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SHORT COMMUNICATION ***Reproductive epidemiology***

Physical activity is not related to risk of early menopause in a large prospective study

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STUDY QUESTION: Is physical activity associated with incident early menopause?

SUMMARY ANSWER: Physical activity is not associated with incident early menopause.

WHAT IS KNOWN ALREADY: Lifestyle factors such as physical activity may influence menopause timing, but results from prior research are inconsistent.

STUDY DESIGN, SIZE, DURATION: We evaluated the association between physical activity and the occurrence of early natural menopause in a prospective cohort study, the Nurses' Health Study II. Women were followed prospectively from 1989 to 2011.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Our analysis included 107 275 women who were premenopausal at baseline. Menopause status was self-reported biennially. Time per week participating in specific activities was reported approximately every 4 years and used to calculate metabolic task hours per week (MET h/week). We used Cox proportional hazards model to evaluate the association between physical activity and incidence of natural menopause before age 45 years while controlling for potential confounding factors.

MAIN RESULTS AND THE ROLE OF CHANCE: There were 2 786 study members who experienced menopause before the age of 45. After adjustment for age, smoking and other factors, we observed no association between adulthood physical activity and early menopause. For example, compared to women reporting <3 MET h/week, the hazard ratio for women in the highest category (≥42 MET h/week) of cumulatively-averaged total physical activity was 0.89 (95% confidence interval: 0.76–1.04; *P*-trend: 0.26). Neither moderate nor strenuous activity in adolescence and young adulthood were related to risk. The relation of physical activity and early menopause did not vary across strata of body mass index or smoking status.

LIMITATIONS, REASONS FOR CAUTION: Physical activity and menopausal status were self-reported, but repeated assessment of physical activity and prospective report of menopause status likely reduce the potential for non-differential misclassification. While the majority of our study participants were white, it is unlikely that the physiological relation of activity and early menopause varies by ethnicity.

WIDER IMPLICATIONS OF THE FINDINGS: Findings from our large prospective study do not support an important association between physical activity and early menopause.

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Introduction

Early menopause, defined as the cessation of menstruation before age 45, is experienced by approximately 10% of women (Jacobsen *et al.*, 2003; Broekmans *et al.*, 2009; Shuster *et al.*, 2010). Early menopause is associated with an increased risk of premature mortality, cardiovascular disease and other chronic conditions (van Der Voort *et al.*, 2003; Miller, 2012; Wellons *et al.*, 2012; Bleil *et al.*, 2013; Torrealday and Pal, 2015). Genetic factors alone do not explain the development of early menopause, and recent studies suggests that modifiable lifestyle factors may also influence risk, including physical activity (Aydin *et al.*, 2005; Ortega-Ceballos *et al.*, 2006; Dratva *et al.*, 2007; Dorjgochoo *et al.*, 2008; Nagata *et al.*, 2012; Emaus *et al.*, 2013; Gold *et al.*, 2013).

In premenopausal women, physical activity may influence ovarian function by altering production of estrogens and other steroid hormones via the hypothalamic–pituitary–ovarian axis (Tworoger *et al.*, 2007). Intense physical activity can disrupt regular ovarian cycles, leading to luteal phase insufficiency, anovulation and amenorrhea; these may be associated with a lower risk of early menopause as they are associated with a lower frequency of ovulation and a slower rate of exhaustion of the follicle pool (Gudmundsdottir *et al.*, 2009). Most prior research of physical activity and menopause has primarily addressed a potential relation with menopausal timing more generally. Prospective studies have yielded inconsistent findings. Only two studies of physical activity and early menopause specifically have been conducted; both were based on small sample sizes and observed point estimates consistent with a strong inverse association, but the results were not statistically significant. It thus remains unclear whether physical activity may be importantly related to risk of early menopause.

We evaluated the relation of physical activity at multiple ages with risk of early menopause in the prospective Nurses' Health Study II (NHSII).

Materials and Methods

Participants

The NHSII cohort includes of 116 429 female US registered nurses aged 25–42 years in 1989. Participants completed questionnaires assessing lifestyle factors and medical conditions every two years thereafter. Follow-up rates for each questionnaire cycle were least 89%. The study protocol was approved by the Institutional Review Board at Brigham, Women Hospital in Boston, MA and the Harvard TH Chan School of Public Health.

