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PHYSICAL ACTIVITY AND EARLY MENOPAUSE IN THE NURSES' HEALTH STUDY II

A Thesis Presented

by

Mingfei Zhao

Submitted to the Graduate School of the
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by

MINGFEI ZHAO

Approved as to style and content by:

_____
Elizabeth Bertone-Johnson, Chair

_____
Brian Whitcomb, Member

_____
Paula Stamps, Graduate Program Director
Department of Biostatistics and Epidemiology

ABSTRACT

PHYSICAL ACTIVITY AND EARLY MENOPAUSE IN THE NURSES' HEALTH STUDY II

FEBRUARY 2018

MINGFEI ZHAO, B.A., FUDAN UNIVERSITY

M.P.H., DREXEL UNIVERSITY

M.S., UNIVERSITY OF MASSACHUSETTS AMHERST

Directed by: Dr. Elizabeth Bertone-Johns

Early menopause, the cessation of menstrual function before age 45, occurs in 10% of women, and is associated with higher premature mortality and increased risk of cardiovascular disease. Lifestyle factors like physical activity may influence menopause timing, but results from prior research are inconsistent. We evaluated the association between physical activity and the occurrence of early natural menopause in the Nurses' Health Study II. Premenopausal women were followed prospectively from 1989 to 2011. Menopause status was self-reported biennially. Time per week participating in specific activities was reported every four years and used to calculate metabolic task hours (MET). Moderate and vigorous activity in adolescence and young adulthood was reported in 1997. We used Cox proportional hazards model to evaluate the association between physical activity and incidence of natural menopause before age 45 controlling for potential confounding factors. We observed no significant association between adulthood physical activity and early menopause. For example, compared to women with <3 MET h/wk, the hazard ratio for women in the highest category (≥42 MET h/wk) of cumulatively-averaged total physical activity was 0.90 (95% confidence interval: 0.76-1.07; P-trend: 0.63). Similarly, activity in adolescence and young adulthood were unrelated to risk. Body mass index did not modify the relation of physical activity and early menopause. Our findings suggest that physical activity is not associated with incident early menopause.

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CHAPTER 1

INTRODUCTION

Early menopause is defined as the final menstrual period occurs before 45.[1] In Western

countries, about 10% of women experience early menopause.[2,3] Previous research suggests that

early menopause is associated with an increased risk of premature mortality, cardiovascular

disease, osteoporosis, cognitive decline, and clinical depression.[4-7] Genetic factors alone cannot

explain the development of early menopause, and.recent studies suggests that modifiable

lifestyle factors may impact the timing of menopause.[8-14] In particular, physical activity may be

related to timing of menopause.[15-21]

In premenopausal women, physical activity may influence ovarian function by altering

serum estrogens and other steroid hormone production via the hypothalamic-pituitary-ovarian

axis.[22] Intense physical activity can disrupt regular ovarian cycles, leading to luteal phase

decrease, anovulation and amenorrhea, which are related to age at menopause.[23]

Results from prior studies evaluating physical activity and menopause timing have been

inconsistent. Some studies observed later age at menopause in more physically active women,[15-16]

while others have reported earlier age at menopause,[17-21] Additional studies have found no

association.[24-27] To our knowledge, prior studies have not evaluated the relation of physical

activity with early menopause, which may be distinct from menopause occurring at later age.

We have assessed the relation between physical activity and incidence of natural early

menopause in the prospective Nurses' Health Study II (NHS2).

CHAPTER 2

SUBJECT AND METHODS

NHS2 cohort consist of 116,429 female U.S. registered nurses who aged 25 to 42 years old in 1989. Biennial mailed questionnaires collected longitudinal information on lifestyle factors and medical conditions starting in 1989. Follow up rates have reached at 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.

A. Assessment of Physical Activity

On study questionnaires in 1989, 1991, 1997, 2001, 2005 and 2009, women reported the average hours per week during the past year spent on the following activities: walking, jogging, running, bicycling (including on a stationary machine), racquet sports, lap swimming, calisthenics, and other aerobic activities. Response options ranged from 0 minutes to ≥11 per week. In 1997, women also reported the average amount of time per week spent in moderate and in strenuous recreational activities at three ages: grades 7-8 (ages 12-13), grades 9-12 (ages 14-17), and ages 18-22. Response options were none;0-0.5 hour/week; 1-2 hours/week; 3-4 hours/week; 5-6 hours/week; 7-10 hours/week; and ≥11 hours/week.

