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Life Course Exposure to Smoke and Early Menopause and Menopausal Transition

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Abstract

Objective—Early age at menopause is associated with increased risk of cardiovascular disease, stroke, osteoporosis and all-cause mortality. Cigarette smoke exposure in adulthood is an established risk factor for earlier age at natural menopause and may be related to age at menopausal transition. Using data from two U.S. birth cohorts, we examined the association between smoke exposure at various stages of the life course (prenatal, childhood exposure to parental smoking and adult smoke exposure) with menopause status in 1,001 women aged 39 – 49 years at follow-up.

Methods—We used logistic regression analysis, adjusting for age at follow-up, to estimate odds ratios (ORs) and 95% confidence intervals (CI) relating smoke exposure to natural menopause and menopausal transition.

Results—The magnitudes of the associations for natural menopause were similar, but not statistically significant after adjustment for confounders for *i*) women with prenatal smoke exposure who did not smoke at adult follow-up (OR= 2.7 [95% CI 0.8, 9.4]) and *ii*) current adult smokers who were not exposed prenatally (OR= 2.8 [95% CI 0.9, 9.0]). Women who had been exposed to prenatal smoke and were current smokers had three times the risk of experiencing natural menopause (adjusted OR=3.4 [95% CI 1.1, 10.3]) compared to women without smoke

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exposure in either time period. Only current smoking of long duration (>26 years) was associated with the timing of the menopausal transition.

Conclusion—Our data suggest that exposure to smoke both prenatally and around the time of menopause accelerates ovarian aging.

Keywords

menopause; tobacco smoking; maternal exposure

Introduction

While the menopausal transition and menopause are stages of life experienced by all women, the age at which women experience these changes may influence their health risks. Natural menopause is defined as at least 12 months of amenorrhea that is not attributable to surgery, chemotherapy, or any other known cause and the menopausal transition is a biologic phase that precedes natural menopause. Earlier age at natural menopause is associated with an increased risk of certain diseases including osteoporosis, some types of cancer, stroke, heart disease; and studies have even reported an increase in all-cause mortality associated with earlier menopause¹⁻⁴. For this reason it is important to identify modifiable risk factors that can increase a woman's risk of experiencing an early menopausal transition or menopause. Current cigarette smoking in adulthood is an established risk factor for earlier age at natural menopause (reviewed⁵⁻⁸). Current smoking has also been associated with an earlier onset of the menopausal transition⁹⁻¹².

Menopause occurs when the ovarian follicle pool falls below some critical threshold¹³⁻¹⁵. One possible explanation for the association between current smoking and earlier age at menopause is that smoking byproducts decrease the quantity or quality of the ovarian follicles¹⁶⁻¹⁸. Smoking is also associated with changes in reproductive hormone levels during reproductive years and in years preceding menopause¹⁹⁻²¹. These associations may reflect alterations in the patterns of follicle development which could then manifest in changes in levels of follicle stimulating hormone (FSH) or other hormones; or they may reflect a primary effect on the pituitary.

As ovarian follicles are only formed during fetal development, it is possible that smoke exposure during the intrauterine period may also affect the follicle pool and influence menopausal timing. If exposure to prenatal smoke accelerates menopause, it may do so either by suppressing the formation of follicles or by damaging them. Evidence from a Danish study by Lutterodt *et al* suggests that prenatal smoke exposure may damage somatic cells in the developing ovary²².

Few studies have examined the association between prenatal smoke exposure and age at menopause. A prospective study that used data from the National Cooperative Diethylstilbestrol Adenosis Project (DESAD), reported a modest association between prenatal smoke exposure and earlier age at menopause (RR =1.2, 95% CI 1.0, 1.43)²³. Two other studies that relied on daughters' report of maternal smoking did not observe an association. One was a cross-sectional study of data from the U.S. Sister Study²⁴ and the

other reported no association between prenatal smoke exposure and indicators of ovarian age including antral follicle count, levels of FSH, inhibin B and estradiol in women aged 22-49 years²¹. We examined lifecourse smoke exposures and early menopausal transition and natural menopause, using data from two birth cohorts in which information on smoking was collected prospectively from the mothers themselves during their pregnancies, and the daughters were followed-up for more than four decades.