Assessment of physical activity

In study questionnaires in 1989, 1991, 1997, 2001, 2005 and 2009, women reported the average time per week during the past year spent on recreational activities. In 1989, activities included walking, jogging, running, bicycling (including on a stationary machine), racquet sports, lap swimming, calisthenics and other aerobic activities. In later years, activities were expanded to include weight training, low intensity exercises like yoga and high intensity activities like lawn mowing. Response options ranged from 0 minutes to ≥11 h/week. In 1997, women also reported the average amount of time per week spent on moderate and strenuous recreational activities at three ages: grades 7–8 (ages 12–13), grades 9–12 (ages 14–17) and ages 18–22, 23–30 and 30–34. Response options ranged from none to ≥11 h/week. To incorporate the frequency, duration and intensity of activity, we multiplied hours per week of each activity by its metabolic equivalent (MET) score, with one MET equal to 1 kcal/kg/h or the energy expended by sitting quietly (Ainsworth *et al.*, 2000), and then summed values for all activities to create total MET hours/week.

Assessment of early menopause

In 1989 and on each subsequent biennial questionnaire, women were asked if their menstrual periods had ceased permanently, and if so, at what age, and whether cessation was related to surgery, radiation or chemotherapy or occurred naturally. Information regarding use of hormone therapy (HT) was collected as well. Age at menopause was defined as age after 12 consecutive months of amenorrhea. A small number of women reported being postmenopausal on one questionnaire and then subsequently reported being premenopausal. For these women, we defined age at menopause as age after which periods were absent for 12 months or more, and then confirmed that this status persisted for at least three consecutive questionnaires.

Eligibility for the current analysis was limited to women who were premenopausal and reported physical activity at the baseline 1989 questionnaire (n = 107 275). Women were followed for incidence of menopause until June 2011. We defined cases as those women who reported natural menopause before age 45.

Covariate assessment

Information on race, ethnicity, age, education, height and age at menarche was collected at baseline. Information on parity, oral contraceptive (OC) use, HT use and smoking was collected biennially since baseline. Current weight and body mass index (BMI; weight (kg)/height $(m)^2$) were also assessed biennially. Information on diet was collected using semi-quantitative food frequency questionnaires (FFQ) in 1991 and every 4 years thereafter (Willet *et al.*, 1985). Additional information on dietary supplement use, including vitamin D and calcium, was collected on main NHSII questionnaires. Nutrient intake was adjusted for total energy using the residual method (Willett, 2012).

Statistical analysis

We divided women into categories of total MET hours/week and then compared the distribution of covariates at baseline with physical activity in age-adjusted general linear models. We evaluated the relation of category of physical activity with incidence of early menopause using Cox proportional hazard models to calculate hazard ratios (HR) and 95% confidence intervals (CI). Women contributed person-time in months from the date of return of the baseline questionnaire (1989) until menopause, hysterectomy, oophorectomy, diagnosis of cancer (other than non-melanoma skin cancer), death, loss to follow-up, age 45 or June 2011, whichever came first.

We modeled total physical activity participation in adulthood in three ways: (1) MET h/week at baseline (1989) only; (2) updating MET h/week data every 4 years; (3) cumulatively averaging MET h/week, updated every 4 years; this method uses the mean MET h/week from all prior physical activity assessments as a measure of long-term physical activity (Eliassen *et al.*, 2010). In addition, we evaluated associations of early menopause with the cumulative average of time spent walking, as walking was the most common activity reported by participants. Risk associated with moderate and strenuous activity in adolescence, early and middle adulthood was also assessed.

In addition to models adjusting for age, we built a multivariate model controlling for time-varying factors including age, pack-years of smoking, parity, breastfeeding duration, alcohol intake, percentage of total calories from vegetable protein, and vitamin D from dairy intake, as well as age at menarche (time invariant); these covariates were selected a priori based

on previous studies of early menopause in our population (Purdue-Smithe et al., 2017, Boutot et al., 2018, Whitcomb et al., 2018). We created a second multivariate model additionally controlling for BMI (time-varying), given that adiposity could be a confounder or intermediate in the pathway; BMI and physical activity are closely related, and prior research in the same population found that underweight women are at increased risk for early menopause (Szegda et al., 2017). To test for linear trend, we assigned the median activity level of each category to all women in that category and used median values in regression models.

