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Leisure time physical activity and bone mineral density preservation during the menopause transition and postmenopause: a longitudinal cohort analysis from the Study of Women's Health Across the Nation (SWAN)

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Summary

Background Whether greater leisure time physical activity (LTPA) is associated with less bone mineral density (BMD) loss during the menopause transition (MT) remains an open question. We hypothesized that: 1) larger increases in LTPA from pre-/early perimenopause (period 1) to late perimenopause/postmenopause (period 2) would be associated with a slower period 2 BMD loss rate; and 2) greater entire-study LTPA levels would be associated with better final absolute BMD (g/cm^2).

Methods Data were from of the Study of Women's Health Across the Nation (1996–2017). Exclusions were: bone beneficial medications, inability to identify start of the MT, and extreme BMD change rates. LTPA measures were a validated ordinal scale and number of metabolic equivalents per hour per week (MET hr wk^{-1}) from sport/exercise. Multiply adjusted, linear regression models estimated: 1) BMD decline rate (annualized %) as a function of LTPA change; and 2) final BMD as a function of entire-study LTPA.

Findings Median [p25, p75] MET hr wk^{-1} were 4.2 [0.9, 10.1] and 4.9 [1.4, 11.2] in periods 1 and 2, respectively; walking was the commonest activity. In adjusted models (N = 875), greater increases in LTPA ordinal score and MET hr wk^{-1} were statistically significantly associated with a slower decline in femoral neck (FN) BMD. Larger entire-study averages of each LTPA measure were statistically significantly related to better final FN and lumbar spine BMD levels.

Interpretation Findings suggest that LTPA, at modest levels, mitigate MT-related BMD decline and even small increases in intensity, duration or frequency of common activities may lessen bone loss at the population level.

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Keywords: Menopause; Physical activity; Bone mineral density; Women

Introduction

Low bone mass and osteoporosis occur in >158 million adults worldwide, disproportionately affecting women, in part due to menopause-related bone loss.[1] Pharmacological interventions deter postmenopausal bone loss and diminish osteoporotic fracture risk, but their uptake for primary prevention is limited by long-term safety concerns.[2] Thus, there remains an avid interest in non-pharmacological strategies, such as physical activity (PA), to target bone loss.[3] In addition to its osteoanabolic

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Research in context

Evidence before this study

Whether greater leisure time physical activity (LTPA) is associated with less bone mineral density (BMD) loss during the menopause transition (MT) remains an open question. We searched PubMed during the interval of Jan 1, 2000, to May 1, 2022 for primary research articles (longitudinal cohort studies and randomized, controlled trials [RCTs]), reviews, meta-analyses, and guidelines. Search terms were "menopause", "physical activity", "bone mineral density", "osteoporosis", and "gender differences"; articles were restricted to English language. Overall, in premenopausal and postmenopausal women, RCTs find that physical activity (PA) benefits bone, and that the degree of benefit is greater in the former than in the latter. These RCTs are, however, limited by small sample sizes and short durations. No RCTs have examined whether PA can prevent BMD loss specifically during the MT, and the results from scant longitudinal cohorts studies of this topic are inconclusive. Because life-stage influences the degree to which PA is bone trophic, lack of evidence during the MT is an important omission.

Added value of this study

Our multi-ethnic, longitudinal study, which spans ~2 decades and has repeated measures of LTPA and BMD, can quantify LTPA-BMD relations across lifestage, within women, in a single cohort. Our analysis newly finds that a greater increase in LTPA during the MT is statistically significantly associated with slower femoral neck BMD decline. We also demonstrate that greater entire-study average levels of LTPA are statistically significantly related to greater final femoral neck and lumbar spine BMD levels, independent of change in LTPA during the MT. Absolute levels of LTPA were modest: the median entire-study MET hr wk^{-1} was 4.9 (IQR 8.9) and the commonest form of LTPA was walking. Thus, the unique contributions of the current study are its findings that greater LTPA is associated with less BMD loss during the MT and that this association is evident at low levels of LTPA.

Implications of all the available evidence

Our findings that more LTPA is related to BMD preservation concur with a large body of interventional research that supports optimizing physical activity, but generally at levels higher than those of the participants in our study, to minimize bone loss in postmenopause. However, there are practical barriers to optimally maximal interventions targeted at bone loading, such as lack of access to proper training, physical limitations, competing responsibilities, and personal activity preferences. Thus, while identifying the ideal bone loading PA regimen that prevents bone loss remains an important research priority, the current study suggests that it may be feasible to lessen menopause-related bone loss at the population level with even small increases in the intensity, duration, or frequency of common activities.

potential, the attractiveness of PA as a health promotion tool is amplified by strong evidence that it is effective in the prevention of several other common, chronic conditions such as cardiovascular disease, diabetes, and cancer.[4]

Varied forms of moderate-to-high intensity exercise interventions result in bone mineral density (BMD) gains in premenopausal women and lessen BMD loss in postmenopausal women.[5–10] While findings from randomized controlled trials (RCTs) argue that PA benefits bone, individual RCTs are limited by small sample sizes and short durations.[5–10] To our knowledge, there have been no trials of PA for the prevention BMD loss specifically during the transition from pre-to postmenopause. Yet, because the reproductive stage influences the degree to which PA is bone trophic, the absence of such studies is an important omission.[11,12]

Observational studies are positioned to make substantial contributions to gaps in knowledge about the relation between PA and bone across women's life span. They can examine exposures that are impractical to test in an RCT, such as maintenance of habitual PA, relevant because RCTs find that longer duration interventions are more likely to have a positive bone effect than are shorter ones.[10,13] However, extending RCTs beyond a few years is impracticable. Further, the differential effect of PA on bone depending on female life stage is a difficult thesis to assess in a single RCT.[12] The relevance of a life stage is illustrated by comparing results from separate interventions conducted in various age ranges. The greatest occurs in girls and adolescents, in whom exercise can increase BMD by up to 8% compared to non-exercise.[14] In contrast, in postmenopause, exercise diminishes BMD loss compared to the control condition, rather than increasing BMD.[6,12]

The overarching aim of this analysis is to explore the association between leisure time physical activity (LTPA), at the levels observed in the Study of Women's Health Across the Nation (SWAN), and BMD during the transition from pre-to postmenopause. Because SWAN's repeated measures of LTPA and BMD span ~2 decades and cross reproductive stages, it can quantify the relations between long-term LTPA and BMD across lifestage, within women, in a single cohort. In pre- and early perimenopausal women with mean age 43 years, SWAN's baseline, cross-sectional analysis found a graded, positive, relation between LTPA and BMD level.[15] The present study builds on this by investigating the hypothesis that women with greater longitudinal increases in LTPA experience slower BMD loss during the MT and postmenopause (Hypothesis 1). Moreover, based on the demonstrated association between greater

LTPA and better baseline BMD, and our thesis that increasing LTPA over time will diminish the menopause-related BMD loss, we also propose that a greater average level of LTPA during the entire study (pre-menopause through postmenopause) will be associated with a greater final BMD level (Hypothesis 2).

