



Published in final edited form as:

Menopause. 2008 ; 15(5): 924–933. doi:10.1097/gme.0b013e3181786adc.

Dietary and lifestyle predictors of age at natural menopause and reproductive span in the Shanghai Women's Health Study

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Abstract

Objectives: Modifiable factors predicting the onset of menopause, a transition with important implications for women's health, have not been fully characterized. We evaluated the impact of dietary, lifestyle and reproductive factors on age at natural menopause and reproductive span in Chinese women.

Design: Study participants were Chinese women aged 40–70 who experienced natural menopause and participated in a population-based, prospective study, the Shanghai Women's Health Study (n=33,054). Dietary intakes at the baseline survey were assessed by food-frequency questionnaire. Regression (β) coefficients, calculated by multivariable linear regression, were used to estimate the effects of dietary, lifestyle, and reproductive patterns on age at menopause and the number of reproductive years, adjusting for potential confounding factors.

Results: Early menarche, younger age at first-live birth, older age at last live-birth, longer duration of breastfeeding, and higher parity were associated with longer reproductive years ($P_{trend} < 0.01$ for all). Higher body-mass index at age 20, mid-life weight gain, and leisure-time physical activity during adolescence and adulthood predicted later menopause and longer reproductive span ($P_{trend} < 0.01$ for all). Total intakes of calories, fruits, protein, and possibly carbohydrates were positively associated with later menopause ($P_{trend} < 0.05$ for all) and longer reproductive span [$P_{trend} < 0.05$, except for carbohydrates ($P_{trend} = 0.06$)], and long-term tea consumption predicted longer reproductive span ($P_{trend} = 0.03$). Vegetable, fat, soy, and fiber intakes did not significantly affect reproductive span or age at menopause. Smoking was inversely related to both age at menopause and reproductive span ($P_{trend} < 0.01$).

Conclusions: In addition to reproductive factors, intakes of fruit, protein, smoking, and tea consumption, lifetime patterns of physical activity, and weight gain influenced the onset of menopause and/or reproductive span in Chinese women.

Keywords

Age at onset of menopause; Dietary intake; Physical activity; Reproductive span; Smoking; Tea; Weight gain

INTRODUCTION

Menopause marks the natural cessation of reproductive capacity in women as well as the onset of increased risk for many chronic health problems.¹⁻³ Early menopause (at age 40-45) is associated with the development of osteoporosis, obesity and other features of the metabolic syndrome, and cardiovascular disease,⁴⁻⁶ whereas delayed menopause (occurring at age 55-60) is associated with an increased risk of estrogen-responsive cancers.^{7,8}

Considerable research has been published regarding lifestyle and reproductive factors that may predict the age of onset of menopause in women of different racial/ethnic and socioeconomic backgrounds.⁹⁻¹² The results of these studies, primarily conducted in Western countries, have been largely inconsistent. Several factors reported to affect the timing of menopause include educational level, occupation, marital status, age at menarche, parity, oral contraceptive use, and smoking.¹³⁻¹⁵ A few studies have suggested that physical activity and diet influence the age at which natural menopause occurs.^{16,17} Some studies have observed earlier menopause among malnourished women or women with a low body-mass index (BMI), while overweight or obese women may experience menopause at a later age.¹⁷⁻²⁰ However, other studies have shown no such correlations.^{14,21} The few prospective cohort and cross-sectional studies that have investigated the effects of dietary fat and protein intake on menopause have had somewhat inconsistent results.²²⁻²⁵ A German cohort study reported that higher total intakes of fat, meat and protein all correlated with later onset of menopause.²⁵ In Japanese women, an inverse association was observed between the intake of vegetables and the age at onset of menopause,²⁴ but no effect of fat intake was observed, in contrast to findings from an earlier cross-sectional study in the same population.¹⁶ Finally, in a recent interventional study, women who followed a low-fat, high-carbohydrate diet showed no demonstrable change in the timing of menopause compared to control women who followed their usual diet.²²

Some of the inconsistent findings in prior studies may be due to small sample sizes, selection bias in some instances, and the genetic and environmental heterogeneity among the populations studied. We examined the role of specific dietary nutrients as well as reproductive and lifestyle factors on the age of onset of natural menopause and on the duration of regular menses in a large, population-based cohort of urban Chinese women.

METHODS

Study population

The Shanghai Women's Health Study (SWHS) is a prospective cohort study that was designed to investigate associations of diet and lifestyle with chronic diseases. The study comprises 74,942 women from urban Shanghai, aged 40-70 years at recruitment (March 1997 - May 2000). Details regarding subject recruitment methods and baseline surveys have been published elsewhere.²⁶ Briefly, baseline assessment of women included a self-administered questionnaire to elicit information regarding socioeconomic and demographic characteristics, lifestyle factors, medical, surgical, and reproductive history. A separate questionnaire was administered by trained personnel during an in-person interview to obtain detailed information on dietary habits, weight history, physical activity, and standardized anthropometric measurements. A total of 37,256 (49.6%) women were postmenopausal at study recruitment. Women who reported cessation of menstruation as a result of hysterectomy, bilateral ovariectomy or the use of HRT were excluded ($n=4,202$). The remaining 33,054 women who had experienced natural menopause (44.1% of all subjects and 88.7% of all postmenopausal women) were included in the current study. The study protocols were approved by all institutes involved in the study, and written informed consent was obtained from all subjects.

Outcome ascertainment

The primary outcomes in this study were age at onset of natural menopause and the total number of reproductive years as of the baseline recruitment. Menopausal status was defined as the absence of menstruation for ≥ 12 months, according to the World Health Organization definition of menopause. The age at which menopause occurred and the reasons for its occurrence [natural menopause, hysterectomy, or hormone replacement therapy (HRT)] were recorded. The number of reproductive years, or reproductive span, was defined as the duration between age at menarche and age at menopause.