We conducted several sensitivity analyses. We stratified analyses to evaluate whether hazard ratio estimates were comparable across categories of BMI, smoking status and current OC use, using likelihood ratio tests to compare models with and without multiplicative interaction terms. Finally, because HT use may contribute to misclassification of menopause status, we ran additional models censoring at first use of HT. Statistical analyses were conducted with SAS v9.3 software (SAS Institute Inc, Cary, NC).

Results

During 20 years of follow-up, 2786 members of the analytic cohort experienced incident early menopause. Overall, women reporting higher physical activity were somewhat younger, had lower BMI at baseline and recalled BMI at age 18, and lower parity compared to those reporting lower activity overall (Table I). Greater physical activity was associated with slightly longer duration of OCs use, and higher intake of alcohol, vegetable protein and vitamin D.

In results from age-adjusted Cox proportional hazard models, physical activity at baseline was not associated with risk of early menopause (Table II). For example, compared to women who reported <3 MET h/week, women reporting ≥42 MET h/week of activity had a HR of early menopause of 0.92 (95% CI = 0.81–1.06; *P*-trend = 0.34). Results adjusting for covariates (Model 2) were similar, and additional adjustment for BMI had minimal impact. Results from analyses modeling updated and cumulatively-averaged physical activity were consistent with models of baseline activity, suggesting no association with early menopause risk. No association was observed for time spent walking and early menopause risk. In results from fully adjusted models, women reporting a cumulative average of 4 or more h/week of walking had a HR of early menopause of 0.89 (95% CI = 0.76–1.04) compared to women reporting no walking (*P*-trend = 0.26). Time spent per week in moderate and strenuous activity at ages 23–39 and 30–34 were also unrelated to risk of early menopause (results not shown).

Table I Age-Standardized characteristics of premenopausal women according to category of total physical activity at baseline (1989): Nurses' Health Study II, 1989

Characteristic	Total physical activity (MET h/week)					
	<3 (*n* = 16,086) Mean (SE)	3 – <9 (*n* = 24,298) Mean (SE)	9 – <18 (*n* = 22,413) Mean (SE)	18 – <27 (*n* = 14,133) Mean (SE)	27 – <42 (*n* = 12,867) Mean (SE)	≥42 (*n* = 17,478) Mean (SE)
Age, *y*[a]	34.7 ± 4.5	34.4 ± 4.6	34.2 ± 4.6	34.1 ± 4.6	33.8 ± 4.6	33.2 ± 4.7
Age at menarche, *y*	12.4 (0.01)	12.4 (0.01)	12.4 (0.01)	12.4 (0.01)	12.4 (0.01)	12.5 (0.01)
BMI at age 18, kg/m[b]	21.4 (0.03)	21.3 (0.02)	21.3 (0.02)	21.2 (0.03)	21.2 (0.03)	21.1 (0.03)
BMI, kg/m[b]	25.2 (0.04)	24.5 (0.03)	24.0 (0.03)	23.6 (0.04)	23.3 (0.04)	23.1 (0.04)
Pack-years of smoking[b]	12.2 (0.10)	11.6 (0.08)	10.8 (0.09)	10.7 (0.11)	10.6 (0.11)	10.5 (0.10)
Duration of oral contraceptive use (m)[c]	52.5 (0.4)	52.6 (0.3)	53.1 (0.3)	53.6 (0.4)	53.7 (0.4)	54.6 (0.4)
Alcohol intake (g/d)	2.4 (0.05)	2.7 (0.04)	2.9 (0.04)	3.2 (0.05)	3.4 (0.05)	3.7 (0.04)
Parity (pregnancies > 6 m)[d]	2.1 (0.01)	2.1 (0.01)	2.1 (0.01)	2.0 (0.01)	2.0 (0.01)	2.0 (0.01)
Breastfeeding duration (m)[d]	12.0 (0.1)	12.8 (0.1)	13.2 (0.1)	13.0 (0.1)	12.9 (0.2)	12.5 (0.1)
Dietary vitamin D intake (IU/d)	235 (1.1)	246 (0.9)	255 (0.9)	260 (1.1)	263 (1.2)	266 (1.1)
Vegetable protein intake (% of kcal)	4.8 (0.01)	4.9 (0.01)	5.0 (0.01)	5.1 (0.01)	5.2 (0.01)	5.2 (0.01)
	%	%	%	%	%	%
Oral contraceptive use						
Past	69.5	70.1	69.5	69.4	68.4	67.2
Current	13.0	12.6	13.6	13.8	14.2	15.5
Nulliparous	24.2	25.3	27.3	31.4	33.4	38.5
Smoking status						
Past	21.3	21.6	23.2	24.0	24.5	25.0
Current	13.9	12.3	10.3	9.8	9.3	10.5