Methods

Study design and participants

SWAN is a seven-site, longitudinal cohort study of the MT conducted in the US. Baseline eligibility criteria were age 42–52 years, intact uterus and at least one ovary, not using hormone therapy (HT), ≥1 menstrual period in the 3 months prior to screening, and self-identification as Black, Chinese, Hispanic, Japanese or White (N = 3302).[16] All sites enrolled White, 4 enrolled Black, and the remaining 3 enrolled Chinese, Hispanic or Japanese women; 5 sites measured BMD, yielding 2413 bone cohort participants. This analysis uses 17 waves of data from women who experienced natural menopause, from baseline (1996) through the 16th follow-up (2017). Exclusion criteria were: use of bone beneficial medication (systemic HT, bisphosphonates, raloxifene, calcitonin, parathyroid hormone, calcitriol, or postmenopausal tamoxifen), inability to define the start of the MT (i.e., participant transitioned directly from premenopause to postmenopause), and BMD loss rate outliers (uppermost or lowest 2.5% of BMD decline distribution; applies to change-in-BMD outcome model only). Follow-up was censored at first report of any bone beneficial medication. Inclusions, applied after exclusion and censoring criteria, were: BMD available at the same bone site (lumbar spine [LS] or femoral neck [FN]) at least once in period 1 (premenopause and early perimenopause) and at least once in period 2 (late perimenopause and postmenopause) and LTPA measured at least once in each period. Participants may have had some missing measures of LPTA or BMD, but were included if they met the above criteria. After applying inclusions and exclusions, there were no missing covariates. Participants gave written informed consent and all sites obtained IRB approval.

Outcomes

We acquired BMDs with Hologic densitometers (Hologic, Inc., Waltham, Massachusetts). Cross-site densitometer calibration and BMD quality control program have been described.[17] Short-term in vivo measurement variability was 0.014 g/cm^2 (1.4%) for the LS and 0.016 g/cm^2 (2.2%) for the FN. Outcomes for hypothesis 1 are BMD decline rate at the LS and FN (% per year) in late perimenopause and postmenopause (period 2), because statistically significant bone loss is measurable in late perimenopause.[18] Period 1 ends and period 2 starts at the first visit in late perimenopause; period 2 continues until end of study. If a participant did not have a late perimenopause visit, we designated her last visit in early perimenopause as the switch from period 1 to period 2. Denoting first and last BMD dates by Time0 and TimeL, using T1 for the date when period 1 ends and period 2 starts, annualized decline rate (% per year) was calculated as 100*(BMD at Time1 – BMD at TimeL)/[(BMD at Time 1)*(TimeL – Time1)].

Independent variables

We assessed LTPA at baseline and visits 3, 5, 6, 9, 12, 13, and 15 with the sport/exercise domain of the Kaiser Physical Activity Survey (KPAS), a past-year recall questionnaire. Using age-adjusted Spearman correlations, the KPAS sport/exercise domain was criterion validated against activity logs (0.73), accelerometers (0.56), maximal oxygen consumption (0.76) and percent body fat (–0.59). Its one-month test-retest reliability estimated using intra-class correlation was 0.84.[19] Our analysis uses two LTPA exposure variables. First, the original sport/exercise scale (referred to herein as the LTPA ordinal score), which ranges from 1 (lowest) to 5 (highest) and is calculated from frequency of engaging in sports/exercise, frequency of sweating from during sport/exercise, self-rated amount of recreational PA compared to similarly aged women, and frequency and duration of up to two sports/exercises. Second, we computed leisure-time metabolic equivalents per hour per week (MET hr wk^{-1}) from the two reported sports/exercises.[20] METs quantify the ratio of an activity's metabolic cost to the metabolic rate at rest; one MET is one kcal/kg/hour, approximately the amount of energy used when sitting quietly. LTPA ordinal score permits comparison to SWAN's baseline analysis of PA and BMD and MET hr wk^{-1} facilitates the translation of findings. We computed the average level of each LTPA exposure separately for periods 1 and 2 (for hypothesis 1) and during all visits (for hypothesis 2). We calculated the average LTPA with the area under the LTPA curve (AUC) divided by interval length, using the trapezoidal rule. Entire-study average LTPA was (Time0 to TimeL AUC)/(TimeL – Time0); period 1 average LTPA was (Time0 to Time1 AUC)/(Time1 – Time0); period 2 average LTPA was (Time1 to TimeL AUC)/(TimeL – Time1). LTPA was available at Time0 for all women, but not at exactly Time1 or TimeL for everyone. If LTPA was not measured at TimeL, we assumed that it was the same as the last measurement between Time1 and TimeL. If LTPA was not measured at Time1, we interpolated it linearly, using last preceding and first following observations. Change in LTPA was calculated as a difference: average LTPA in period 2 minus average LTPA in period 1.

Covariates

Education, household income, and household composition were assessed at baseline and used to capture the socio-economic status of the sample. We

collapsed education level into four categories: high school or less, some college, baccalaureate, or at least some postgraduate education. We calculated the family-adjusted poverty-to-income ratio (FPIR), which indexes total household income to the number of householders and the census-defined poverty level by geographic region. An FPIR of 3, for example, means that the total household income, adjusted for the number of householders, is three times greater than the census-specific poverty level. Other than age, all covariates used in multivariable models were measured at each visit. Standardized questionnaires and interviews ascertained age (years); race/ethnicity (Black, Chinese, Japanese, White); menstrual bleeding (premenopausal [regular menses], early perimenopausal [menses within 3 months, but less predictable], late perimenopausal [≥3 months but <12 consecutive months of amenorrhea] or postmenopausal [no menses for ≥12 consecutive months]; bone adverse medication use (yes/no [yes if any: GnRH agonists, aromatase inhibitors, oral glucocorticoids, or anti-seizure medications]); current use of calcium, vitamin D, cigarettes or alcohol (any/none of each). SWAN measured weight (kilograms) and height (meters) using calibrated scales and stadiometers.

Statistical analysis

We estimated the correspondence between the entire-study ordinal LTPA scale and the entire study MET hr wk^{-1} in two ways: using the Spearman rank correlation coefficient and computing the median [p25, p75] MET hr wk^{-1} by discrete categories of the ordinal scale. We compared values of all covariates among those in the analysis sample to values of those excluded from it using t-tests or chi-squared tests.

