteristics, the PA index, and the bone traits were similar between zygosities.

Associations between PA and distal tibia bone traits are presented in Table 2. Results show that higher levels of PA were associated with higher total vBMD and BMC but not larger total CSA. Higher PA was associated with a larger cortical CSA, thicker cortices, lower porosity of the inner TZ, and higher cortical BMC. Higher PA was associated with a smaller medullary cavity, thicker trabeculae, and higher trabecular vBMD.

Variables with significant within-individual associations in Table 2 were selected for examination of the cross-pair cross-trait association (Table 3). PA in an individual's twin was associated with cortical thickness, cortical CSA, and medullary CSA in that individual. No other cross-pair cross-trait associations were significant.

The causal effect of PA on cortical thickness, cortical CSA, and medullary CSA was assessed using ICE FALCON models. The cross-pair cross-trait association between PA in an individual's twin and cortical thickness in that individual attenuated toward zero and remained significant following adjustment for the within-individual association ($\beta = -0.12$, $p = 0.034$, Table 3). The absolute change in the cross-pair cross-trait association from before and following adjustment for the within-individual association was significant ($\beta = -0.04$, $p = 0.048$). The cross-pair cross-trait association of PA with cortical CSA and medullary CSA became nonsignificant after adjustment for the within-individual association ($\beta = -0.09$ and 0.09, both $p > 0.05$). However,

Table 3. ICE FALCON Analyses for Associations of Distal Tibia Bone Traits and Physical Activity

	Univariable cross-pair cross-trait association			Cross-pair cross-trait association allowing for within-individual association			Absolute change in cross-pair cross-trait association		
Distal tibia bone trait (outcomes)	Estimate	SE	p	Estimate	SE	p	Estimate	SE	p
Cortical thickness (mm)	−0.158	0.060	0.008	−0.118	0.055	0.034	−0.040	0.020	0.048
Cortical CSA (mm^2)	−0.130	0.059	0.027	−0.094	0.056	0.089	−0.036	0.019	0.062
Medullary CSA (mm^2)	0.143	0.064	0.024	0.095	0.058	0.105	0.049	0.022	0.028

Note: p-values (p) were two-sided. The analyses were adjusted for age, as well as height, body mass index, lean body mass, and distal tibia total CSA whenever significant.

Abbreviations: CSA = cross-sectional area; Estimate = regression coefficient; ICE FALCON = Inference about Causation through Examination of FAmiliaL CONfounding, SE = standard error.

the absolute change in cross-pair cross-trait association was marginal for cortical CSA ($p = 0.062$) and significant for medullary CSA ($p = 0.028$).

Discussion

In this study of females with a mean age of 50 years, higher levels of PA were associated with a more robust individual microarchitecture of both the cortical and trabecular compartments of the distal tibia. PA was associated with a larger cortical area, thicker cortices and lower porosity of the inner TZ, and smaller medullary area and thicker trabeculae. Additionally, PA was associated with higher cortical, trabecular, and total vBMD without any change in the total area of the distal tibia. There was a cross-trait cross-pair association between cortical thickness and cortical area and medullary area. Moreover, these cross-pair cross-trait associations attenuated after accounting for the within-individual association. Following the reasoning of the ICE FALCON approach, the attenuation of the associations was consistent with PA having a causal effect on bone microarchitecture. However, the attenuation was modest and did not explain all the cross-trait cross-pair associations, so we conclude that there could also be familial factors contributing to these associations. Familial confounding could include both genetic and shared environmental factors.[8]

In twin studies, as much as 80% of the variance in the lumbar spine and proximal femur BMD are explained by genetic factors.[25-27] For middle-aged female twins, genetic factors accounted for 51%–81% of the variance in cortical and trabecular microarchitecture.[10] Environmental factors are also important for the variance in bone structure, including intake of calcium and vitamin D, use of glucocorticoids, and estrogen levels.[28]

For women with a mean age of 78 years, current PA was associated with larger cortical CSA and thicker cortices, whereas exercise during growth and young adulthood was not independently associated with cortical bone size.[29] Similarly, for men with a mean age of 80 years, current PA was associated with a larger cortical CSA and thicker cortices and trabeculae.[30] We confirmed the findings of increased cortical CSA, cortical thickness, and trabecular thickness in the current study. The association of PA with lower porosity of the inner transitional zone was a novel finding. Moreover, total bone CSA did not change with PA. This suggests that PA has no effect on periosteal apposition in adults but reduces endocortical resorption or increases bone formation on the endocortical bone surfaces, which makes the cortices thicker from the inside. Accordingly, a study using histomorphometry reported increased bone formation on the endocortical surface in mice as a response to loading.[31]