To incorporate the frequency, duration, and intensity of activity, we calculated a metabolic equivalent (MET) score for each of the 8 physical activities above. One metabolic equivalent, the energy expended by sitting quietly, is equivalent to 3.5 mL of oxygen uptake per kilogram of body weight per minute, or to 1 kcal/kg of body weight per hour.[28] We multiplied the hours per week of each activity by the MET score and added these values to create MET hours/week of total activity.

The validity and reliability of physical activity questionnaire in NHS II have been demonstrated in previous studies. In a subset of NHS II women (n=151), the correlation

coefficient between past-week activity recalls and the physical activity questionnaire was 0.79, and the test-retest correlation over 2 years was 0.59.[29]

B. Assessment of Early Menopause

In 1989 and on each subsequent biennial questionnaire, women were asked if their menstrual periods had ceased permanently. Those who indicated that their periods had ceased reported further information on the age when their menstrual periods ceased, and whether cessation was related to surgery, radiation or chemotherapy, or occurred naturally. Information regarding use of replacement sex hormones was collected as well. Eligibility for the current analysis was limited to women who were premenopausal and reported no age at menopause on the baseline 1989 questionnaire (n=108,812).

In this analysis, premenopausal women were followed for incidence of menopause until June, 2011 . We defined cases of early menopause as those women who reported natural menopause before age 45. The validity of the prospective assessment of menopausal status and timing has been assessed in a similar cohort (the Nurses' Health Study). Eighty-two percent of women experiencing natural menopause reported the same age at menopause within 1 year on repeated questionnaires, and 99% of women whose age at menopause was confirmed via medical records accurately reported their age at menopause within 1 year.[30]

C. Covariate Assessment

Demographic information including race, ethnicity, age, education and other information including height and age at menarche was collected in the baseline questionnaire in 1989. In the follow-up questionnaires, information on current weight, parity, oral contraceptive use, breastfeeding, hormone therapy use, and smoking was collected biennially. Updated body mass index (BMI) as weight (kg)/ height (m)^2 was calculated biennially with baseline height and updated weight.

Information on diet was collected using semi-quantitative food frequency questionnaires (FFQ) in 1991 and every four years thereafter. The FFQ assessed intake of 131 foods, beverages, and supplements, asking women to estimate how often they consumed specific foods and beverages on average over the previous year.[31-33] Additional information on dietary supplement use, including vitamin D and calcium, was collected on biennial questionnaires. Nutrients intake was adjusted for total energy using the residual method.[34] These FFQs have been previously assessed for validity.[35]

D. Statistical analysis

We divided women into categories of total MET hours/week of activity MET hours/ (<3, 3-9, 9-18, 18-27, 27-42, ≥42 MET hrs/wk) and time spent walking (None, 1-19 min/weeks; 20-60 min/weeks; 1-3 hours/week; ≥ 4 hours/week) as walking was the most common activity reported. We then compared the distribution of covariates measured at baseline with MET hrs/wk in 1989 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), stratifying on age in months and questionnaire cycle. Women were followed from 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, or June 2011, whichever came first.

We modeled current physical activity in three ways: 1) MET hrs/wk at baseline (1989) only; 2) current physical activity, using updated MET hrs/wk every 4 years; 3) cumulative average, of MET hrs/wk throughout follow-up.Walking was assessed as cumulative average hours per week. Adolescent moderate and strenuous activity time spent per week was also assessed.

Besides age adjusted model, we performed a multivariate model controlling age (years), age at menarche, smoking, parity, breastfeeding duration, alcohol intake, percentage of total calories from vegetable protein, and dairy vitamin D intake. We also performed a second multivariate model additionally controlled for BMI because BMI is strongly related to physical activity. These covariates were selected a priori based on previous studies of early menopause in our population. 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.