For hypothesis 1, we constructed separate simple, linear regression models for each dependent variable, annualized LS and FN BMD decline rate (% per year during period 2). Models were adjusted for baseline age; baseline MT stage (premenopause or early perimenopause); SWAN site; race/ethnicity; proportion of visits (entire study) at which participant used calcium supplements, vitamin D supplements, bone detrimental medications, cigarettes or alcohol; average BMI (in the entire study); amount of BMI change between initial and last visit, and proportion of visits during which BMI was ≥41 kg/m^2. We controlled for BMI ≥41 kg/m^2 because LOESS-smoothed plots of baseline BMD (both bone sites) *vs.* BMI demonstrated a linear relation for BMI<41 kg/m^2, but a flatter curve when BMI ≥41 kg/m^2 (data not shown). To assess the influence of starting LTPA level, we subsequently added the entire-study average LTPA to the model. When analyzing change, adjusting for starting level leads to spurious results in the presence of measurement error; average LTPA adjustment avoids this problem and results in a conservative bias.[21,22]

Hypothesis 2 outcomes were final value (TimeL) of LS and FN BMD (g/cm^2). We constructed separate linear regression models for study-final LS and FN BMD (g/cm^2); the primary predictor was entire-study average LTPA. We used a parallel series of models as those used to test hypothesis 1, with two modifications: as initial covariates, we used age at final BMD (not baseline) and did not adjust for baseline MT stage. To disaggregate the contributions of entire-study LTPA and change in LTPA, we additionally adjusted models for LTPA change. To assess for departures from linearity, we added cubic and quadratic terms to fully-adjusted models for both hypotheses; each higher order term p-value was >0.05 (data not shown).

To assess the sensitivity of findings to outliers, we conducted a sensitivity analysis: we tightened the criteria for outliers from the top and bottom 2.5% of the distribution of the annualized BMD change rate to top and bottom 1% of this distribution. To describe the trajectories of the exposure variables over time, we stratified the sample into those whose LTPA ordinal score increased (average score period 2 > average score period 1) and those whose score decreased (average score period 2 < average score period 1). Then we created a LOESS plot of LTPA ordinal scale scores by study visit in these two groups. We followed the same procedure for MET hr wk^{-1} values. We used Stata SE version 16.1 (StataCorp LP, College Station, TX) to conduct analyses.

Role of the funding source

The funder had no role in study design, data collection, analysis, interpretation, and manuscript writing.

Results

Figs. 1 and 2 display the derivation of the analysis samples (N = 875 for change-in-BMD outcome and N = 903 for final BMD outcome). Baseline LTPA and BMD values did not differ between those included vs. excluded from the analysis (each p ≥ 0.33, data not shown). At baseline, the average age of participants was 45.7 years (SD, 2.5), mean BMI was 27.4 kg/m^2 with standard deviation (SD) of 6.8, 68% of the sample was premenopausal, and the remainder early perimenopausal. Ethnic/racial groups were Black (N = 246 [27%]), Chinese (N = 126 [14%]), Japanese (N = 123 [14%]), and White (N = 408 [45%]). Educational levels were high school or less, 21%; some college, 31%; college degree, 24%; and at least some postgraduate education, 24%. The median [p25, p75] family-adjusted poverty-to-income ratio (total household income adjusted for number of occupants, indexed to poverty level by geographic region and calendar year) was 3.1 [1.8, 4.8] (Table 1). Initial LS and FN BMD averaged 1.08 (SD, 0.14) g/cm^2 and 0.85 (SD, 0.13) g/cm^2, respectively. Comparison of values of all covariates among those in the analysis sample to values in those

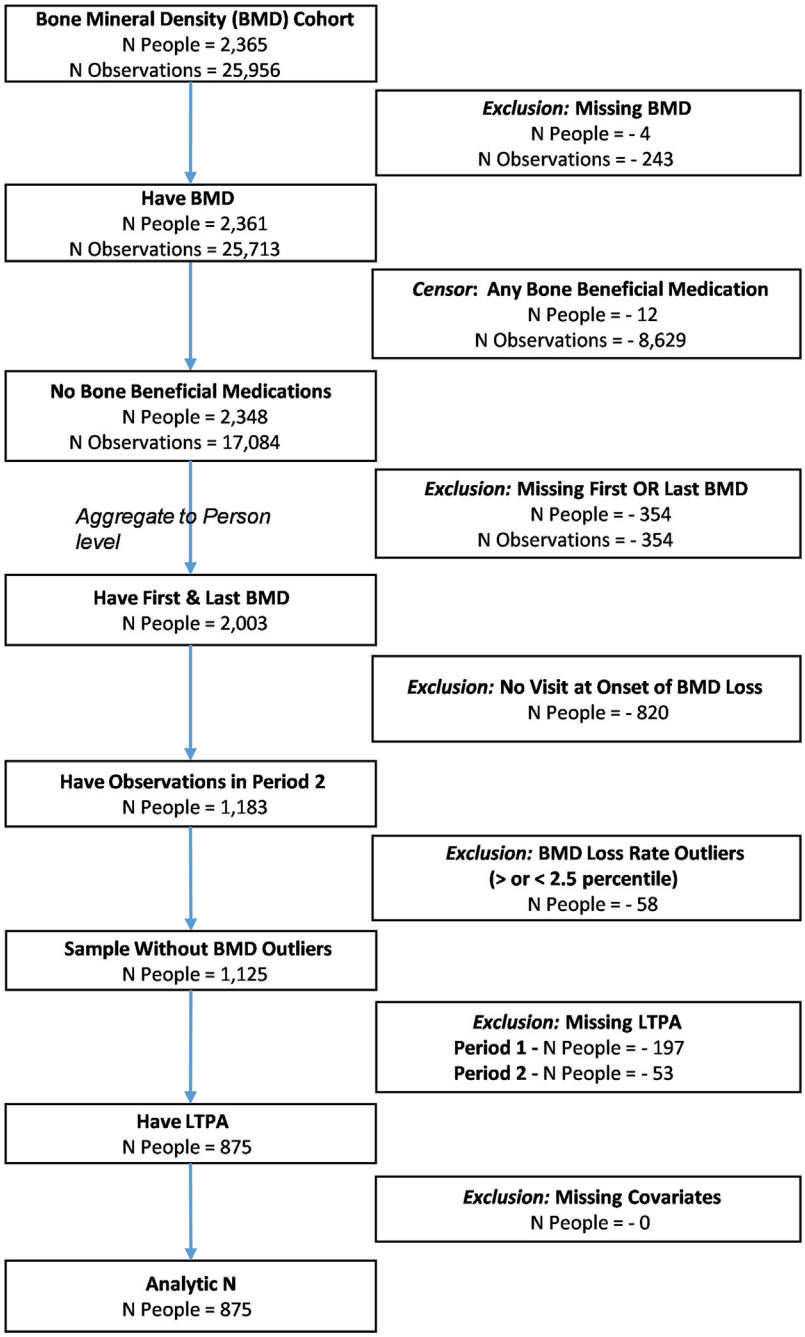

Fig. 1: Derivation of analytic sample for the change-in-BMD outcome.

excluded from it revealed several statistically significant differences, but these differences were small in magnitude (Table 1). For example, baseline age was 45.5 ± 2.5 years in the analysis sample and 46.0 ± 2.7 years in those excluded ($p < 0.001$).