Materials and Methods

Study Participants

We used prospectively collected data from the Early Determinants of Mammographic Density Study (EDMD) (for details see ^{25,26}) to examine the association between smoke exposure throughout the life course and early menopausal transition and natural menopause. In brief, the EDMD is a follow-up study of women whose mothers enrolled in one of two birth cohorts -the New England Collaborative Perinatal Project (CPP) or the California Child Health and Development Study (CHDS) ²⁷⁻²⁹. The EDMD used baseline data obtained from the mothers during their pregnancies (1959-1967). Because the protocols of the CPP and CHDS were very similar, we were able to analyze both samples in the EDMD study. In 2006-2008, when the daughters (referred to as participants throughout this paper) were 39-49 years of age, we conducted an adult follow-up study. We used the following criteria to determine eligibility for inclusion in the adult follow up study: singleton birth, recorded birth weight and birth length, recorded childhood weight/height measurements, availability of third trimester serum, and female gender.

In the CPP, 1775 daughters met the eligibility criteria. We had resources to contact a little over half of the women who were eligible and we did so based on sampling randomly from the eligible pool of 1,775 daughters (n=1090 (61%)). Of these, we were able to locate 644 (59%); 567 (88%) participated. In the CHDS, 1481 daughters met the eligibility criteria. We had resources to contact 835 (56%) and therefore sampled randomly from the eligible pool. Of these, we located 675 (81%); 567 (84%) participated. We used the last known address of the daughter or her mother to locate the potential participant. Routine surveillance methods employed by the CHDS are described elsewhere ^{25,26}. Participants in the adult follow-up study did not differ from eligible non-participants with respect to the baseline variables of interest including birthweight, prenatal smoke exposure, and maternal age (data not shown).

Of the 1134 women who were interviewed for the EDMD, our analyses excluded 133 women who had experienced a surgical menopause, menopause induced by chemotherapy or radiation or whose menopausal status could not be determined with certainty because of hormone replacement therapy or incomplete medical histories.

Data Collection

Mother data—All prenatal and early life data were collected based on uniform protocols for CPP and CHDS using interview instruments and clinical measurements during the mother's pregnancy. Covariates included the mother's education at participant's birth, family income at birth, birthweight and birthlength.

Participant data—Trained interviewers using a standard protocol interviewed adult participants by telephone. The interview included information on the participant's smoking status and smoking history, smoke exposure during childhood, menstrual status, parity, hormone use, weight, height, participant's education and participant's annual family income.

Smoke Exposure Variables

Prenatal smoke exposure—We defined prenatal smoke exposure based on the pregnant mother's report on whether or not she smoked. Mother's report had a very high correlation to cotinine measures in a subset of mothers tested ³⁰. We carried out a secondary analysis in which we defined prenatal exposure by the reported number of cigarettes smoked per day during pregnancy.

Childhood household smoke exposure—We asked the participants whether anyone (mother/stepmother, father/stepfather, or someone else) who lived with them at any time in their first 18 years of life had smoked and if so, for how many years they were exposed to one or more household members' smoke. We classified childhood smoke exposure as follows: dichotomously (ever vs. never), by number of smokers with whom the participant lived (none, one, two or more), and by duration of exposure (> 10 years, ≤ 10 years). We used the latter two measures as proxies for degree of exposure.

Adult active smoking—We asked participants if they had ever smoked in the past and if they currently smoked. We also asked ever smokers how old they were when they started and stopped smoking and the average number of cigarettes they smoked per day. We classified participants as non-smokers if they had never smoked, former smokers if they had smoked at least one cigarette per day for at least one month but were not smoking at the time of interview, and current smokers if they were smokers at the time of interview. We did not collect data on passive smoke exposure in adulthood.

Menopause Status

Premenopause—We classified as premenopausal participants who were menstruating, had not gone 60 consecutive days without a period during the 12 months preceding the interview, or were pregnant at the time of the interview.

Menopausal transition—We classified participants as being in the menopausal transition if, in the 12 months prior to the interview, they had i) at least one period and ii) at least one 60+ day episode of amenorrhea in the absence of pregnancy or lactation. This definition accords with those set out by the Stages of Reproductive Aging Workshop (STRAW) ³¹ and the ReSTAGE Collaboration ³². Because participants who have experienced natural menopause have, by definition, experienced 60 days or more of amenorrhea during the 12 months preceding the interview, we report ORs for associations with the timing of menopausal transition including participants who have experienced natural menopause. We also report ORs for women in the menopausal transition excluding women who have reached natural menopause.