Ascertainment of exposures

Reproductive factors—Data on other reproductive variables, which were obtained by self-administered questionnaire or via in-person interview, included: age at menarche, number of pregnancies, number of abortions, miscarriages and stillbirths, number of live births, ages at first and last live births, duration of breastfeeding for each live birth, usual length and regularity of menstrual cycles, and ever-use of birth control methods (contraceptive pills, injections, intrauterine devices, and tubal ligation).²⁶

Anthropometrics and physical activity—Current weight and height were estimated by two measurements taken by interviewers using standard protocols. Data on recalled weight and height at age 20 and 50 years were collected. BMI was calculated as (weight, kg)/(height, meter²). Information about physical activity patterns during adolescence and adulthood was ascertained from all participants through the validated SWHS Physical Activity Questionnaire (PAQ).²⁷ Exercise during adolescence (age 13-19) and adulthood was defined as participation in leisure-time or sports activities at least once per week for more than 3 months continuously. In addition, regular exercise during adolescence was defined by the time spent (years) and duration (hours per week) of participation in the 3 most common types of exercise in school, both of which were summarized as the average duration of exercise during adolescence (hrs/wk/yr). Participants were also asked to rate the amount of time spent on exercise in adolescence and adulthood (in the past 5 years) in comparison to other people using Likert-type responses (*i.e.*, more than average, a little more than average, about average, a little less than average, and less than average). From the above responses, a single lifetime physical activity variable was created with four groups: 1) low activity during adolescence and adulthood, 2) low activity during adolescence but medium-high during adulthood, 3) moderate-high activity during adolescence but low during adulthood, and 4) moderate-high activity during adolescence and adulthood.

Dietary factors and smoking—Dietary intake data were collected during in-person interviews using a validated food-frequency questionnaire (FFQ) that included 77 food items/groups commonly consumed over the 12 months preceding the interview.²⁸ During the face-to-face interview, each participant was first asked about how often, on average, during the previous year she had consumed a specific food or food group (the possible responses were daily, weekly, monthly, yearly, or never), followed by a question on the amount consumed in grams per unit of time. Intake of nutrients was then calculated by multiplying the amount of food consumed by the nutrient content per gram of food according to the Chinese Food Composition Tables.²⁹ We also collected information on changes in eating habits with respect to main food groups such as red meat, vegetables and fruits in the 5 years preceding the interview compared to the past year.

Smoking was defined as smoking ≥ 1 cigarette per day for >6 months continuously at some point during a woman's life. Regular drinking of beer or wine and tea ≥ 3 times/week for >6 months continuously was defined as regular consumption of alcohol or tea, respectively.

Statistical Analysis—Age at menopause and reproductive years were normally distributed in this study population. The age-adjusted mean age at onset of menopause or mean number of reproductive years by demographic variables were calculated. Multivariable linear regression analysis was used to estimate adjusted mean differences and their 95% confidence intervals (CI) for age at natural menopause and number of reproductive years associated with exposures of interest. Variables adjusted for in models with non-reproductive outcome variables included age (continuous), educational level (no formal education/elementary, middle, high school, and college or higher), type of occupation (manual worker, clerical/administrative, and professional), age at menarche (≤ 11 , 12-13, 14-15 and ≥ 16 years), number of live births (nulliparous, 1, 2, 3, and ≥ 4), oral contraceptive use (never/ever), weight gain between the ages 20 and 50 years (in quartiles), lifetime physical activity pattern, cigarette smoking (never/ever), and total energy intake (continuous). Additional adjustment for tea or alcohol use, regular exercise (yes/no), family income, current employment (yes/no), total months of breastfeeding, age at last live birth, menstrual cycle pattern, and years between age at menarche and first live birth did not appreciably alter the results. Therefore, these variables were not included in the final model. Tests for trend were performed by entering the categorical variables as continuous parameters in the model.

The Bonferroni correction was applied to account for multiple comparisons, in order to reduce the frequency of false-positive results. All statistical tests were two-sided and were performed using SAS statistical software, version 9.1 (SAS Institute, Cary, NC).

RESULTS

The mean age of the study population was 60.2 years. The age at which natural menopause occurred ranged from 40.6-50.0 years with an overall mean of 49.2 ± 3.7 . The number of reproductive years ranged from 31.6 to 36.7 with a mean of 34.0 ± 4.1 . Only 4.7% of women had experienced a menopause at age of ≤ 45.4 years (data not shown).

The distributions of socioeconomic and demographic factors in relation to age at natural menopause and reproductive span are shown in Table 1. The latest onset of menopause and longest reproductive span were reported by women in the cohort who were 55-59 years of age. Socioeconomic and demographic factors associated with later menopause and longer reproductive span (adjusted for age at enrollment to account for potential confounding by birth cohort) included: higher educational level, higher income group, a professional occupation, current employment, and married status.

Reproductive factors

Associations of reproductive factors with age at menopause onset and reproductive span are presented in Table 2. The mean age at menarche was 15.2 ± 1.8 years (range 14-16 years) in this study population. Approximately 0.7% of women experienced early menarche (at age ≤ 11 years) and 42.1% experienced late menarche (at age ≥ 16 years). Older age at menarche was significantly associated with later menopause and shorter reproductive span ($P_{trend} < 0.01$). Number of live births was positively associated with later menopause and extended reproductive span ($P_{trend} < 0.01$). After proper adjustments, younger age at first and older age at last live birth and longer duration of breastfeeding were each associated with slightly delayed menopause and more reproductive years ($P_{trend} < 0.01$). Menstrual irregularity was related to fewer reproductive years ($P_{trend} < 0.01$), but not to menopausal age. A significant proportion (24.5%) of women in the cohort had used birth control methods (oral contraceptive pill, intrauterine device, or tubal ligation), and their use was positively associated with the timing of menopause and with the number of reproductive years ($P_{values} < 0.01$ for all methods, Table 2). The time between menarche and the first live-birth was negatively associated with menopausal age and positively associated with reproductive span ($P_{values} < 0.01$). Self-reported

abortions and miscarriages or stillbirths had no detectable effect on age at menopause or number of reproductive years (data not shown).

Anthropometrics and physical activity

As shown in Table 3, the recalled weights of women at 20 years of age ranged from 45.0 to 54.0 kg with a mean of 49.4 ± 6.6 kg. Weight ≥ 54 kg and BMI ≥ 21.4 at age 20 predicted a slightly later onset of menopause and longer reproductive span ($P_{trend} < 0.01$ for both factors). Overall, women reported gaining an average of 7.5 kg between ages 20 and 50, and greater weight gain during this age period was associated with slightly later menopause and a longer reproductive capacity ($P_{trend} < 0.01$). More than half of the women in this study reported low exercise participation during their lifetime (54.4% in adolescence and 57% in adulthood, data not shown). Presented in Table 4 are the associations of physical activity with age at menopause and reproductive span. Women who reported moderate-to-high exercise participation and more intensive exercise during adolescence were significantly more likely to experience later menopause and more reproductive years than their less physically active counterparts ($P_{values} < 0.05$). Overall, women who exercised at moderate to high levels during both adolescence and adulthood were more likely to have later menopause and a longer reproductive span ($P_{values} < 0.01$).