Mean number of years between first and last observation was 16.2 (SD, 4.5), time elapsed in period 2 (late perimenopause and postmenopause) was 10.0 years (SD, 4.6), and years observed in postmenopause-only averaged 8.0 (SD, 4.1). During period 2, crude mean annualized BMD decline rate was 1.41% (SD, 1.32%) at the LS and 1.43% (SD, 1.13%) at the FN. At the final observation, crude mean values of LS and FN BMD were 0.96 g/cm^2 (SD, 0.17) and 0.74 g/cm^2 (SD, 0.13), respectively.

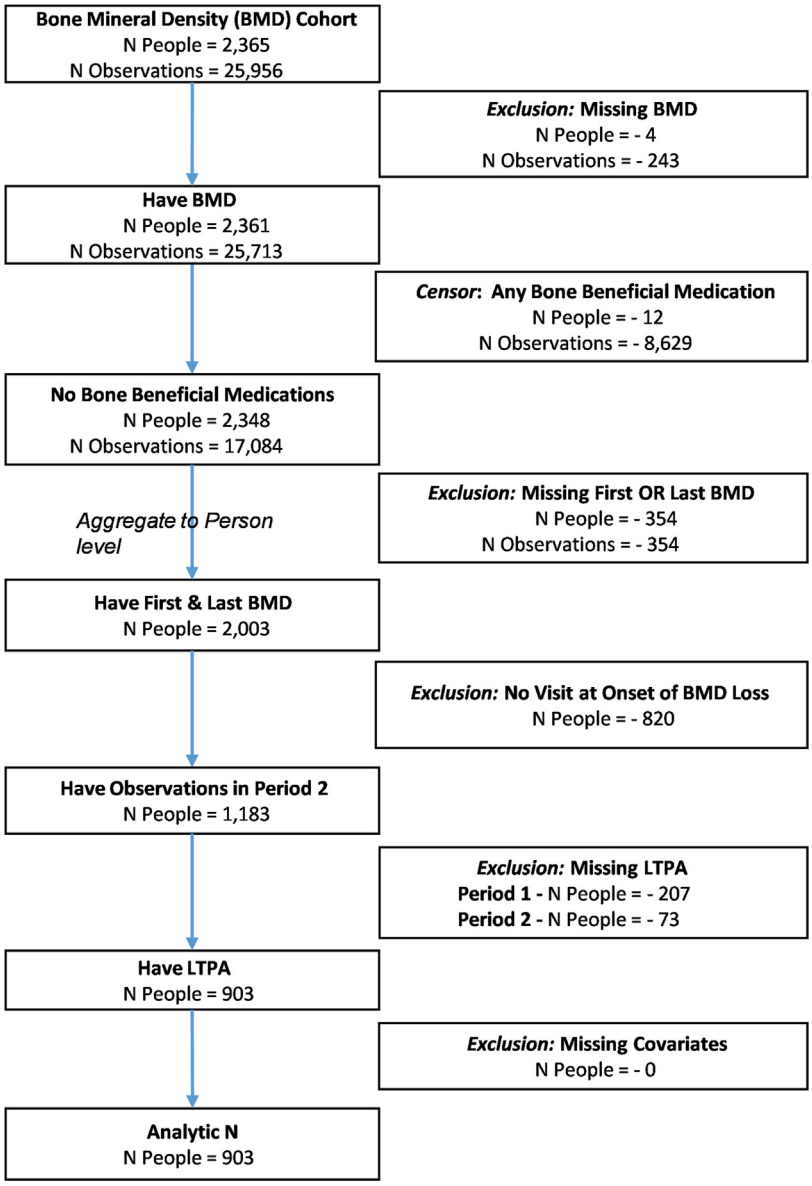

Fig. 2: Derivation of analytic sample for the final BMD outcome.

During each period and the entire study, LTPA ordinal score values were normally distributed, while MET hr wk^{-1} distributions were non-normal (Table 2). Entire-study average values of the LTPA ordinal score and MET hr wk^{-1} were strongly correlated (Spearman's Rho = 0.86). In this sample, the median [p25, p75] MET hr wk^{-1} in the LTPA ordinal score categories of 1 ± .5, 2 ± .5, 3 ± .5 and 4 ± .5 were: 0.08 [0, 0.57], 1.96 [0.68, 3.79], 6.22 [3.98, 9.29], and 15.96 [11.86, 21.48], respectively. Mean change in the LTPA ordinal score from period 1 to period 2 (0.05) was small; however, SD of the change score was large, indicating substantial between-women variability. Similarly, for MET hr wk^{-1}, median change (0.53) was small, but its IQR was large. Supplemental Figs. S1 and S2 illustrate the trajectories of the PA exposure variables over time, separately in women whose PA increased and in those whose PA decreased from period 1 to period 2.

Women could report up to two sports/exercises: during the entire study, of the activities listed first, the five commonest were walking (35%), calisthenics (6%) swimming (5%), bicycling/spinning (5%), and stretching/yoga (4%). Considering period 1 and period 2 separately, walking, calisthenics, and swimming were the top three sports in each and prevalences did not differ from those during the entire study.

Characteristic[a]	Analysis sample[b] (N = 875)	Remainder of bone cohort[c] (N = 1490)	P
Age (years), *Mean (SD)*	45.5 (2.5)	46.0 (2.7)	<0.001
Body Mass Index (kg/m^2), *Mean (SD)*	27.4 (6.7)	27.9 (7.2)	0.07
Menopausal status, %			<0.001
Premenopausal	67%	46%	
Early perimenopausal	33%	53%	
Late perimenopausal		0.2%	
Early postmenopausal		0.1%	
Race/ethnicity, %			<0.001
Black	45%	53%	
White	27%	29%	
Chinese	13%	10%	
Japanese	14%	9%	
Education, %			0.037
≤High school	21%	22%	
Some college	31%	36%	
Baccalaureate degree	24%	20%	
> Baccalaureate education	24%	22%	
Family poverty-to-income ratio, *Mean (SD)*	3.66 (2.65)	3.89 (2.80)	0.06
LTPA ordinal score, *Mean (SD)*	2.67 (1.03)	2.71 (1.02)	0.36
METhr wk^{-1}, *Median [p25th, p75th]*	3.6 [0.1, 11.5]	3.6 [0.3, 10.7]	0.74
Lumbar spine BMD, *Mean (SD)*	1.08 (0.14)	1.08 (0.14)	0.54
Femoral neck BMD, *Mean (SD)*	0.846 (0.134)	0.846 (0.136)	0.96

[a]Premenopausal defined as having regular menses and perimenopausal defined as having menses within 3 months, but less predictable than previously; family-adjusted poverty-to-income ratio (FPIR) indexes participant's total household income to the number of householders and the census-defined poverty level, by geographic region; self-reported leisure-time physical activity (LTPA) based on the Kaiser Physical Activity Survey (KPAS) sport/exercise domain ordinal scale, ranging from 1 (lowest) to 5 (highest); number of metabolic equivalents per hour per week (MET hr wk^{-1}) estimated from each participant's top 2 reported sports/exercises. [b]Analysis sample N = 875 for the change-in-bone mineral density (BMD) outcome and N = 903 for final BMD outcome. Values shown for the analysis sample are generated from the change-in-BMD outcome analysis sample. [c]Exclusion criteria were: use of any bone beneficial medication (systemic hormone therapy, bisphosphonates, raloxifene, calcitonin, parathyroid hormone, calcitriol, or postmenopausal tamoxifen), inability to define the start of the menopause transition (i.e., the participant transitioned directly from premenopause to postmenopause). For the change-in-BMD outcome model only, an additional exclusion was a BMD loss rate in the uppermost or lowest 25% of the BMD decline distribution.