In order to evaluate whether estimates were comparable across categories of BMI, we conducted analysis stratified our population byon BMI (<25 vs. ≥25kg/m2), updated throughout follow-up, to evaluate if the association between physical activity and early menopause vary by adiposity. Likelihood ratio tests of effect measure modification were conducted to compare models with and without the multiplicative interaction of updated BMI and cumulative average total activity. Similar analysis was conducted by smoking and oral contraceptive. We evaluated potential effect modification by smoking (pack-years) and oral contraceptive use (specify variable used) similarly.

Finally, we evaluated if physical activity in adolescence and young adulthood was related to risk in age-adjusted and multivariable models.

Statistical analyses were conducted with SAS v9.3 software (SAS Institute Inc, Cary, NC).

CHAPTER 3

RESULTS

After 22 years of follow up, 2786 members of the analytic cohort experienced incident early menopause. Age-adjusted characteristics at baseline according to MET hr/wk of activity are presented in **Table 1**. In summary, women reporting higher physical activity were somewhat younger, had lower current BMI and BMI at age 18, and lower parity. Greater physical activity was associated with slightly longer duration of oral contraceptives use, and higher intake of alcohol vegetable protein and vitamin D.

Results from Cox proportional hazards models of the associations of total activity with risk of early menopause are shown **Table 2**. In the age-adjusted model, physical activity at baseline was not associated with risk of early menopause. For example, compared to women reported <3 MET hr/wk, women reporting ≥42 MET hr/wk of activity had a HR of 0.92 (95% CI = 0.81-1.06; p-trend = 0.34). Results adjusting for covariates (Models 2) were highly similar and additional adjustment for BMI had minimal impact. Similarly, results from analyses modeling updated and cumulative average physical activity showed no association with early menopause risk.

Time spent walking was not associated with early menopause risk (Table 2). In fully adjusted models, women reporting cumulative average of 4 or more hours per week of walking had a HR of 0.97 (95% CI = 0.79-1.20) compared to women reporting no walking (P trend = 0.94).

Results for models stratified by BMI are shown in **Table 3**. Estimates were very similar between strata, and we observed no evidence of effect modification by BMI (P = 0.98). Also, no evidence of effect modification was observed by smoking, and oral contraceptive (results not shown).

Results from fully-adjusted models evaluating associations of adolescent and young adult

physical activity with early menopause are shown in **Table 4**. We did not find moderate or

strenuous activity at any age (12-13 years, 14-17 years of 18-22 years) to be associated with risk.

CHAPTER 4

DISSCUSSION

In our study, physical activity was not found to be related to the occurrence of early natural menopause. Results were null for analyses modeling baseline physical activity level, updated physical activity level, and cumulative average physical activity level, even for the highest level of activity (equivalent to more than 8 hours of brisk walking or 4 hours of running per week), [28] did not have a lower risk of early menopause than those reporting less than 3 MET hours/week. Furthermore, we did not find an association between early menopause and participation in moderate or vigorous activity during adolescences or early adulthood.

To our knowledge, this is the first analysis of physical activity and risk of early menopause. Consequently, our results cannot be directly compared to prior studies evaluating how physical activity is related to the menopause timing overall. While there is some inconsistency in results from prior studies relating physical activity and age at menopause, most studies have observed no association, the sample size range from 185 to 17070.[24-27] Some studies have observed significant positive[17-21] or inverse associations,[15-16] but the associations in these studies have been consistently modest in magnitude. For example, in a prospective analysis of 3115 premenopausal Japanese women, Nagata et al (2012) reported that the likelihood of experiencing menopause during 10 years of follow-up was 17% higher for women with the highest level of physical activity (median: 59.5 METs h/wk) compared with lowest physical activity (median: 1.5 METs h/wk); HR: 1.17 95% CI 1.02-1.34; P-trend: 0.004.[18] In contrast, a retrospective analysis in the Shanghai Women's Health Study (n=33,054), reported a significant but modest lower age at menopause related to higher activity, comparing women reporting 4 or more hours per week of leisure-time physical activity during adolescence and adulthood vs. no

activity (49.1 vs. 49.5 years of age at menopause; p trend <0.01).[10] The mean age at menopause

difference is only several months, the significance is due to the large sample size. Overall, prior

literature suggested that the association between physical activity and and age at menopause is

weak or null, which is further confirmed in our study.