Dietary factors and smoking

Associations between dietary factors and reproductive outcomes are presented in Table 5. Total energy intake was significantly associated with older age at menopause and longer reproductive span ($P_{trend} < 0.01$ for both outcomes). Higher intakes of total fruit, protein and carbohydrates were positively associated with slightly later menopause and longer reproductive span ($P_{trend} < 0.05$ for all factors, except for carbohydrates and reproductive span with $P_{trend} < 0.06$). Intake of total fiber also tended to predict later menopause, but the association did not reach statistical significance ($P_{trend} = 0.09$). Intakes of total vegetables, soy, fiber, and fat had no discernible impact on the timing of menopause or the number of reproductive years. We also examined mean differences in the age at menopause and in reproductive span across dietary exposure categories, using the residual method to adjust for total energy intake³⁰, but the results did not differ from the results presented. Additionally, we conducted analyses among study participants who reported that their dietary habits in the 5 years prior to enrollment had not changed or had only slightly changed compared with their dietary habits within a year prior to enrollment. Associations of dietary red meat, vegetable and fruit intakes with reproductive outcomes in this analysis were similar to our initial findings for these dietary intakes (data not shown).

Among the 4.4% of women who reported ever smoking, those who had smoked for ≥ 28 years were significantly more likely to have experienced early menopause and fewer reproductive years (Table 6). Similarly, current smokers were more likely to have experienced earlier menopause and a shorter reproductive span compared to former smokers ($P_{values} < 0.01$ for both factors). In contrast, women who regularly drank tea for ≥ 19 years were more likely to have had an extended reproductive span ($P_{trend} = 0.03$). Alcohol consumption, which was rare in this cohort, was not associated with menopausal age or reproductive span.

Application of the Bonferroni correction for multiple statistical tests did not significantly change any of our results; initially significant p -values remained significant (data not shown).

DISCUSSION

Menopause marks an important transition for a woman and has significant implications for the risk of cardiovascular diseases and cancer. Identifying predictors, particularly modifiable

factors, for onset of menopause would thus have a significant impact on etiological research and the prevention of these chronic diseases. The current study is one of very few studies to systematically evaluate the effects of a wide variety of factors on the timing of menopause as well as on the duration of reproductive life in Chinese women. Age at menopause and the reproductive span in this population were associated with specific dietary factors and with patterns of physical activity and weight gain during adolescence and adulthood, although the magnitude of these effects was small (on the order of several months to <1.5 years). The mean age at natural menopause in this population was similar to the mean age at menopause that has been reported for Asian women in other studies (49.0-50.0).^{31,32} The mean number of reproductive years in our study population was 34.0±4.1, slightly less than that of women in the United States.³³

Consistent with many studies,^{10,11,34,35} various socioeconomic factors predicted the age of menopause and reproductive span in Chinese women. Lower educational attainment and manual work were associated with an earlier age at menopause and fewer reproductive years, whereas married status, and increased parity predicted slightly later menopause and a longer reproductive span as demonstrated in other studies.^{9,36} Socioeconomic factors may impact the onset of menopause through effects on dietary pattern and quality, physical activity, obesity, and access to contraceptives, but the precise nature of these relationships is unclear.

With regard to reproductive factors such as parity, fewer cumulative menstrual cycles in parous women may be associated with a larger reserve of oocytes and longer exposure to estrogen.^{37,38} A similar mechanism may explain our finding, in accord with previous studies, that oral contraceptives slightly delayed menopause and prolonged the reproductive span.³⁹ However, other studies have reported no such effects,^{13,25} or opposite effects with oral contraceptives.^{11,39} We also observed that women who reported having lifelong menstrual cycle irregularity tended to have earlier menopause and fewer reproductive years in this study, consistent with most previous studies.^{40,41} Increased duration of breastfeeding was associated with delayed onset of menopause and longer reproductive span in this study, possibly because prolonged breastfeeding can prevent follicle depletion and preserve ovarian function.^{42,43} Similarly, later age at menarche may have resulted in delayed exhaustion of ovarian follicles and later menopause in this study,^{15,25} although other studies have found either no association or an inverse association between age at menarche and the timing of menopause.^{13,44} In this study, later age at first live birth was associated with earlier menopause and fewer reproductive years,⁴⁵ supporting the concept that a decline in follicle count and/or sex hormone levels may lead to both reduced fertility, earlier menopause, and fewer overall reproductive years. Not all studies have reported the same association between age at first live birth and onset of menopause, however.⁴²

Few studies,^{20,46,47} including this one, have investigated the effects of weight gain and physical activity during adolescence, young adulthood, and the reproductive years on the timing of menopause and overall reproductive span. Our study suggests that weight gain between ages 20 and 50 and increased BMI during early adulthood (at age 20) may predict a later age at menopause and more reproductive years. We also found that higher LTPA during both adolescence and adulthood was associated with later age at menopause and a longer reproductive span, similar to other reports.^{46,48} Although severe weight loss or vigorous exercise may suppress ovarian function by lowering estrogen levels and increasing sex-hormone-binding globulin levels, the mechanisms underlying the associations between moderate premenopausal weight gain or physical activity and onset of menopause remain to be determined.^{25,49,50}

The effects of nutrition on sex hormone levels and reproductive function have been investigated in animal models.^{51,52} The results of the few published studies conducted on the impact of

diet on the timing of menopause have been inconsistent.^{16,22,24,25} In our study, high intake of total calories was significantly associated with delayed age at menopause and a longer reproductive span. Other studies have also associated aging, menstrual irregularity and infertility in women with total energy consumption.⁵³⁻⁵⁵ High fruit intake may delay the onset of menopause and increase the overall reproductive span due to the antioxidant content of fruit; oxidative stress has been implicated in menopause onset and the age-related decline in fertility via the adverse effects of reactive oxygen species on the number and quality of ovarian follicles produced.^{56,57} High protein intake and, to a lesser extent, high carbohydrate intake among the Chinese women in this study predicted a delay in menopause and an increase in the reproductive span. The European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study found a similar association with protein intake, but carbohydrate intake was inversely related to age at natural menopause.²⁵ Other studies failed to find any association.^{22,24} In contrast to previous studies^{16,25} but consistent with some other reports,²²⁻²⁴ our results failed to support any association between total fat, saturated fat, or red meat intake and the onset of menopause. Although two previous prospective studies found that early menopause was associated with high vegetable intake,^{24,25} we did not substantiate that observation. Contrary to a report of a positive relationship between soy intake and the onset of menopause,¹⁶ we observed no significant impact of dietary soy products on either the age at which menopause occurred or on the overall number of reproductive years in the women in our study. These results concur with two other studies that failed to find such an association.^{24,25} Similarly, our study findings are consistent with prior reports that dietary fiber does not significantly alter sex hormone levels in premenopausal women.^{58,59}