Few studies have been conducted on the possible effect of PA on bone structure at the distal tibia using HR-pQCT in postmenopausal women.[32,33] A randomized controlled trial of a 6-month jumping program found an increase in trabecular thickness in the exercise leg but no other significant changes in bone microarchitecture.[32] The lack of effect of PA on cortical bone in that study could be due to the short duration of the intervention, as the efficacy of exercise programs is best evaluated after a minimum of 1 year.[34] In studies where pQCT images were obtained of both the tibial shaft and the distal tibia, the results were ambiguous.[35-37] From a cross-sectional study that compared twins who were discordant for leisure time PA during the last 30 years, active twins had larger cortical CSA, thicker cortices, and higher trabecular vBMD at the tibial shaft than their inactive co-twin.[36] Another cross-sectional study reported increased cortical thickness and higher total BMC at the tibial shaft with moderate to vigorous activity in older adults.[37] A third cohort study reported increased cortical area and total area at the tibial shaft with high-impact PA in women and men with a mean age of 81 years, while there were no changes in the bone structure of the distal tibia.[35] The discrepancy between the results of these studies may be due to differences in study design, sample size, and responses of the tibia site that was measured, which depends on the type of activity. The tibial shaft contains almost exclusively cortical bone and a thick cortex, while the distal tibia contains mainly trabecular bone and a thin cortex. Biomechanical studies have suggested that the shaft is mainly adapted to bending and/or torsion, while the distal part mainly adapts to compression.[38]

Results from this study supports recommendations of PA to be one of the interventions for preventing fragility fractures. In contrast to antiosteoporotic drugs, PA is low-cost, has no side effects, and reduces the risk of falls.[39] It has been argued that exercise should be of high intensity and with progressive resistance to achieve improvements in bone structure.[40,41] The use of BMD as a proxy for bone strength might underestimate the effect of PA.[39] The use of HR-pQCT, which allowed for examination of the bone microarchitecture, was one of the strengths of this study. Another strength was the ability to test consistency with causation in cross-sectional data using the ICE FALCON method. A limitation was the self-reported PA using nonvalidated questionnaires, which could have caused inaccurate estimates due to recall bias. The PA index does not differentiate between bone loading activities, such as running versus swimming, and includes leisure-time not occupational PA. This crude method for quantification of PA may have diluted the associations with bone traits, and the true association of bone-specific PA with bone microarchitecture might be stronger. Using a validated bone-specific physical activity questionnaire (BPAQ) would be a better method of determining historical PA exposure of relevance to bone in future studies.[42] Alternatively, pedometers and accelerometers, which are objective measures of the number of steps, could be used. However, pedometers and accelerometers are not able to quantify the intensity of the PA or provide contextual information, and they are expensive.[43] In addition, they can induce reactivity bias. Additional limitations of our study were the moderate sample size, which could have caused a lack of statistical power. The inclusion of women whose ages fell within a wide range and who were of varying menopausal status might also have diluted the effect of PA on bone microarchitecture, as individuals with the lowest bone mass may have the largest response to mechanical loading.[39,44] However, the analyses were adjusted for age, and the results were similar when adjusted for age or menopausal status. Finally, voluntary participants might be prone to healthy selection bias, which affects the generalizability of the results.

In conclusion, increasing levels of PA were associated with improved cortical and trabecular microarchitecture in adult females with a mean age of 50 years. We confirmed that increasing levels of PA were associated with cortical cross-sectional area, cortical thickness, and trabecular thickness. A novel finding was the association of PA with lower porosity of the inner transitional zone. The attenuation of the cross-pair cross-trait associations after accounting for the within-individual associations were consistent with PA having a causal effect on the improved bone

microarchitecture, in addition to unmeasured familial factors that influence both bone microarchitecture and PA.

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Author Contributions

Frida Igland Nissen: Conceptualization; writing – original draft; methodology; validation; visualization; writing – review and editing; investigation; resources. **Vivienne Esser F C:** Data curation; methodology; formal analysis; writing – review and editing; writing – original draft; conceptualization; software. **Minh Bui:** Methodology; writing – review and editing; formal analysis; supervision; conceptualization; software; data curation. **Shuai Li:** Data curation; supervision; formal analysis; writing – review and editing; methodology; conceptualization; software. **John Hopper L:** Data curation; funding acquisition; conceptualization; writing – review and editing; formal analysis; supervision; methodology; software. **Åshild Bjørnerem:** Conceptualization; investigation; funding acquisition; writing – original draft; methodology; validation; visualization; writing – review and editing; project administration; supervision; data curation; resources. **Ann Kristin Hansen:** Conceptualization; investigation; writing – original draft; methodology; validation; visualization; writing – review and editing; supervision.

Peer Review

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1002/jbmr.4826.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Disclosures

The authors have no conflicts of interest to declare.

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