[a]For age, values presented are unadjusted mean and standard deviation. All characteristics were calculated with the use of generalized linear models adjusted for the age of participants in 1989. All variables are significant at the $P < 0.05$ level.
[b]Among ever-smokers.
[c]Among ever users of oral contraceptives.
[d]Among parous women.

Table II Hazard ratios (95% CIs) for early menopause by level of physical activity: Nurses' Health Study II (1989–2011)[a]

	n Cases	Age-adjusted HR (95% CI)	MV1[a] HR (95% CI)	MV2[b] HR (95% CI)
Physical activity, 1989 (MET h/week)				
<3	437	1	1	1
3 – <9	648	0.98 (0.87, 1.10)	1.00 (0.88, 1.13)	1.00 (0.88, 1.13)
9 – <18	574	0.94 (0.83, 1.06)	0.97 (0.85, 1.10)	0.96 (0.85, 1.09)
18 – <27	363	0.94 (0.81, 1.08)	0.97 (0.84, 1.11)	0.96 (0.83, 1.10)
27 – <42	336	0.97 (0.84, 1.12)	1.01 (0.87, 1.16)	0.99 (0.86, 1.14)
≥42	418	0.92 (0.81, 1.06)	0.94 (0.82, 1.08)	0.92 (0.81, 1.06)
P-trend		0.34	0.42	0.24
Physical activity, updated (MET h/week)				
<3	515	1	1	1
3 – <9	795	1.01 (0.90, 1.12)	1.03 (0.92, 1.16)	1.03 (0.92, 1.15)
9 – <18	438	0.94 (0.82, 1.07)	0.98 (0.86, 1.12)	0.97 (0.84, 1.10)
18 – <27	284	1.02 (0.88, 1.19)	1.07 (0.92, 1.24)	1.05 (0.90, 1.22)
27 – <42	241	0.98 (0.83, 1.14)	1.01 (0.86, 1.19)	0.99 (0.84, 1.16)
≥42	234	0.91 (0.78, 1.07)	0.94 (0.80, 1.11)	0.91 (0.77, 1.07)
P-trend		0.26	0.41	0.21
Physical activity, cumulative average (MET h/week)				
<3	308	1	1	1
3 – <9	634	0.93 (0.81, 1.06)	0.94 (0.82, 1.08)	0.94 (0.82, 1.08)
9 – <18	667	0.90 (0.79, 1.04)	0.94 (0.82, 1.07)	0.93 (0.81, 1.07)
18 – <27	466	1.03 (0.89, 1.19)	1.06 (0.91, 1.22)	1.04 (0.90, 1.21)
27 – <42	358	0.92 (0.79, 1.08)	0.95 (0.81, 1.11)	0.93 (0.80, 1.09)
≥42	348	0.89 (0.76, 1.04)	0.91 (0.78, 1.07)	0.89 (0.76, 1.04)
P-trend		0.42	0.53	0.26

[a]Multivariable (MV) model adjusted for age (continuous, months), pack-years of smoking (0–10, 11–20 or ≥21), age at menarche (continuous), parity (nulliparous, 1–2, or ≥3), breastfeeding duration (in months; continuous), oral contraceptive use (never/past/current), % of calories from vegetable protein (quintiles), alcohol intake (<10, ≥10 g/day), and intake of vitamin D from dairy source (quintiles).
[b]MV model additionally adjusted for BMI (<18.5, 18.5–<25, 25–<30 or ≥30 kg/m^2).