To our knowledge, this is the first study to investigate the relationship between tea consumption and reproductive outcomes. Regular tea consumption predicted an extended reproductive span, although the assessment of tea consumption in this study did not distinguish between types of tea. Recently, the antioxidant effects of tea have been extensively investigated,⁶⁰ and it has been suggested that some constituents of green and black tea, such as tea flavonoids (e.g., epigallocatechin gallate, or EGCG), exert non-steroidal estrogenic effects that counteract degenerative processes.^{56,61} However, studies exploring these effects remain inconclusive,^{62,63} and this issue requires further study.

Polycyclic, aromatic hydrocarbons present in cigarette smoke may be toxic to ovarian follicles, resulting in earlier ovarian failure and menopause.^{64,65} We found an inverse association between smoking and age at menopause, supporting some prior reports that smoking, and particularly a long smoking history, predict earlier onset of menopause and a shorter reproductive span.^{62,66} However, the prevalence of smoking in our study population is low, which limited our ability to evaluate the dose-response relationship previously observed.^{11,14} Similarly, the effects of alcohol on reproductive outcomes could not be adequately evaluated in our study, because very few women (2.4%) reported regular alcohol consumption.

Our study represents the first large, population-based study to comprehensively evaluate a variety of factors, including diet and physical activity, on the age at natural menopause and number of reproductive years among Asian women. Many previous epidemiological studies on the timing of menopause were small or were conducted among highly selected populations such as clinic-based populations. The high response rate (92%) in this study further enhances the validity and generalizability of our findings; the detailed and comprehensive exposure assessments and strict quality control procedures are other noticeable strengths. However, several methodological limitations should also be considered. Assessments of some exposures, including menstrual and reproductive history, dietary intakes, and patterns of weight gain and physical activity, were entirely based on self-report and may therefore be subject to misclassification. Information on maternal menstrual history, which has been shown to influence both age at menarche and menopause in Chinese women, was not available. Dietary

intakes and physical activity were assessed at enrollment, after menopause had occurred. Changes in dietary intake and physical activity after menopause may therefore have influenced the study results. However, analyses in a subset of the cohort that reported a stable dietary pattern over the 5 years prior to study enrollment showed similar associations. Continued follow-up of the premenopausal women in this cohort and/or future prospective studies are therefore needed to verify our findings. Finally, given the large sample size of the study, some of the significant small differences may not have clinical significance.

CONCLUSIONS

Consistent with the literature, we found in this Chinese population that delayed onset of menopause and longer reproductive span were associated with earlier age at first live birth, longer duration of breastfeeding, and oral contraceptive use, as well as high intakes of calories, fruits, protein, and possibly carbohydrates. Novel findings include positive associations with weight gain, a pattern of lifelong physical activity, and tea consumption. Future studies incorporating repeated, prospective measurements of these exposures and correlations with sex hormone levels are needed to replicate these associations and to explore their underlying mechanisms and significance of the associations.

ACKNOWLEDGEMENTS

This study was supported by research grants R01CA70867 and HL079123 from the National Institutes of Health, USA.

Sources of support: This study was supported by research grants R01CA70867 and HL079123 from the National Institutes of Health, USA.

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Table 1
Mean age at the onset of natural menopause and mean reproductive span according to socioeconomic and demographic factors

	No. of women n=33,054	Proportion (%)	Age at menopause (y) Mean (SD)	p value	Reproductive span* Mean (SD)	p value
Age group (y)						
40-44	179	0.5	40.6 (2.1)		26.1 (2.9)	
45-49	1385	4.2	45.4 (2.4)		30.6 (2.8)	
50-54	5523	16.7	48.8 (2.7)		33.9 (3.3)	
55-59	6901	20.9	50.0 (3.4)		35.2 (3.8)	
60-64	9072	27.5	49.6 (3.8)		34.3 (4.3)	
65-70	9994	30.2	49.1 (3.9)	<0.01	33.5 (4.3)	<0.01
Education						
College/above	4637	14.0	50.2 (3.7)		35.9 (4.1)	
High school	6812	20.6	49.6 (3.7)		35.0 (4.1)	
Middle school	7408	22.4	49.0 (3.7)		33.9 (4.1)	
Elementary school/below	14186	43.0	48.7 (4.0)	<0.01	33.0 (4.4)	<0.01
Family income						
High	8405	25.4	49.6 (3.8)		34.8 (4.2)	
Middle	12753	38.6	49.1 (3.7)		33.9 (4.1)	
Low	11889	36.0	48.9 (3.5)	<0.01	33.5 (4.6)	<0.01
Occupation						
Professional	9710	29.6	49.8 (3.7)		35.2 (4.1)	
Clerical & administrative	5710	17.4	49.1 (3.6)		33.8 (4.1)	
Manual worker	17405	53.0	48.8 (3.7)	<0.01	33.4 (4.1)	<0.01
Marital status						
Never married	194	0.6	48.2 (3.7)		33.4 (4.1)	
Presently married	27554	83.3	49.2 (3.7)		34.1 (4.1)	
Widowed	4622	14.0	48.9 (3.8)		33.5 (4.2)	
Separated/Divorced	684	2.1	49.1 (3.7)	<0.01	34.0 (4.1)	<0.01
Currently employed						
No	25386	76.8	49.1 (3.8)		33.9 (4.2)	
Yes	7668	23.2	49.4 (3.9)	p<0.01	34.4 (4.5)	p<0.01

Note: p values were derived from ANOVA

* Adjusted for age at enrollment (continuous) except for the 'age group' variable

Adjusted mean differences in age at onset of natural menopause and in reproductive span according to reproductive factors