In premenopausal women, physical activity may influence ovarian function by altering

serum estrogens and other steroid hormone production via the hypothalamic-pituitary-ovarian

axis.[22] Moderate physical activity can inhibit gonadotropin-releasing hormone and gonadotropin

activity, accompanied by a decline in serum estrogen levels. Such hormonal alternations may

lead to the luteal phase inadequacy, atresia or degeneration of follicles, which has been

associated with earlier age at menopause.[36-40] However, intense physical activity may disrupt

ovarian function, leading to luteal phase inadequacy, anovulation and amenorrhea. As fewer

cumulative ovulations are associated with greater oocytes reserve, physical activity leading to

anovulation may contribute to later age at menopause.[23] Thus, the weak association between

physical activity and early menopause, if existed, may be due to the coexistence of two possible

mechanisms.

Physical activity may also be associated with menopause timing through its association

with adiposity. [41-43] In a recent analysis in our population, Szegda et al., 2017 reported a J-shaped

association between BMI and early menopause, with risk highest among underweight women.

In the present analysis, we did not find that level of adiposity to modify a relation of physical

activity and early menopause, which suggested mo effect modification.

A main limitation of our study is that we relied on self-report of physical activity. Thus,

measurement error may have attenuated associations and could potentially explain our null

results. However, our physical activity questionnaire has been shown to have good

reproducibility and validity as compared with seven day diaries in a subgroup of NHSII

women.[29]Also, our physical activity measures have been associated with other health outcomes such as depression, breast cancer, and colon cancer. in the NHS2, suggesting that misclassification is not substantial enough to obscure important associations. [44-48]

We also relied upon self-report of age at menopause and measurement error in determination of early menopause is possible. However, prior study in comparable NHS population suggested that the prospective report of onset of menopause has high reproducibility over multiple questionnaire cycles.[30] Furthermore, as the majority of our study population were mostly white, and results may not be directly applied to women of other racial/ethnic groups, to our knowledge there is no evidence that the physiology underlying differs relation of activity and menopause timing differs by race/ethnicity.

Strengths of our study included the prospective design, repeated assessment of physical activity, and high follow-up rate, large sample size, large number of women with early menopause and the novelty of evaluating the relation of PA with risk of early menopause.In summary, we observed no evidence that physical activity is associated with risk of early menopause.

Given that results from previous studies of activity and time to menopause also have been modest at best, it appears unlikely that physical activity is importantly related to early menopause.

Table 1. Age-Standardized Characteristics of premenopausal women according to category of total physical activity at baseline (1989): Nurses' Health Study II, 1989[1]

	Total Physical Activity(MET-h/week)					
Characteristic	<3 (n=16,287)	3-9 (n=24,544)	9-18 (n=22,645)	18-27 (n=14,282)	27-42 (n=12,989)	≥ 42 (n=17,669)
	Mean (SE)					
Age, y[2]	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 18, kg/m^2	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^2	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	4.3 (0.06)	3.9 (0.04)	3.6 (0.05)	3.6 (0.06)	3.6 (0.06)	3.7 (0.05)
OC use duration	43.3 (0.4)	43.5 (0.3)	44.1 (0.3)	44.7 (0.4)	44.4 (0.4)	45.2 (0.3)
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	1.6 (0.01)	1.6 (0.01)	1.5 (0.01)	1.4 (0.01)	1.4 (0.01)	1.3 (0.01)
Breastfeeding duration,m	12.2 (0.1)	13.1 (0.1)	13.5 (0.1)	13.5 (0.2)	13.3 (0.2)	13.0 (0.2)
Vitamin D						
Total	357.1 (2.3)	370.3 (1.8)	389.3 (1.9)	405.9 (2.4)	408.7 (2.5)	419.5 (2.2)
Dietary	235.0 (1.1)	245.7 (0.9)	254.6 (0.9)	260.0 (1.1)	263.1 (1.2)	265.7 (1.1)
Dairy	126.0 (0.9)	130.4 (0.8)	132.8 (0.8)	132.1 (1.0)	130.8 (1.0)	128.1 (0.9)
Supplemental	122.1 (1.9)	124.6 (1.6)	134.8 (1.6)	145.9 (2.0)	145.5 (2.1)	153.8 (1.9)
Vegetable protein intake, % of total 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)
	%					
OC use Status						
never	17.4	17.2	16.8	16.7	17.3	17.2
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
Parious						
Yes	75.8	74.7	72.7	68.6	66.6	61.5
No	24.2	25.3	27.3	31.4	43.4	38.5
Smoking Status						
never	64.7	65.9	66.3	66.1	66.0	64.4
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