In results stratified by BMI and OC use, estimates were very similar between strata and we observed no evidence of effect modification (Table III). In results stratified by smoking status, we observed no association among ever-smokers. Among never smokers, we observed some evidence of an inverse relation between activity and risk, with women averaging at least 42 MET h/week having a 23% lower risk of early menopause compared to women reporting <3 MET h/week (HR = 0.77; 95% CI = 0.63–0.95; *P*-trend = 0.07), but the test for interaction was not significant (*P*-interaction = 0.34). Results from models censoring at first HT use were highly similar to those of the main analysis (results not shown).

We did not find moderate or strenuous activity at any age (12–13 years, 14–17 years or 18–22 years) to be associated with risk of early menopause (Table IV).

Discussion

In this prospective study, we did not find any substantial evidence that participation in physical activity was associated with risk of early menopause. In our main analyses, the results were null across all levels of physical activity, even for women reporting the equivalent to 4 or more hours of running or 8 or more hours of brisk walking per week compared to inactive women. Analyses limited to never smokers suggested the possibility of a modestly lower risk among women reporting consistently high levels of activity. High levels of moderate and intense physical activity in adolescence and early adulthood were unrelated to risk of early menopause.

The association of physical activity and early menopause was assessed previously in a prospective study among 3 435 women followed for approximately 12 years, during which time 124 cases of early menopause were observed (Gudmundsdottir *et al.*, 2013). Compared to women reporting no activity, HRs of early menopause (95% CI) among women reporting high and very high activity were 0.68 (0.28–1.68) and 0.21 (0.02–1.78), respectively. In a cross-sectional analysis of 1 829 women in the Oslo Health Study that observed early menopause in 9.6% of the cohort, the odds ratio for early menopause among women reporting ≥3 h/week of activity versus none was 0.70 (95% CI = 0.38–1.30) (Mikkelsen *et al.*, 2007). Despite low point estimates in these two studies, small numbers of cases and low statistical power resulted in wide confidence intervals; our large prospective study including more than 2 700 incident early menopause cases suggests no inverse association.

Table III Hazard Ratios (95% CIs) for early menopause by level of physical activity (cumulatively averaged), stratified by current body mass index, smoking status and oral contraceptive use: Nurses' Health Study II (1989–2011)

Physical activity, (MET h/week)	Current body mass index			
	BMI < 25 kg/m^2		BMI ≥ 25 kg/m^2	
	n cases	HR (95% CI)[a]	*n* cases	HR (95% CI)[a]
<3	182	1	126	1
3 – <9	394	0.94 (0.79, 1.12)	240	0.95 (0.76, 1.18)
9 – <18	453	0.94 (0.79, 1.12)	214	0.91 (0.73, 1.14)
18 – <27	327	1.04 (0.86, 1.25)	139	1.07 (0.84, 1.38)
27 – <42	261	0.93 (0.77, 1.13)	97	0.95 (0.72, 1.25)
≥42	265	0.87 (0.72, 1.06)	83	0.94 (0.71, 1.25)
P-trend		0.21		0.98
P-interaction		0.98		
	Current smoking status			
	Never smokers		Ever-smokers	
Physical activity, (MET h/week)	*n* Cases	HR (95% CI)[b]	*n* Cases	HR (95% CI)[b]
<3	187	1	118	1
3 – <9	373	0.87 (0.73, 1.04)	261	1.07 (0.85, 1.33)
9 – <18	403	0.86 (0.72, 1.03)	265	1.02 (0.82, 1.28)
18 – <27	256	0.89 (0.73, 1.08)	210	1.28 (1.01, 1.61)
27 – <42	212	0.87 (0.71, 1.06)	144	1.01 (0.79, 1.30)
≥42	191	0.77 (0.63, 0.95)	155	1.00 (0.78, 1.28)
P-trend		0.07		0.71
P-interaction		0.34		
	Current oral contraceptive use			
	Current		Not current	
Physical activity, (MET h/week)	*n* Cases	HR (95% CI)[c]	*n* Cases	HR (95% CI)[c]
<3	12	1	274	1
3 – <9	39	1.41 (0.70, 2.83)	564	0.95 (0.82, 1.10)
9 – <18	49	1.33 (0.68, 2.63)	582	0.93 (0.80, 1.07)
18 – <27	25	1.02 (0.48, 2.13)	426	1.10 (0.94, 1.28)
27 – <42	29	1.39 (0.67, 2.88)	309	0.93 (0.80, 1.10)
≥42	23	1.08 (0.51, 2.29)	305	0.92 (0.77, 1.08)
P-trend		0.56		0.49
P-interaction		0.08		