Natural menopause—We classified as having experienced natural menopause participants whose final menstrual period (FMP) had occurred more than 12 months before the interview and who did not report surgical, radiation, or chemotherapy as reasons for cessation of their periods.

Hormone Replacement Therapy (HT)—We excluded from the analysis participants who were using HT at the time of interview and who were premenopausal or in the menopausal transition. We also excluded from the analysis participants in the premenopausal category or menopausal transition who were past HT users and had not experienced an observed un-medicated period after stopping the HT. Women who had experienced a FMP at least 12 months before starting HT were classified as menopausal.

Statistical Analysis

Analytic approach—We used logistic regression analysis to estimate the odds ratios (OR) and 95% confidence intervals (CI) relating the various measures of smoke exposure to menopausal status. All models included age at the time of interview and study site. Thus, ORs are interpreted as the odds of an earlier menopause (or being in the menopausal transition) given exposure status. Because 499 of the participants in this sample were sisters, we used generalized estimating equations (GEE) logistic regression analysis to allow proper estimation of standard errors. For each smoke exposure construct (prenatal, childhood, and adult), we examined associations with menopausal status in three separate analyses that compared: *i*) participants who had reached natural menopause with premenopausal women and *ii*) participants who had experienced the menopausal transition, but were not yet menopausal, with premenopausal women *iii*) participants who had experienced the menopausal transition including those who had reached menopause with premenopausal women. We refer to the last category as the “combined category” throughout this paper. Initially we examined each type of smoke exposure separately (prenatal, passive childhood and adult smoking). In the final model all three types of smoke exposure were adjusted for simultaneously.

Adjusting for age, site and other confounders—We included age at interview as a continuous variable and study site (New England (CPP) or California (CHDS)) in all models. We examined the following covariates: birth weight, maternal education at birth, family income at birth, the participant's adult body mass index (BMI), oral contraceptive use, parity, level of education and annual family income at the time of interview. We included covariates in the final analytic model if their inclusion or exclusion produced a 10% change in the regression coefficient relating exposure status to menopause status. We also examined interactions between smoke exposure at the three stages: prenatal smoke exposure, passive childhood smoke exposure and adult smoke exposure. The interactions were assessed by evaluating the significance of the cross product term created by multiplying smoke exposure for different life periods for each outcome.

We had incomplete smoke exposure data for four participants and missing data on prenatal smoke exposure for 29 participants. To examine whether this small proportion of missing data had influenced the results significantly, we conducted sensitivity analyses in which we

modeled the association between prenatal smoke exposure and menopausal outcomes under different assumptions for the missing data. The age and site adjusted ORs did not vary appreciably under all modeled circumstances.

Results

The final analytic sample included 1001 women of whom 499 were siblings. Mean age at interview was 43.6 years (SD=1.87). A total of 773 women (77.2%) were premenopausal, 190 (19.0%) were in the menopausal transition, and 38 (3.8%) had reached natural menopause. Approximately 41% of all participants had been exposed to prenatal smoke, and 73% had been exposed to household smoke during childhood. About 51% of all participants had never smoked; 32% were former smokers, and 16% were current smokers. Birthweight, maternal education at registration, prenatal smoke exposure, adult smoking status, annual household income, education, BMI, and age at interview were associated with menopausal status. Table 1 shows relevant characteristics of the participants.

Prenatal smoke exposure

The proportion of participants reaching early natural menopause was higher among participants with prenatal smoke exposure than those without exposure. Adjusting for age and site, the OR relating prenatal smoke exposure to natural menopause was OR =2.0 (95% CI 1.0, 4.1) (Table 2). Adjustment for maternal education at birth decreased the OR to 1.7 (95% CI 0.8, 3.3). Further adjustment for adult smoking, which is associated with earlier age at menopause, did not change the association appreciably. The association of prenatal smoke exposure with the odds of menopause did not vary with the number of cigarettes the mother smoked (Table 3). The number of cigarettes mother smoked during pregnancy was not associated with experiencing the menopausal transition (combined category, including women who experienced menopause) in the age and site adjusted models. Potential confounders that did not change the estimates appreciably were not included in the final models (birth weight, family income at birth, oral contraceptive use, participant's parity, level of education and annual family income at the time of interview).

Childhood household smoke exposure

Passive childhood smoke exposure was not associated with experiencing natural menopause or menopausal transition (combined category) in this cohort (Table 4).