	No. of women (n=33,054)	Age at natural menopause (years)			Reproductive span (years)		
		Mean (SD)	Mean difference β (95% CI)*	<i>P</i> for trend	Mean (SD)	Mean difference β (95% CI)	<i>P</i> for trend
Age at menarche (y)							
≤11	216	48.9 (4.3)	0.00 (referent)		38.1 (4.3)	0.00 (referent)	
12-13	6066	49.2 (3.7)	0.40 (0.1, 0.9)		36.4 (3.7)	-1.47 (-2.0, -1.0)	
14-15	12858	49.2 (3.6)	0.51 (0.0, 1.0)		34.7 (3.7)	-3.11 (-3.6, -2.6)	
≥16	13911	49.2 (3.8)	0.55 (0.1, 1.0)	<0.01	32.2 (4.0)	-5.43 (-5.9, -4.9)	<0.01
Delay from menarche to first live birth (y)**							
<8	15917	49.3 (3.8)	0.00 (referent)		33.3 (4.2)	0.00 (referent)	
≥8	16097	49.2 (3.6)	-0.19 (-0.3, -0.1)	<i>p</i> <0.01	34.7 (3.9)	0.91 (0.8, 1.0)	<i>p</i> <0.01
Age at first live birth (y)**							
<20	6882	49.3 (3.9)	0.00 (referent)		34.0 (4.3)	0.00 (referent)	
20-24	13951	49.2 (3.6)	-0.16 (-0.3, 0.0)		33.9 (4.1)	-0.61 (-0.7, -0.5)	
25-29	8865	49.1 (3.6)	-0.32 (-0.4, -0.2)		34.2 (4.1)	-0.81 (-1.0, -0.7)	
≥30	2319	49.0 (3.5)	-0.49 (-0.7, -0.3)	<0.01	34.2 (3.9)	-0.86 (-1.1, -0.6)	<0.01
Number of live births							
0	1037	48.3 (3.8)	0.00 (referent)		33.2 (4.3)	0.00 (referent)	
1	6177	48.3 (3.6)	0.30 (0.0, 0.6)		33.6 (4.0)	0.29 (0.0, 0.6)	
2	11234	49.6 (3.5)	1.23 (1.0, 1.5)		34.6 (4.0)	1.18 (0.9, 1.5)	
3	7174	49.5 (3.7)	1.10 (0.8, 1.3)		34.0 (4.2)	1.06 (0.8, 1.3)	
≥4	7432	49.2 (4.0)	0.73 (0.5, 1.0)	<0.01	33.5 (4.3)	0.73 (0.4, 1.0)	<0.01
Cumulative breastfeeding (months)**							
No breastfeeding	3015	48.8 (3.8)	0.00 (referent)		34.0 (4.2)	0.00 (referent)	
≤12	7236	48.8 (3.6)	0.14 (0.0, 0.3)		34.1 (4.0)	0.04 (-0.1, 0.2)	
≤24	8888	49.5 (3.5)	0.75 (0.6, 0.9)		34.5 (3.9)	0.56 (0.4, 0.7)	
≤36	5515	49.4 (3.7)	0.63 (0.5, 0.8)		33.9 (4.2)	0.44 (0.3, 0.4)	
>36	7363	49.2 (3.9)	0.45 (0.3, 0.6)	<0.01	33.5 (4.4)	0.25 (0.1, 0.4)	<0.01
Age at last live birth (y)**							
<25	4185	49.2 (3.7)	0.00 (referent)		34.3 (4.1)	0.00 (referent)	
25-29	15926	49.1 (3.7)	-0.26 (-0.4, -0.1)		33.9 (4.1)	-0.57 (-0.7, -0.4)	
30-34	9750	49.2 (3.7)	-0.36 (-0.5, -0.2)		34.0 (4.2)	-0.79 (-0.9, -0.6)	
≥35	2156	49.6 (3.7)	-0.17 (-0.4, 0.0)	<0.01	34.4 (4.2)	-0.62 (-0.8, -0.4)	<0.01
Menstrual cycle regularity							
Always regular	11029	49.2 (3.7)	0.00 (referent)		34.0 (4.1)	0.00 (referent)	
Sometimes regular	19870	49.2 (3.7)	-0.02 (-0.1, 0.1)		34.0 (4.1)	-0.04 (-0.1, 0.1)	
Irregular	2153	49.0 (4.1)	-0.14 (-0.3, 0.0)	0.17	33.6 (4.6)	-0.40 (-0.6, -0.2)	<0.01
Oral contraceptive (OC) use							
Never	24654	49.1 (3.8)	0.00 (referent)		33.9 (4.2)	0.00 (referent)	
Ever	8400	49.4 (3.4)	0.48 (0.4, 0.6)	<i>p</i> <0.01	34.4 (3.8)	0.50 (0.4, 0.6)	<i>p</i> <0.01
Intrauterine device (IUD) use							
Never	23521	49.2 (3.8)	0.00 (referent)		33.9 (4.3)	0.00 (referent)	
Ever	9533	49.0 (3.5)	0.18 (0.1, 0.3)	<i>p</i> <0.01	34.0 (3.8)	0.11 (0.0, 0.2)	<i>p</i> =0.047
Tubal sterilization							
No	23694	49.1 (3.6)	0.00 (referent)		34.0 (4.1)	0.00 (referent)	
Yes	9360	49.3 (3.8)	0.21 (0.1, 0.3)	<i>p</i> <0.01	33.9 (4.3)	0.23 (0.1, 0.3)	<i>p</i> <0.01

Note:

P for trend values were derived from multivariable linear regression by entering the categorical variables as continuous parameters in the model*p* values for dichotomous variables were driven from the linear regression model

p values <0.01 did not change after Bonferroni corrections

* Adjusted for age (continuous), education, occupation, income, marital status, current employment (yes/no), energy intake (kcal, continuous), weight gain between age 20 and 50 yrs (categorized), cigarette smoking (never/ever), and leisure-time physical activity patterns in adolescence and adulthood (categorized)

** Among parous women only

Adjusted mean differences in age at onset of menopause and in reproductive span according to anthropometric factors