Table 1: **Baseline characteristics of the analysis sample and the remainder of the bone cohort participants who were ineligible for the analysis, Study of Women's Health Across the Nation (SWAN).**

Women with larger increases (from period 1 to period 2) in average LTPA, estimated by either the ordinal score or MET hr wk^{-1}, had slower FN BMD decline during period 2 (Table 3). Adjusted for baseline age, baseline MT stage, race/ethnicity, time-varying BMI, use of calcium supplements, vitamin D supplements, bone detrimental medications, cigarettes, and alcohol, a one unit larger increase in the LTPA ordinal score was associated with 0.211% per year slower FN BMD decline ($p < 0.001$). Per each MET hr wk^{-1} greater activity increase, annualized rate of BMD decline was 0.021% slower ($p = 0.002$). The associations of (period 1 to period 2) change in the ordinal score and MET hr wk^{-1} with FN BMD decline rate in period 2 were unaltered by additionally controlling for entire-study average of each LTPA exposure. We did not identify a statistically significant association between change in LTPA ordinal score or change in MET hr wk^{-1} and LS BMD decline rate (Table 3).

Fig. 3 illustrates fully adjusted model-predicted relations between change in LTPA (periods 1 to 2) and rate of FN BMD decline in period 2. Compared to the period 2 FN BMD loss of 1.4% per year in women whose LTPA did not change, the loss rate was 1% per year in those whose LPTA ordinal score increased by two units (Fig. 3a) and 1.3% per year in women whose MET hr wk^{-1} went up by eight (Fig. 3b).

Greater levels of average entire-study LTPA were positively related to better final absolute FN and LS BMD values (Table 4). Each one unit greater entire-study average LTPA ordinal score was associated with 0.015 g/cm^2 larger final FN BMD ($p < 0.001$) and final FN BMD was 0.001 g/cm^2 better per each entire-study average MET hr wk^{-1} increment ($p = 0.004$). Similarly, entire-study average LTPA ordinal score was positively associated with final LS BMD, which was 0.017 g/cm^2 larger per one unit increment ($p = 0.007$). Final LS BMD was also 0.002 g/cm^2 greater per each one unit increment in entire-study average MET hr wk^{-1} ($p < 0.001$). Further adjustment for change in PA exposures between periods 1 and 2 did not alter the estimated associations

Time interval	KPAS ordinal score	MET hr wk^{-1}
Period 1	2.7 (0.9)	7.1 (8.2)
	2.6 [2.0, 3.4]	4.2 [0.9, 10.1]
Period 2	2.8 (0.9)	7.6 (8.0)
	2.7 [2.0, 3.4]	4.9 [1.4, 11.2]
Entire study	2.7 (0.9)	7.4 (7.6)
	2.7 [2.1, 3.4]	4.9 [1.8, 10.7]
Change in LPTA[e]	0.05 (0.58)	0.53 (5.13)
	0.03 [−0.30, 0.37]	0.25 [−1.94, 2.95]

[a]Average LTPA in each period and for the entire study is computed using area under the curve. [b]For each table entry, the first row shows the mean (standard deviation) and the second row provides the median [p25, p75]. [c]Self-reported LTPA using the Kaiser Physical Activity Survey (KPAS) sport/exercise domain ordinal scale; values range from 1 (lowest) to 5 (highest). [d]MET hr wk^{-1}, estimated from each participant's top 2 reported sports/exercises; value based on each activity's MET value, frequency, and duration. [e]Change in LTPA calculated as a difference: average LTPA in period 2 minus average LTPA in period 1.

Table 2: **Average leisure time physical activity (LTPA) values during period 1 (premenopause & early perimenopause), period 2 (late perimenopause & postmenopause), both periods (the entire study), and change in average LTPA between period 1 and period 2, Study of Women's Health Across the Nation (SWAN), n = 903.[a,b,c,d]**

between entire-study average PA levels and final FN or LS BMD.

Model-predicted final FN BMD level as a function of entire-study average levels of each LTPA exposure is illustrated in Fig. 4. Compared to the final FN BMD of 0.732 g/cm^2 in women with an average entire-study LTPA at the 25th percentile (2.1), those with an average LTPA ordinal score at the 75th percentile (3.4) had final BMD of 0.750 g/cm^2 (Fig. 4a); this reflects an absolute BMD difference of 0.15 SD. The final FN BMD difference between women who were at the 25th percentile of MET hr wk^{-1} (1.8) and those who were at the 75th percentile of MET hr wk^{-1} (10.7) was 0.09 SD (Fig. 4b).

To assess sensitivity to outliers in rate of BMD change, we tightened the outlier criteria from the top and bottom 2.5% of the distribution of annualized BMD change rate to the top and bottom 1% of this distribution. Findings did not change substantially; however, the standard error of the estimates increased, consistent with diminution in the protective effect of LTPA on BMD decline in women with extreme rates of change in BMD (data not shown).

Discussion

Our first hypothesis, that increasing LTPA during midlife (from premenopause/early perimenopause to late perimenopause/postmenopause), would be associated with slower BMD loss in the late peri- and postmenopause, was supported by the results. In fully adjusted models, greater increases in the LTPA ordinal score and in number of MET hr wk^{-1} were statistically significantly associated with a slower rate of FN BMD decline. The second hypothesis was also upheld: greater entire-study average levels of LTPA score and number of MET hr wk^{-1} were statistically significantly related to a better final BMD level at the FN and LS, independent of an increase in PA during mid-life.