Adult smoking

The odds of women experiencing early natural menopause was higher among current smokers than among never smokers (OR 2.6, 95%CI 1.0, 6.7) (Table 2). The odds of women experiencing the menopausal transition (combined category) was also higher among current smokers than among never smokers (OR 1.8, 95%CI 1.2, 2.7). Among current smokers, longer duration of adult smoking, and more cigarettes per day were associated with increased odds of having reached natural menopause. Similar associations were observed with menopausal transition (combined category) with current smokers of more than 10 cigarettes per day or smoking for more than 26 years having a higher odds of experiencing

the menopausal transition (Table 2). Former smoking was not associated with being in the menopausal transition or with having had natural menopause.

Smoke exposure throughout the life course

Table 4 shows the results obtained when exposures throughout the life course were examined simultaneously. Compared with participants who had neither prenatal nor current adult smoke exposure, participants had higher adjusted odds of reaching natural menopause if they had: i) prenatal smoke exposure only (OR = 2.7), ii) current smoke exposure only (OR = 2.8), or iii) both prenatal and current exposure (OR = 3.4). Childhood exposure to household smoke was not associated with the odds of early natural menopause or the menopausal transition. Current smoking was associated, albeit not significantly so, with occurrence of the menopausal transition (combined category) (OR=1.5); prenatal smoke exposure was unrelated to the occurrence of the menopausal transition (combined category, OR = 1.2).

Discussion

Our data suggest that prenatal smoke exposure and adult current smoking are each associated with a two-fold or larger increase in the odds of earlier menopause. Although the magnitude of the associations for each of the two types of smoke exposure with natural menopause were similar, neither was statistically significant. However, women who were exposed both prenatally and were current active adult smokers experienced an over three-fold increased odds of early menopause. Our finding relating current smoking to the odds of menopause, given age, is similar to those reported in the literature^{5,10,11,33-35}. Our finding for prenatal smoke exposure and the odds of menopause is similar to that reported by Strohsnitter *et al* using data from the DESAD²³. Neither prenatal and current smoke exposure, when assessed in the same regression model, were associated with the menopausal transition.

Prenatal smoke exposure may influence the development of ovarian follicles and subsequent exposures throughout the life course may either lead to follicle death or impair follicle development to the antral stage. Several chemicals in cigarette smoke can damage ovarian follicles, causing genetic damage¹⁸ and oxidative stress¹⁶. There is also evidence that smoking affects the levels of several hormones including FSH^{21,36-39}, estradiol^{20,40,41} and prolactin¹⁹, although findings for estradiol are inconsistent showing both increases and decreases in levels among smokers. In a recent Danish study, 29 fetal ovaries from first-trimester induced abortions were examined. Prenatal exposure to smoke was associated with a decrease in the number of somatic cells in follicles and a non-significant decrease in the number of germ cells²². The survival of the follicle requires somatic cells and a reduction in the number of somatic cells might promote oocyte death over time. The three previous studies of prenatal smoke exposure and menopause relied on report by the daughter or recall by the mother many years after the daughter was born. In the DESAD, researchers found an association²³ using data on prenatal smoke exposure that were obtained from the mothers 9-39 years after the birth of their daughters. In the Sister Study, a cross-sectional study of more than 22,000 participants aged 35 to 59 years that obtained data on prenatal smoke

exposure from the daughters, who were told to ask their mothers, researchers did not observe an association with the timing of the menopause²⁴. A third study that also classified maternal smoking based on report of the adult daughter reported no association between prenatal smoke exposure and a number of measures of ovarian aging²¹. Adult daughters' reports of their mother's smoking status before their own birth are probably less accurate than recalled data from the mothers themselves, and may be one reason why no associations were detected in the two studies that obtained maternal smoking status from adult daughters. Because our data on prenatal smoke exposure were collected from the mothers during their pregnancy, misclassification is likely to be minimal.

We did not detect an association between household smoke exposure during childhood and menopausal status. Even among participants with no prenatal exposure, no association was observed between household smoke in childhood and early natural menopause. However, because we collected data on household smoke in childhood from the adult interview, measurement error may have reduced our ability to detect an association. With respect to former active smoking exposure, our data are consistent with other studies suggesting former smoking is unrelated to earlier age at menopause^{5,10,11}.