Table 3

	No. of women**	Age at natural menopause (y)		Reproductive span (y)		
		Mean (SD)	Mean difference β (95% CI)*	Mean (SD)	Mean difference β (95% CI)*	$P_{for\ trend}$
Weight at age 20 (kg, Q_{1-4})	n=27,165					
<45.0	5803	49.1 (3.7)	0.00 (referent)	33.9 (4.2)	0.00 (referent)	
45.0-48.0	7141	49.2 (3.6)	0.15 (0.0, 0.3)	34.2 (4.0)	0.19 (0.1, 0.3)	
49.0-53.0	7298	49.3 (3.6)	0.21 (0.1, 0.3)	34.2 (4.0)	0.25 (0.1, 0.4)	
≥ 54.0	6923	49.2 (3.7)	0.30 (0.2, 0.54)	34.1 (4.2)	0.31 (0.2, 0.5)	<0.01
Height at age 20 (m, Q_{1-4})	n=26,104					
<1.55	5869	49.1 (3.7)	0.00 (referent)	34.0 (4.2)	0.00 (referent)	
1.55-1.57	5477	49.3 (3.7)	0.13 (0.0, 0.3)	34.3 (4.1)	0.14 (0.0, 0.3)	
1.58-1.60	7792	49.2 (3.6)	0.05 (-0.1, 0.2)	34.2 (4.0)	0.06 (-0.1, 0.2)	
≥ 1.61	6966	49.2 (3.7)	0.06 (-0.1, 0.2)	34.1 (4.1)	0.03 (-0.1, 0.2)	0.96
BMI at age 20 (kg/m ² , Q_{1-4})	n=24,648					
<18.0	6166	49.1 (3.7)	0.00 (referent)	34.0 (4.1)	0.00 (referent)	
18.0-19.4	6053	49.2 (3.6)	0.10 (0.0, 0.2)	34.3 (4.1)	0.12 (0.0, 0.3)	
19.5-21.3	6305	49.3 (3.6)	0.20 (0.1, 0.3)	34.2 (4.0)	0.24 (0.1, 0.4)	
≥ 21.4	6124	49.2 (3.7)	0.22 (0.1, 0.4)	34.1 (4.2)	0.24 (0.1, 0.4)	<0.01
Weight gain between ages 20 and 50 years (kg, Q_{1-4}) [†]	n=25,926					
<2.0	6073	49.0 (3.7)	0.00 (referent)	33.7 (4.2)	0.00 (referent)	
2.0-6.9	6661	49.3 (3.7)	0.25 (0.1, 0.4)	34.1 (4.1)	0.26 (0.1, 0.4)	
7.0-12.4	6283	49.3 (3.6)	0.36 (0.2, 0.5)	34.3 (4.0)	0.40 (0.3, 0.5)	
≥ 12.5	6912	49.2 (3.7)	0.44 (0.3, 0.6)	34.3 (4.1)	0.48 (0.4, 0.6)	<0.01

Note: p values <0.01 did not change after Bonferroni corrections

* Adjusted for age (continuous), education, occupation, age at menarche (categorized), number of live births (categorized), past use of oral contraceptives (never/ever), weight gain between age 20 and 50 years (categorized) except for the same variable, cigarette smoking (ever/never), leisure-time physical activity pattern in adolescence and adulthood (categorized), and energy intake (continuous)

** Number of women with information on anthropometric factors at age 20

[†] Weight gain for women <50 years was defined as recalled weight gain between age 20 and current age; for women ≥ 50 years, weight gain was defined as recalled weight gain between ages 20 and 50

Table 4
Adjusted mean differences in at age of onset of menopause and reproductive span according to patterns of leisure-time physical activity (LTPA)

	No. of women n=33,054	Age at natural menopause (y)			Reproductive span (y)		
		Mean (SD)	Mean difference β (95% CI)*	<i>P</i> _{for trend}	Mean (SD)	Mean difference β (95% CI)*	<i>P</i> _{for trend}
Self-rated adolescent LTPA (age 13-19 y)	N=32,597						
Low	17510	49.1 (3.8)	0.00 (referent)		33.6 (4.2)	0.00 (referent)	
Moderate-High	15087	49.3 (3.6)	1.35 (0.0, 2.7)	<i>p</i> =0.048	34.4 (4.0)	1.04 (-0.3, 2.4)	<i>p</i> =0.14
Intensity of LTPA, hrs/wk/yr [†] (age 13-19 y)	N=33,054						
None	14289	49.1 (3.9)	0.00 (referent)		33.4 (4.3)	0.00 (referent)	
<1.2	4675	48.7 (3.7)	0.06 (-0.1, 0.2)		33.6 (4.0)	0.16 (0.0, 0.3)	
1.2-1.9	1831	49.0 (3.6)	0.16 (0.0, 0.4)		34.1 (4.0)	0.26 (0.0, 0.5)	
2.0-3.9	8283	49.4 (3.5)	0.35 (0.2, 0.5)		34.8 (3.9)	0.45 (0.3, 0.6)	
≥4.0	3976	49.5 (3.5)	0.47 (0.2, 0.7)	<0.01	34.9 (3.8)	0.56 (0.3, 0.8)	<0.01
Self-rated adolescent/adult LTPA	N=32,481						
Low/Low	10373	49.1 (3.8)	0.00 (referent)		33.6 (4.2)	0.00 (referent)	
Low/Moderate-High	7068	49.1 (3.9)	-0.10 (-0.2, 0.0)		33.6 (4.3)	-0.08 (-0.2, 0.0)	
Moderate-High/Low	8073	49.1 (3.6)	0.09 (0.0, 0.2)		34.3 (4.0)	0.11 (0.0, 0.2)	
Moderate-High/Moderate-High	6967	49.5 (3.5)	0.23 (0.1, 0.3)	<0.01	34.6 (3.9)	0.28 (0.1, 0.4)	<0.01

Note:

*P*_{for trend} were derived from multivariable linear regression by entering the categorical variables as continuous parameters in the model

p values for dichotomous variables were driven from the linear regression model

p values <0.01 did not change after Bonferroni corrections

* Adjusted for age (continuous), education, occupation, age at menarche (categorized), number of live births (categorized), past use of oral contraceptives (never/ever), weight gain between age 20 and 50 (categorized), cigarette smoking (ever/never), leisure-time physical activity pattern in adolescence and adulthood (categorized) except for the same variable, and energy intake (continuous)

Table 5
Adjusted mean differences in age at onset of menopause and in number of reproductive years according to dietary intakes