PA's anabolic effects on BMD during premenopause and mitigation of BMD loss in later postmenopause are supported by RCTs and observational studies; however, the influence of PA on the rate of bone loss specifically during the MT and early postmenopause remains an open question.[5–12] To our knowledge, there are no trials of PA targeting bone loss during the MT and results from scant observational studies are inconclusive.[23,24] One cohort analyzed the relation between 3

Change in LTPA exposures[e,f]	Rate of decline, FN BMD[g,h,i]		Rate of decline, LS BMD[g,h,i]	
	b (95% CI)	p	b (95% CI)	p
LTPA ordinal score	−0.211 (−0.324, −0.097)	<0.001	−0.057 (−0.188, 0.073)	0.389
LTPA ordinal score, adjusted for average	−0.210 (−0.323, −0.097)	<0.001	−0.057 (−0.189, 0.074)	0.393
MET hr wk^{-1}	−0.021 (−0.034, −0.007)	0.002	−0.005 (−0.020, 0.011)	0.553
MET hr wk^{-1}, adjusted for average	−0.021 (−0.034, −0.007)	0.002	−0.005 (−0.020, 0.011)	0.555

[a]Average LTPA in each study period and during the entire study is computed using area under the curve. [b]Change in LTPA calculated as a difference: average LTPA in period 2 minus average LTPA in period 1. [c]Period 2 decline in BMD in % per year, [(initial minus final BMD)/(time * initial BMD)] * 100. [d]Models using LTPA ordinal score, N = 875; models using MET hr wk^{-1}, N = 872. [e]LTPA ordinal score from the Kaiser Physical Activity Survey (KPAS) sport/exercise domain scale; values range from 1 (lowest) to 5 (highest). [f]MET hr wk^{-1} is estimated based on each participant's top 2 reported sports/exercises; value computed using each activity's MET value, frequency, and duration. [g]Model adjusts for baseline age, baseline menopause transition stage (pre- or early perimenopausal), race/ethnicity, SWAN site, and proportion of visits during the entire study during which participant reported using calcium supplements, vitamin D supplements, bone-detrimental medications (see Methods for list), cigarettes, or alcohol, average body mass index (BMI) during the entire study, BMI change between initial to last visit, and proportion of visits at which BMI exceeded 41 kg/m^2. [h]Models additionally adjusted for the entire-study average value of each model's LTPA exposure variable, to account for possible influence of starting values (see Methods for details); results are shown in the "adjusted for average" rows. [i]Regression coefficients represent percent change in BMD per 1 unit increase in LTPA scale or per 1 MET hr wk^{-1}. Negative values signify a slower rate of BMD decline (i.e., less decline per year).

Table 3: **Association between change in leisure time physical activity (LTPA) from period 1 (premenopause & early perimenopause) to period 2 (late perimenopause & postmenopause) and rate of decline in femoral neck (FN) or lumbar spine (LS) bone mineral density (BMD) during period 2, Study of Women's Health Across the Nation (SWAN).[a,b,c,d]**

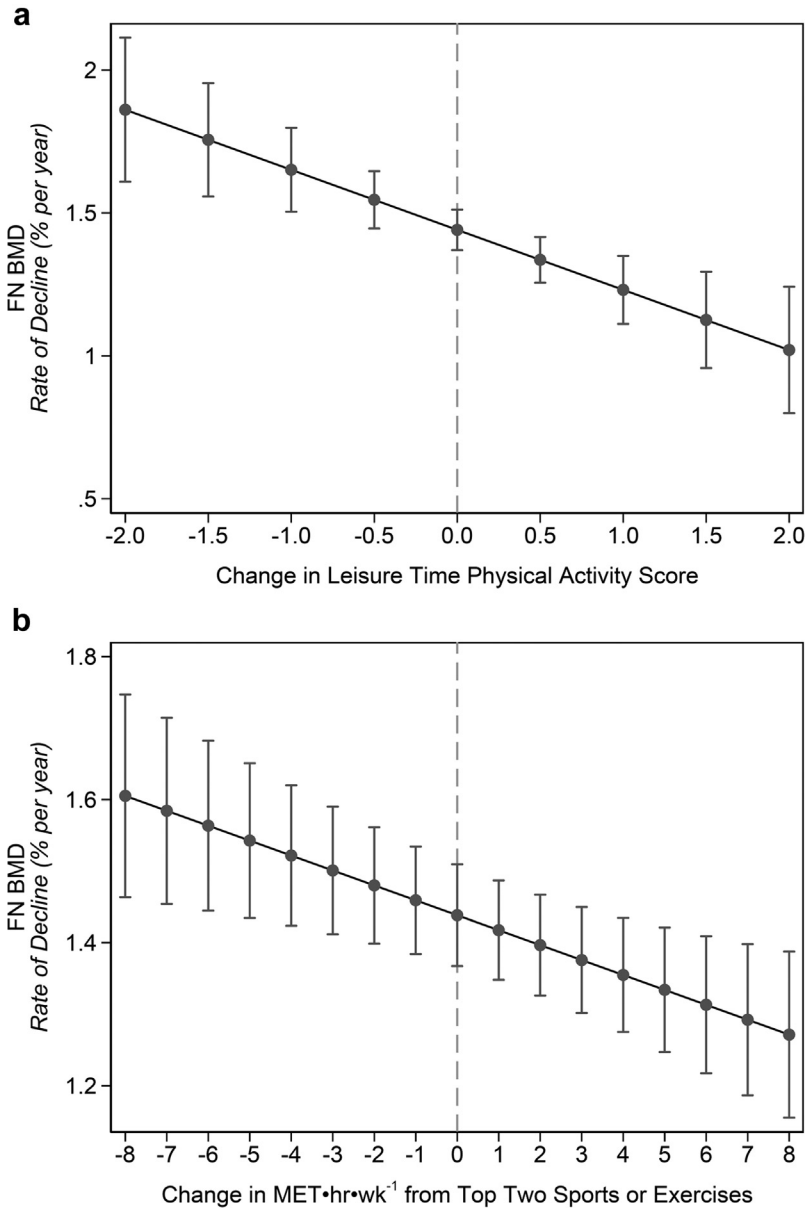

Fig. 3: a. Model-predicted relation between change in leisure-time phyisical activity (LTPA) ordinal score from period 1 (premenopause & early perimenopause) to period 2 (late perimenopause & postmenopause) and rate of decline in femoral neck (FN) bone mineral density (BMD) during period 2. Mean and SD of change in LPTA score were 0.05 (0.58) units. Values shown on the X-axis are those in the observed range, excluding extreme values (top and bottom 5%). Error bars depict the 95% confidence intervals. b. Model-predicted relation between change in MET hr wk^{-1} based on top 2 sports/exercises between period 1 and period 2 and rate of decline in FN BMD during period 2. Median and p25, p75 of change in MET hr wk^{-1} were 0.25 [−1.94, 2.95]. Values shown on the X-axis are those in the observed range, excluding extreme values (top and bottom 5%). Error bars depict the 95% confidence intervals.

assessments of self-reported PA and 2 BMD measures over an average of ~6 years, in initially perimenopausal (early *vs.* late unspecified) and postmenopausal women with mean baseline age of 53 years.[23] The active group consisted of 527 women reporting ≥1 h/wk of LTPA at all assessments (most commonly walking/jogging, skiing, aerobics, and rowing); the comparator was 231 women reporting no LTPA during all assessments. Of the active group, 57% used HT. LS, but not FN, BMD loss rate was 27% lower in active *vs.* inactive women, but the small sample size, lack of perimenopause definition, absence of testing for effect modification by HT, and