[1]Values are means ± SEs or percentages, unless otherwise indicated. All characteristics were calculated with the use of generalized linear models adjusted for the age of women in 1989.Values are age-adjusted.
[2]Values are means ± SDs.

Table 2. Hazard Ratios (95% CIs) for early menopause by level of physical activity: Nurses' Health Study II (1989-2011)[1]

	Cases	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
Activity in 1989				
<3 MET h/wk	437	1	1	1
3-9 MET h/wk	648	0.98 (0.87, 1.10)	1.00 (0.88, 1.13)	1.00 (0.88, 1.13)
9-18 MET h/wk	574	0.94 (0.83, 1.06)	0.97 (0.85, 1.10)	0.96 (0.85, 1.09)
18-27 MET h/wk	363	0.94 (0.81, 1.08)	0.97 (0.84, 1.11)	0.96 (0.83, 1.10)
27-42 MET h/wk	336	0.97 (0.84, 1.12)	1.01 (0.87, 1.16)	0.99 (0.86, 1.14)
≥ 42 MET h/wk	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
Updated Activity				
<3 MET h/wk	515	1	1	1
3-9 MET h/wk	795	1.01 (0.90, 1.12)	1.03 (0.92, 1.16)	1.03 (0.92, 1.15)
9-18 MET h/wk	438	0.94 (0.82, 1.07)	0.98 (0.86, 1.12)	0.97 (0.84, 1.10)
18-27 MET h/wk	284	1.02 (0.88, 1.19)	1.07 (0.92, 1.24)	1.05 (0.90, 1.22)
27-42 MET h/wk	241	0.98 (0.83, 1.14)	1.01 (0.86, 1.19)	0.99 (0.84, 1.16)
≥ 42 MET h/wk	234	0.92 (0.78, 1.07)	0.94 (0.80, 1.11)	0.91 (0.77, 1.07)
P-trend		0.26	0.41	0.21
Cumulative Average Activity				
<3 MET h/wk	308	1	1	1
3-9 MET h/wk	634	0.93 (0.81, 1.06)	0.94 (0.82, 1.08)	0.94 (0.82,1.08)
9-18 MET h/wk	667	0.90 (0.79, 1.04)	0.94 (0.82, 1.07)	0.93 (0.81,1.07)
18-27 MET h/wk	466	1.03 (0.89, 1.19)	1.06 (0.91, 1.22)	1.04 (0.90,1.21)
27-42 MET h/wk	358	0.92 (0.79, 1.08)	0.95 (0.81, 1.11)	0.93 (0.80,1.09)
≥42 MET h/wk	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
Cumulative Average Walking				
None	116	1	1	1
1-19 minutes	334	0.97 (0.78, 1.19)	1.02 (0.82, 1.26)	1.02 (0.83, 1.27)
20-60 minutes	658	0.86 (0.71, 1.05)	0.92 (0.75, 1.13)	0.93 (0.76, 1.13)
1-3 hours	1206	0.88 (0.73, 1.07)	0.96 (0.79, 1.17)	0.96 (0.79, 1.17)
≥ 4 hours	438	0.92 (0.75, 1.13)	0.98 (0.80, 1.20)	0.97 (0.79, 1.20)
P-trend		0.97	0.80	0.94

[1] Adjusted for age only
[2] Adjusted for age, 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), ever use Oral Contraceptive (never/past/current),% of total calories from vegetable protein (quintiles 1-3, 4+5), alcohol intake (<10, ≥10 g/day, and dairy source of vitamin D (quintiles)).
[3] Adjusted for BMI [in kg/m² (<18.5, 18.5-<25, 25-<30, or ≥30)] additionally