[a]All models adjusted for age, pack-years of smoking (0–10, 11–20 or ≥21), BMI (continuous in kg/m^2), age at menarche (continuous), parity (nulliparous, 1–2 or ≥3), breastfeeding duration (in months; continuous), oral contraceptive use (never/past/current), % of total calories from vegetable protein (quintiles), alcohol intake (<10, ≥10 g/day), and intake of vitamin D from dairy source (quintiles).
[b]Adjusted for age, pack-years of smoking (continuous), BMI [in kg/m^2 (<18.5, 18.5–<25, 25–<30 or ≥30)], age at menarche (continuous), parity (nulliparous, 1–2 or ≥3), breastfeeding duration (in months; continuous), oral contraceptive use (never/past/current), % of total calories from vegetable protein (quintiles), alcohol intake (<10, ≥10 g/day), and intake of vitamin D from dairy source (quintiles).
[c]Adjusted for age, pack-years of smoking (0–10, 11–20 or ≥21), BMI [in kg/m^2 (<18.5, 18.5–<25, 25–<30 or ≥30)], age at menarche (continuous), parity (nulliparous, 1–2 or ≥3), breastfeeding duration (in months; continuous), % of total calories from vegetable protein (quintiles), alcohol intake (<10, ≥10 g/day), and intake of vitamin D from dairy source (quintiles).

Associations from previous cohort studies of activity and menopause timing have generally been small in magnitude, if not entirely null (Bromberger *et al.*, 1997; Nilsson *et al.*, 1997; Nagata *et al.*, 2000; Palmer *et al.*, 2003; Nagel *et al.*, 2005; Dorjgochoo *et al.*, 2008; Nagata *et al.*, 2012; Emaus *et al.*, 2013; Gold *et al.*, 2013; Gudmundsdottir *et al.*, 2013). For example, in a cross-sectional analysis in the Breakthrough Generations Study (n = 50 678) women, women reporting any strenuous exercise at ages 30–49 had a HR for menopause of 0.96 (95% CI = 0.93–0.98; P = 0.003) compared to women with no strenuous activity (Morris *et al.*, 2012). Though statistically

Table IV Hazard ratios (95% CIs) for early menopause by level of moderate and strenuous activity in adolescence and young adulthood; Nurses' Health Study II (1989–2011)

Physical activity (h/week)	*n* Cases	Moderate activity HR (95% CI)[a]	*n* Cases	Strenuous activity HR (95% CI)[a]
Age 12–13 (grades 7–8)				
None	118	1	243	1
>0–<1	177	1.12 (0.89, 1.41)	179	1.08 (0.89, 1.31)
1–2	645	1.01 (0.83, 1.23)	500	0.96 (0.82, 1.12)
3–4	585	1.08 (0.89, 1.32)	479	1.03 (0.88, 1.20)
5–6	284	0.98 (0.79, 1.22)	349	1.03 (0.87, 1.21)
7–10	140	0.91 (0.71, 1.17)	206	0.97 (0.80, 1.17)
≥11	110	0.99 (0.76, 1.28)	138	0.98 (0.79, 1.20)
P-trend		0.29		0.80
Age 14–17 (grades 9–12)				
None	106	1	222	1
>0–<1	174	1.14 (0.89, 1.45)	183	1.12 (0.92, 1.36)
1–2	639	1.04 (0.84, 1.27)	463	0.91 (0.77, 1.06)
3–4	588	1.11 (0.90, 1.36)	448	0.93 (0.79, 1.09)
5–6	290	1.01 (0.80, 1.26)	360	0.97 (0.82, 1.14)
7–10	152	1.00 (0.78, 1.28)	238	0.94 (0.78, 1.13)
≥11	109	1.10 (0.84, 1.43)	187	0.97 (0.79, 1.17)
P-trend		0.85		0.76
Age 18–22				
None	127	1	299	1
>0–<1	207	0.99 (0.79, 1.24)	290	1.03 (0.88, 1.21)
1–2	665	1.04 (0.86, 1.25)	575	1.01 (0.87, 1.16)
3–4	577	1.10 (0.91, 1.33)	449	1.05 (0.90, 1.21)
5–6	283	1.03 (0.83, 1.27)	249	0.97 (0.82, 1.15)
7–10	118	0.94 (0.73, 1.21)	137	1.06 (0.86, 1.30)
≥11	77	1.06 (0.79, 1.40)	88	1.17 (0.92, 1.49)
P-trend		0.97		0.31