LTPA exposures[b,c]	Outcome: Final FN BMD[d,e,f]		Outcome: Final LS BMD[d,e,f]	
	b (95% CI)	p	b (95% CI)	P
LTPA ordinal score	0.015 (0.007, 0.023)	<0.001	0.017 (0.005, 0.029)	0.007
LTPA ordinal score, adjusted for change	0.014 (0.006, 0.022)	<0.001	0.017 (0.004, 0.029)	0.007
MET hr wk^{-1}	0.001 (0.000, 0.002)	0.004	0.002 (0.001, 0.004)	<0.001
MET hr wk^{-1}, adjusted for change	0.001 (0.000, 0.002)	0.004	0.002 (0.001, 0.004)	<0.001

[a]Average PA during the entire study computed using area under the curve. [b]LTPA ordinal score from the Kaiser Physical Activity Survey (KPAS) sport/exercise domain scale; values range from 1 (lowest) to 5 (highest). [c]MET hr wk^{-1} is estimated based on each participant's top 2 reported sports/exercises; value computed using each activity's MET value, frequency, and duration. [d]Model adjusts for age at last BMD, race/ethnicity, SWAN site, and proportion of visits during the entire study during which participant reported using calcium supplements, vitamin D supplements, bone-detrimental medications (see Methods for list), cigarettes, or alcohol, average body mass index (BMI) during the entire study, BMI change between initial to last visit, and proportion of visits at which BMI exceeded 41 kg/m^2. [e]Model additionally adjusted for the change in LTPA between from period 1 to 2. LTPA change was calculated as the difference between the area under the PA curve computed for period 2 (late perimenopause and postmenopause) minus area under the PA curve for period 1 (premenopause and early perimenopause). Results are shown in the "adjusted for change" rows. [f]Regression coefficients represent in increment in final on-study BMD (g/cm^2) per 1 unit increase in LTPA scale or per one unit value MET hr wk^{-1} during entire study. Positive values signify a larger absolute final BMD value.

Table 4: **Association between average level of physical activity (PA) during entire study and final femoral neck (FN) bone mineral density (BMD) level or final lumbar spine (LS) BMD level, Study of Women's Health Across The Nation (SWAN), N = 903.[a]**

dichotomous categorization of PA exposure limit inferences about the relation between PA and BMD. Another study reported the relation between concurrent MET hr wk^{-1} (mainly walking and sports) and BMD, each measured five times over an average of ~6 years in 614 women initially 24–50 years old: neither level of LS nor FN BMD, nor their annualized rates of loss, were associated with repeated PA measures.[24] However, 90% of women were premenopausal at baseline and only 9% transitioned to postmenopause by final follow-up, limiting detection of an association between PA and change in BMD during the MT.[24] SWAN's ability to identify a relation between increase in LTPA and slower BMD loss rate during the MT and initial postmenopausal years, as well as the association between greater long-term average LTPA and better final BMD, is made possible by many repeated measures of LTPA and BMD in a large cohort followed through defined stages of the MT, from pre-to postmenopause.

A few examples of MET hr wk^{-1} computations and a discussion of the relation between the LTPA ordinal scale and MET hr wk^{-1} will facilitate understanding of the relations of these PA metrics to BMD and their translation to common behaviours. First, annualized MET hr wk^{-1} are calculated by multiplying the number of METs associated with an activity by duration and weekly frequency; e.g., walking at a moderate pace (3.5 METs) for 1 h, three times per week, yields 10.5 MET hr wk^{-1} (3.5*1*3). By increasing weekly frequency of moderate-paced walking to five times, 17.5 MET hr wk^{-1} could be achieved. A more demanding activity (e.g., aerobic dancing, 7 METs) for 1 h, three times/week would result in 21 MET hr wk^{-1}. Second, how does the ordinal LTPA scale relate to the MET hr wk^{-1} metric? Not surprisingly, they are highly correlated at 0.86; MET hr wk^{-1} are computed from the two exercise/sport activities reported on the ordinal scale. Because the ordinal scale is normed to the specific analysis sample, and because it has no absolute external anchor, we can only conclude that women who score higher on the ordinal scale are doing more activity than women in that sample who score lower. We cannot discern what they are doing or how their PA level relates to that of another sample. These constraints are obviated by gauging LTPA by MET hr wk^{-1} as we have done. It is essential to recognize that our cross-calibration (between the ordinal score and MET hr wk^{-1}) applies only to this SWAN sample.

Women whose LTPA increased more than that of others had slower FN BMD loss: effect sizes were modest, but not inconsequential: a 0.2% per year slower FN decline per unit increase in ordinal LTPA scale would amount to 2% less decline over ten years. As the adjusted mean FN BMD decline rate was 1.5% yearly, over a ten year period, this would be equivalent to preventing 1.3 years' worth of usual decline. Comparing FN BMD loss rates in those at the 25th *vs.* the 75th percentile of the MET hr wk^{-1} change distribution (–1.94 *vs.* 2.95), the 0.021% per year effect size equates to a 0.1% per year difference in decline rates, or ~1% less BMD decline cumulated over ten years.

We can also estimate the clinical relevance of the relation between the entire-study average LTPA and the final BMD value by gauging it to fracture prevention. A one-unit increment in the average LTPA ordinal score was associated with 0.11 SD increment in final FN BMD. Using this metric, a woman at the 75th percentile of entire-study average LTPA (3.4) would have 0.15 SD higher final FN BMD than a woman at the 25th percentile (2.1). Based on SWAN data, this advantage in BMD would translate to 7.8% relative lower fracture hazard.

The median entire-study MET hr wk^{-1} was 4.9 (IQR 8.9) and the commonest form of LTPA was walking; apparent mitigation of menopause-related BMD loss in even this low range of LTPA is notable. Median number