	No. of women n=33,054	Age at natural menopause (y)			Reproductive span (y)		
		Mean (SD)	Mean difference β (95% CI)*	$P_{for\ trend}$	Mean (SD)	Mean difference β (95% CI)*	$P_{for\ trend}$
Total energy (kcal/day)							
≤1281.5	5486	48.9 (3.8)	0.00 (referent)		33.5 (4.3)	0.0 (referent)	
1281.6-1458.6	5519	49.1 (3.7)	0.21 (0.1, 0.3)		33.9 (4.2)	0.24 (0.1, 0.4)	
1458.7-1608.3	5489	49.3 (3.6)	0.35 (0.2, 0.5)		34.2 (4.0)	0.40 (0.3, 0.5)	
1608.4-1774.4	5519	49.3 (3.6)	0.37 (0.2, 0.5)		34.2 (4.1)	0.39 (0.3, 0.5)	
1774.4-2005.0	5520	49.3 (3.6)	0.38 (0.2, 0.5)		34.2 (4.1)	0.42 (0.3, 0.6)	
>2005.1	5521	49.2 (3.7)	0.39 (0.3, 0.5)	<0.01	34.0 (4.2)	0.40 (0.3, 0.5)	<0.01
Total vegetables (g/day)							
≤139.6	5487	49.0 (3.9)	0.00 (referent)		33.7 (4.3)	0.00 (referent)	
140.0-194.7	5519	49.1 (3.6)	0.08 (0.0, 0.2)		33.9 (4.0)	0.05 (-0.1, 0.2)	
194.8-250.1	5487	49.2 (3.7)	0.11 (0.0, 0.2)		34.0 (4.1)	0.09 (0.0, 0.2)	
250.2-318.4	5521	49.2 (3.7)	0.13 (0.0, 0.3)		34.1 (4.2)	0.11 (0.0, 0.3)	
318.5-423.4	5520	49.2 (3.7)	0.11 (0.0, 0.3)		34.1 (4.2)	0.06 (-0.1, 0.2)	
>423.5	5520	49.2 (3.7)	0.06 (-0.1, 0.2)	0.39	34.1 (4.2)	0.00 (-0.1, 0.2)	0.83
Total fruits (g/day)							
≤73.3	5485	48.9 (3.9)	0.00 (referent)		33.4 (4.4)	0.00 (referent)	
73.4-142.4	5520	49.1 (3.7)	0.10 (0.0, 0.2)		33.8 (4.2)	0.13 (0.0, 0.3)	
142.5-209.3	5487	49.3 (3.6)	0.22 (0.1, 0.4)		34.1 (4.1)	0.23 (0.1, 0.4)	
209.4-283.6	5521	49.2 (3.7)	0.10 (0.0, 0.2)		34.1 (4.1)	0.13 (0.0, 0.3)	
283.7-383.1	5521	49.3 (3.6)	0.24 (0.1, 0.4)		34.3 (4.0)	0.26 (0.1, 0.4)	
>383.2	5520	49.2 (3.7)	0.13 (0.0, 0.3)	0.04	34.1 (4.2)	0.15 (0.0, 0.3)	0.03
Red meat (g/day)							
≤17.4	5485	49.1 (3.8)	0.00 (referent)		33.7 (4.2)	0.00 (referent)	
17.5-27.9	5516	49.2 (3.7)	0.11 (0.0, 0.2)		34.0 (4.2)	0.11 (0.0, 0.2)	
28.0-38.1	5492	49.1 (3.7)	0.00 (0.1, 0.1)		33.9 (4.1)	0.00 (-0.1, 0.1)	
38.2-50.9	5519	49.2 (3.6)	0.06 (-0.1, 0.2)		34.1 (4.0)	0.07 (-0.1, 0.2)	
51.0-70.8	5517	49.2 (3.7)	0.04 (-0.1, 0.2)		34.1 (4.1)	0.04 (-0.1, 0.2)	
>70.9	5523	49.2 (3.7)	-0.05 (-0.2, 0.1)	0.37	34.1 (4.1)	-0.05 (-0.2, 0.1)	0.47
Total fat (g/day)							
≤16.0	5481	49.0 (3.8)	0.00 (referent)		33.4 (4.2)	0.00 (referent)	
16.1-21.1	5529	49.1 (3.7)	0.02 (-0.1, 0.1)		33.7 (4.2)	0.03 (-0.1, 0.2)	
21.2-25.6	5486	49.2 (3.7)	0.08 (-0.1, 0.2)		34.0 (4.2)	0.11 (0.0, 0.2)	
25.7-30.8	5514	49.2 (3.6)	0.05 (-0.1, 0.2)		34.2 (4.1)	0.09 (-0.1, 0.2)	
30.9-38.2	5523	49.3 (3.6)	0.08 (-0.1, 0.2)		34.3 (4.1)	0.12 (0.0, 0.3)	
>38.3	5521	49.2 (3.7)	-0.07 (-0.2, 0.1)	0.90	34.2 (4.2)	-0.03 (-0.2, 0.1)	0.66
Saturated fat (g/day)							
≤4.2	5487	48.9 (3.8)	0.00 (referent)		33.4 (4.2)	0.00 (referent)	
4.3-5.8	5529	49.2 (3.7)	0.15 (0.0, 0.3)		33.8 (4.2)	0.17 (0.0, 0.3)	
5.9-7.3	5494	49.2 (3.7)	0.09 (0.0, 0.2)		34.0 (4.1)	0.12 (0.0, 0.3)	
7.4-9.0	5499	49.2 (3.6)	0.06 (-0.1, 0.2)		34.1 (4.1)	0.12 (0.0, 0.3)	
9.1-11.4	5516	49.3 (3.6)	0.10 (0.0, 0.3)		34.4 (4.0)	0.16 (0.0, 0.3)	
>11.5	5528	49.3 (3.7)	0.01 (-0.2, 0.2)	0.80	34.3 (4.2)	0.06 (-0.1, 0.2)	0.64
Total protein (g/day)							
≤45.7	5490	48.9 (3.8)	0.00 (referent)		33.4 (4.2)	0.00 (referent)	
45.8-54.2	5514	49.1 (3.8)	0.17 (0.0, 0.3)		33.8 (4.2)	0.19 (0.0, 0.3)	
54.3-61.7	5492	49.2 (3.6)	0.21 (0.1, 0.4)		34.0 (4.1)	0.24 (0.1, 0.4)	
61.8-70.3	5508	49.3 (3.6)	0.26 (0.1, 0.4)		34.2 (4.0)	0.30 (0.1, 0.5)	
70.4-82.6	5527	49.3 (3.7)	0.26 (0.1, 0.4)		34.3 (4.1)	0.30 (0.1, 0.5)	
>82.7	5523	49.3 (3.8)	0.24 (0.0, 0.4)	0.02	34.3 (4.2)	0.28 (0.1, 0.5)	<0.01
Total soy (g/day)							