[a]Adjusted for age (continuous, months), BMI (<18.5, 18.5-<25, 25-<30 or ≥30 kg/m^2), pack-years of smoking (0–10, 11–20 or ≥21), age at menarche (continuous), parity (nulliparous, 1–2, or ≥3), breastfeeding duration (in months; continuous), oral contraceptive use (never/past/current), % of calories from vegetable protein (quintiles), alcohol intake (<10, ≥10 g/day) and intake of vitamin D from dairy source (quintiles).

significant, the magnitude of effect was very small, and the median age at menopause was 52 years in both strenuously active and inactive women.

Results were similar in magnitude in the California Teachers Study (n > 97 000 women), the largest prospective study conducted to date of activity and menopause timing (Emaus *et al.*, 2013). Women in the highest quartile of long-term physical activity (equivalent to ≥6 h/week each year from high school through age 45–54) had a HR for menopause of 0.95 (95% CI: 0.92–0.98; *P*-trend = 0.005) compared to the least active women. Results differed by smoking status, but in the opposite direction from what we observed; associations were null for never smokers but were significant in heavy smokers (HR = 0.89; 95% CI = 0.80–0.99 for current heavy smokers). Cumulatively, physical activity appears either unassociated with early menopause or only modestly linked, with magnitudes of association of likely limited clinical relevance.

A potential limitation of our study is our use of self-reported physical activity, rather than objective measurement, which likely contributes to misclassification. However, our physical activity questionnaire has demonstrated good reproducibility and validity as compared with 7-day diaries (Wolf *et al.*, 1994). Also, these physical activity measures have been significantly associated with other health outcomes such as depression, breast cancer and colon cancer in the NHS2, suggesting that misclassification is likely not substantial enough to obscure important associations (Maruti *et al.*, 2008; Lucas *et al.*, 2011; Morikawa *et al.*, 2011; Zhang *et al.*, 2011; Du *et al.*, 2012). While menopause timing was self-reported as well, the prospective report of onset of menopause has been demonstrated to have high reproducibility over multiple questionnaire cycles (Colditz *et al.*, 1987). We note that residual confounding by psychosocial stress, employment status and other factors potentially related to menopause timing may persist if these were also related to physical activity levels in our population.

Additionally, while we know of no data suggesting that the physiology underlying a relation between physical activity and menopausal timing differs by race/ethnicity, we were unable to evaluate potential effect modification by race/ethnicity, as the majority of NHS2 participants were white.

In summary, although physical activity has been shown to have wide ranging positive health effects overall, results of this large, prospective study do not support an important role of physical activity with regard to risk of early menopause.

Authors' roles

Conception and design of study: M.Z. and E.R.B.J.; analysis and interpretation of data: M.Z., B.W.W., A.C.P.S., J.E.M., S.E.H., B.A.R. and E.R.B.J.; drafting of manuscript or revising critically for important intellectual content: M.Z., B.W.W., A.C.P.S., J.E.M., S.E.H., B.A.R. and E.R.B.J.; and final approval of version to be published: M.Z., B.W.W., A.C.P.S., J.E.M., S.E.H., B.A.R. and E.R.B.J.

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Conflict of interest

No competing interests declared.

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