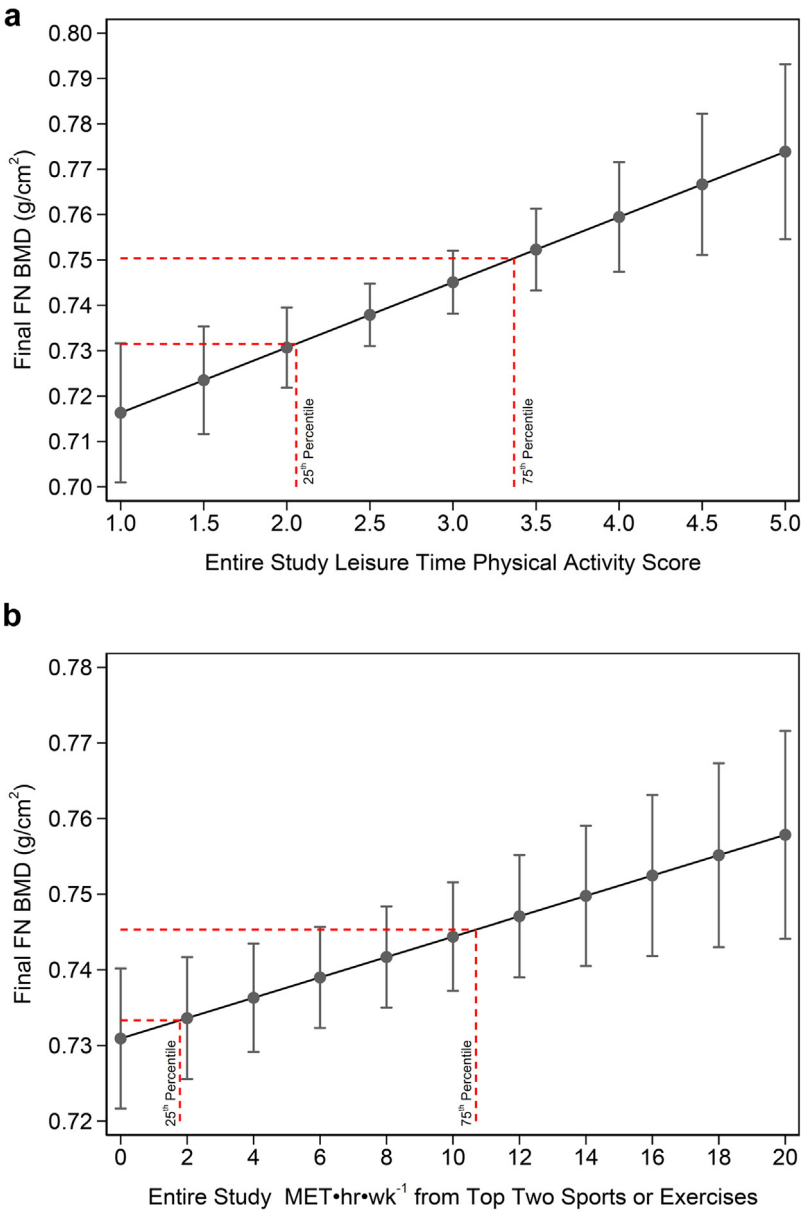

Fig. 4: a. Model-predicted relation between entire-study average LTPA ordinal score and final femoral neck (FN) BMD. Values on the X-axis are those in the observed range. Error bars depict the 95% confidence intervals. Dashed lines illustrate the 25th and 75th percentile values of the LTPA ordinal score and corresponding final FN BMD levels. b. Model-predicted relation between entire-study average MET hr wk^{-1} from top 2 sports/excericses and final FN BMD. Values on the X-axis are those in the observed range. Error bars depict the 95% confidence intervals. Dashed lines illustrate the 25th and 75th percentile values of MET hr wk^{-1} and corresponding final BMD levels.

of MET hr wk^{-1} was well below that recommended in recent US guidelines: ≥2.5 h/week of moderate or greater intensity PA (>7.5 MET hr wk^{-1}) and ≥2 weekly weight training sessions.[4] However, these guidelines also say, "Some physical activity is better than none.[4]" To wit, there is a linear decline in all-cause mortality as LTPA (MET hr wk^{-1}) ranges from 0 to 8.25; even if walking is the only PA, mortality benefit accrues in a graded fashion.[25,26] But whether bone loss prevention is achieved by *any* PA is questionable. For bone, type of activity matters; impact and/or tension forces produce osteogenic stimuli.[27,28] RCTs of walking (which produces low-level ground reaction forces) have not had a measurable effect on postmenopausal BMD loss—except when interventions were greater than one year's duration.[13] The present study's LTPA exposures, although low-level, are

averaged over several years; plausibly, modest amounts of low-impact PA, done persistently, curtail bone loss.

In the change in LTPA analysis, we observed differential associations with BMD loss by bone site, whereas the link between entire-study LTPA final BMD was similar at the FN and LS. LTPA change was related only to FN BMD loss rate, plausibly due to the type of activities in which the sample engaged. The most common ones (walking, calisthenics) would likely engender greater ground and joint reaction forces at the FN than at the LS.[29] That greater entire-study LTPA is associated with higher levels of *both* final FN and LS BMD may seem contradictory to the aforementioned results. However, the relation between entire-study PA and final BMD is the aggregate of PA's relation to baseline BMD and BMD change over time. Cross-sectionally, LTPA and initial (pre- and early perimenopausal) FN and LS BMD were positively related.[15] In this study, the magnitude of the association between entire-study average LTPA and final FN and LS BMD was unaltered by adjustment for PA change during the study. Thus, a greater total amount of LTPA was related to higher final BMD, irrespective of when women started engaging in more LTPA.

Limitations include that the self-report KPAS instrument is subject to measurement error and was not designed to quantify bone loading; these could result in underestimation of the relation between LTPA and BMD. However, pragmatically, the KPAS captured information about usual, self-selected activities (e.g., walking, the commonest PA in US women).[30] The number of women working outside the home diminished greatly over time, making it unfeasible to conduct longitudinal analyses of the relation between occupational PA and BMD. Although multivariable models included several lifestyle factors, the possibility of residual confounding by diet and other healthy behaviors must be acknowledged. We could not test for an interaction between LTPA and HT (HT was an exclusion, precluding classification of menstrually-defined MT stages). Women who remain in SWAN and are included in this analysis are likely to be healthier than the remainder of the cohort; generalizations should be limited to women with characteristics similar to those in the analysis sample. An observational study cannot infer causality, but the change-in-LTPA exposure and change-in-BMD outcome is a strong design. Strengths include 17 waves of longitudinal observations in a large, diverse sample of well-characterized women with up to 17 BMDs and eight LTPA assessments.

Our findings that more LTPA (although at modest levels) is related to BMD preservation (albeit a small diminution of loss rate) are concordant with a large body of interventional work that supports optimizing physical activity to minimize bone loss in postmenopause.[9] However, there are practical barriers to optimally maximal interventions targeted at bone loading, such as lack of access to proper training, physical limitations, competing responsibilities, and personal activity preferences. While identifying ideal bone loading PA to prevent bone loss remains an important research priority, our study suggests that it may be feasible to lessen menopause-related bone loss at the population level with even small increases in intensity, duration or frequency of common activities.

Contributors

All authors are SWAN investigators and have been substantively involved in the overall design and conduct of SWAN. Specific roles related to this manuscript were: obtaining funding (GAG); participant recruitment and enrollment (GAG, CK-G, BS); data management and variable creation (GAG, ASK, NJJ, KRY, KPG, BS); analytic design (GAG, ASK, NJJ); statistical analysis (NJJ, ASK, GAG); primary manuscript drafting (GAG); critical review and revision of manuscript (all). NJJ and ASK accessed and verified the data used in the analysis. All authors approved the final manuscript version.

Data sharing statement

SWAN provides access to public use datasets that include data from SWAN screening, the baseline visit and follow-up visits (https://agingresearchbiobank.nia.nih.gov/). To preserve participant confidentiality, some, but not all, of the data used for this manuscript are contained in the public use datasets. A link to the public-use datasets is also located on the SWAN web site: http://www.swanstudy.org/swan-research/data-access/. Investigators who require assistance accessing the public use dataset may contact the SWAN Coordinating Center at the following email address: swanaccess@edc.pitt.edu.

Declaration of interests

All authors declare that they have no financial relationships with any organisation that might have an interest in the submitted work and have no other relationships or activities that could appear to have influenced the submitted work.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lana.2023.100481.

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