	No. of women n=33,054	Age at natural menopause (y)			Reproductive span (y)		
		Mean (SD)	Mean difference β (95% CI)*	<i>P</i> _{for trend}	Mean (SD)	Mean difference β (95% CI)*	<i>P</i> _{for trend}
	5486	49.0 (3.7)	0.00 (referent)		33.6 (4.2)	0.00 (referent)	
	5519	49.2 (3.6)	0.16 (0.0, 0.3)		34.0 (4.1)	0.16 (0.0, 0.3)	
	5488	49.2 (3.7)	0.12 (0.0, 0.3)		34.0 (4.2)	0.12 (0.0, 0.3)	
	5522	49.3 (3.6)	0.20 (0.1, 0.3)		34.2 (4.0)	0.22 (0.1, 0.4)	
	5519	49.3 (3.7)	0.17 (0.0, 0.3)		34.0 (4.1)	0.16 (0.0, 0.3)	
	5520	49.2 (3.8)	0.07 (-0.1, 0.2)	0.30	34.0 (4.3)	0.08 (-0.1, 0.2)	0.26
Total fiber (g/day)							
≤6.8	5479	48.9 (3.8)	0.00 (referent)		33.5 (4.2)	0.00 (referent)	
6.9-8.6	5525	49.1 (3.7)	0.10 (0.0, 0.2)		34.0 (4.1)	0.12 (0.0, 0.3)	
8.7-10.2	5497	49.2 (3.7)	0.22 (0.1, 0.3)		34.0 (4.1)	0.22 (0.1, 0.4)	
10.3-11.9	5499	49.3 (3.6)	0.25 (0.1, 0.4)		34.2 (4.1)	0.23 (0.1, 0.4)	
12.0-14.4	5533	49.2 (3.7)	0.15 (0.0, 0.3)		34.2 (4.1)	0.15 (0.0, 0.3)	
>14.5	5521	49.2 (3.8)	0.13 (0.0, 0.3)	0.09	34.2 (4.2)	0.11 (-0.1, 0.3)	0.20
Total carbohydrates (g/day)							
≤223.9	5485	49.0 (3.8)	0.00 (referent)		33.7 (4.3)	0.00 (referent)	
224.0-253.5	5521	49.2 (3.7)	0.14 (0.0, 0.3)		34.0 (4.2)	0.17 (0.0, 0.3)	
253.6-277.8	5486	49.2 (3.6)	0.22 (0.1, 0.4)		34.1 (4.1)	0.21 (0.1, 0.4)	
278.9-305.6	5523	49.3 (3.7)	0.24 (0.1, 0.4)		34.2 (4.1)	0.27 (0.1, 0.4)	
305.7-346.7	5518	49.2 (3.7)	0.20 (0.0, 0.4)		34.1 (4.1)	0.22 (0.0, 0.4)	
>346.8	5521	49.2 (3.7)	0.24 (0.0, 0.5)	0.04	33.9 (4.1)	0.21 (0.0, 0.5)	0.06

Note : Dietary intakes categorized into sixths (from low to high)

* Adjusted for age (continuous), education, occupation, age at menarche (categorized), number of live births (categorized), past use of oral contraceptives (never/ever), weight gain between age 20 and 50 (categorized), cigarette smoking (ever/never) except for the same variable, leisure-time physical activity pattern in adolescence and adulthood (categorized), and energy intake (continuous) except for the same variable

Table 6
Adjusted mean differences in age at onset of menopause and in number of reproductive years according to smoking, tea and alcohol consumption

	No. of women n=33,054	Age at natural menopause (y)		Reproductive span (y)	
		Mean (SD)	Mean difference β (95% CI)*	Mean (SD)	Mean difference β (95% CI)*
Smoking status					
Never smoked	31615	49.2 (3.7)	0.00 (referent)	34.0 (4.1)	0.00 (referent)
Former smoker	271	48.9 (4.0)	-0.40 (-0.8, 0.0)	33.3 (4.5)	-0.51 (-0.9, 0.0)
Current smoker	1167	48.4 (4.1)	-0.76 (-1.0, -0.5)	32.8 (4.4)	-0.78 (-1.0, -0.6)
Years of smoking :					
<28 years**	686	48.6 (3.8)	-0.51 (-0.8, -0.2)	33.2 (4.1)	-0.53 (-0.8, -0.2)
≥28 years	752	48.3 (4.3)	-0.86 (-1.1, -0.6)	32.6 (4.7)	-0.90 (-1.2, -0.6)
Regular alcohol consumption					
Never	32252	49.2 (3.7)	0.00 (referent)	33.8 (4.7)	0.00 (referent)
Ever	802	49.1 (4.2)	-0.05 (-0.3, 0.2)	34.0 (4.1)	-0.06 (-0.3, 0.2)
Regular tea use					
Never	24968	49.1 (3.7)	0.00 (referent)	33.9 (4.1)	0.00 (referent)
Ever	8089	49.3 (3.7)	0.08 (0.0, 0.2)	34.4 (4.1)	0.10 (0.0, 0.2)
Years of tea consumption					
<19 years**	3931	49.2 (3.7)	0.07 (-0.1, 0.2)	34.3 (4.1)	0.08 (0.0, 0.2)
≥19 years	4154	49.3 (3.7)	0.09 (0.0, 0.2)	34.5 (4.1)	0.12 (0.0, 0.2)

Note : Years of smoking or years of tea consumption categorized into median distribution

*P*for trend values were derived from multivariable linear regression by entering the categorical variables as continuous parameters in the model

p values for dichotomous variables were driven from the linear regression model

p values <0.01 did not change after Bonferroni corrections

* Adjusted for age (continuous), education, occupation, age at menarche (categorized), number of live births (categorized), past use of oral contraceptives (never/ever), weight gain between age 20 and 50 years (categorized), cigarette smoking (ever/never) except for the same variable, adolescence-adult leisure time-physical activity pattern (categorized), and energy intake (continuous) except for the same variable

** 'never smoked' and 'never regular tea use' categories are used as a referent