Table 3. Hazard Ratios (95% CIs) for the Association of Cumulative Average Activity and Incidence of Early Menopause Stratified by Body Mass Index: Nurses' Health Study II (1989-2011)[1,2]

Total Activity	Cases	BMI <25 HR (95% CI)	Cases	BMI ≥ 25 HR (95% CI)
<3 MET h/wk	182	1	126	1
3-9 MET h/wk	394	0.94 (0.79, 1.12)	240	0.95 (0.76,1.18)
9-18 MET h/wk	453	0.94 (0.79, 1.12)	214	0.91 (0.73,1.14)
18-27 MET h/wk	327	1.04 (0.86, 1.25)	139	1.07 (0.84,1.38)
27-42 MET h/wk	261	0.93 (0.77, 1.13)	97	0.95 (0.72,1.25)
≥ 42 MET h/wk	265	0.87 (0.72, 1.06)	83	0.94 (0.71,1.25)
P-trend		0.21		0.98

[1] Multivariable Cox proportional hazards model 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), ever use Oral Contraceptive (never/past/current), % of total calories from vegetable protein (quintiles 1-3, 4+5), alcohol intake (<10, >=10 g/day, and dairy source of vitamin D (quintiles)).
[2] P-interaction is 0.98

Table 4. Hazard Ratios (95% CIs) for early menopause by level of moderate and strenuous adolescent and young adult activity: Nurses' Health Study II (1989-2011)[1]

	cases	Moderate Activity HR (95% CI)		Strenuous Activity HR (95% CI)
Age 12-13 (grade 7-8)				
None	118	1	243	1
0-0.5 h/wk	177	1.12 (0.88, 1.41)	179	1.08 (0.89,1.31)
1-2 h/wk	645	1.01 (0.83, 1.23)	500	0.96 (0.82,1.12)
3-4 h/wk	585	1.08 (0.89, 1.32)	479	1.03 (0.88,1.20)
5-6 h/wk	284	0.98 (0.79, 1.22)	349	1.03 (0.87,1.21)
7-10 h/wk	140	0.91 (0.71,1.17)	206	0.97 (0.80,1.17)
>11 h/wk	110	0.99 (0.76,1.28)	138	0.98 (0.79,1.20)
P-trend		0.29		0.80
Age 14-17 (grade 9-12)				
None	106	1	222	1
0-0.5 h/wk	174	1.14 (0.89, 1.45)	183	1.12 (0.92, 1.36)
1-2 h/wk	639	1.04 (0.84, 1.27)	463	0.91 (0.77, 1.06)
3-4 h/wk	588	1.11 (0.90, 1.36)	448	0.93 (0.79, 1.09)
5-6 h/wk	290	1.01 (0.80, 1.26)	360	0.97 (0.82, 1.14)
7-10 h/wk	152	1.00 (0.78, 1.28)	238	0.94 (0.78, 1.13)
>11 h/wk	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
0-0.5 h/wk	207	0.99 (0.79, 1.24)	290	1.03 (0.88, 1.21)
1-2 h/wk	665	1.04 (0.86, 1.25)	575	1.01 (0.87, 1.16)
3-4 h/wk	577	1.10 (0.91, 1.33)	449	1.05 (0.90, 1.21)
5-6 h/wk	283	1.03 (0.83, 1.27)	249	0.97 (0.82, 1.15)
7-10 h/wk	118	0.94 (0.73, 1.21)	137	1.06 (0.86, 1.30)
>11 h/wk	77	1.06 (0.79, 1.40)	88	1.17 (0.92, 1.49)
P-trend		0.97		0.31

[1] Multivariable Cox proportional hazards model adjusted for age, pack-years of smoking (0-10, 11-20, or $\geq$21), BMI [in kg/m^2 (<18.5, 18.5-<25, 25-<30, or $\geq$30)] , age at menarche (continuous), parity (nulliparous, 1-2, or $\geq$3), breastfeeding duration (in months; continuous), ever use Oral Contraceptive (never/past/current), % of total calories from vegetable protein (quintiles 1-3, 4+5), alcohol intake (<10, >=10 g/day, and dairy source of vitamin D (quintiles)).

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