One possible explanation for the presence of associations with prenatal smoke exposure and current smoking but not with former smoking is that biologic effects are limited to certain critical time periods. Two such times might be (i) the prenatal period, when the primordial follicles are formed and (ii) near the end of a woman's reproductive lifespan, when the number of follicles is approaching the critical threshold needed to maintain ovulation and menstruation.

Similar to the findings reported by Strohsnitter *et al* using data from the DESAD²³ we observed a stronger association between prenatal smoke exposure and timing of the menopause among non-smokers than among current smokers. It is possible that this finding may be a chance finding since, in our data, the odds ratios relating prenatal smoke exposure to menopause did not differ much between women who never smoked and women who were current smokers. Given the small number of menopause events (n=38) in our data, however, our ability to evaluate differences in the strengths of association is limited. However, if this pattern of results reflects a true biologic phenomenon, one possibility is that the biologic effect of current smoking on follicle development (and the hormone feedback loop) is strong enough to render the biologic effect of in utero smoke exposure undetectable.

Neither prenatal, nor childhood smoke exposure was related to the occurrence of the menopausal transition (combined category). We observed a weak association between current smoking and the occurrence of the menopausal transition (combined category). Interpretation of these findings is hindered by 1) the lack of a standardized operational definition for the menopausal transition and 2) uncertainty about whether or not the timing of the transition is linked to the number of ovarian follicles. One might expect that the same biologic processes influence both the timing of the menopausal transition and of menopause. The primary definition used for the menopausal transition in this study (60 days of amenorrhea during the past year, not due to pregnancy or lactation) is endorsed by researchers in STRAW³¹ and in the ReSTAGE collaboration⁴². However, more recent

research has shown that while this definition predicts the timing of the final menstrual period well in older women, other definitions may be better predictors of menopausal timing in women younger than 45 years of age⁴³. More than half of the participants in this study were younger than 45 years of age. Hence other definitions of menopausal transition, such as more than one episode of 60 days of amenorrhea, may be better indicators of the late transition and may consequently capture associations that were not observed with the definition that we used. Information obtained from our questionnaire did not allow us to refine our definition of the menopausal transition.

A key strength of this study is the collection of data on exposure to *prenatal* smoke from the mothers of participants during their pregnancies. The data were also collected at a time when the hazards of prenatal smoking were less widely known and hence women were less likely to provide inaccurate information on their smoking habits during pregnancy for fear of stigmatization. A limitation of our study is the relatively young age of the sample and the fact that only 38 women had experienced natural menopause. Nevertheless we were still able to address the question of risk factors for very early onset of menopause and early menopausal transition. Following cohorts like ours though mid-life and beyond to ascertain the risks associated with prenatal smoke exposure will be essential as retrospective assessments of prenatal smoke exposure may be subject to greater misclassification.

In conclusion, our study confirms the association between current smoking and earlier age at menopause and adds to a sparse literature on the relation of prenatal smoke to the timing of the menopause. Women who were exposed to smoke prenatally and throughout adulthood had a three-fold increase in early natural menopause. Our findings, if replicated in larger prospective birth cohorts, support the growing literature indicating that various aspects of adult health and aging are influenced by exposures throughout the life course, including prenatal exposures^{26,44,45}.

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Table 1

Characteristics of participants by menopausal status (n=1,001)

	Pre-menopause n=773		Menopausal transition n=190		Natural menopause n=38	
	Mean ± S.D. or n (%)	Mean ± S.D. or n (%)	Mean ± S.D. or n (%)	Mean ± S.D. or n (%)	Mean ± S.D. or n (%)	Mean ± S.D. or n (%)
Early life						
Maternal age at registration	26	(5.9)	26	(5.9)	24	(5.1)
Birth weight (kg) *	3	(0.5)	3	(0.5)	3	(0.6)
Birth length (cm)	51	(3.0)	51	(2.7)	51	(2.5)
Maternal weight gain (kg)	21	(8.6)	21	(8.4)	21	(8.2)
Maternal education at registration *						
<High School	275	(35.8)	59	(31.4)	4	(10.5)
High School graduate	316	(41.1)	80	(42.6)	13	(34.2)
Some college, college grad	177	(23.0)	49	(26.1)	21	(55.3)
Maternal race						
Non-Hispanic White	644	(83.3)	160	(84.2)	32	(84.2)
Non-Hispanic Black	83	(10.7)	20	(10.5)	5	(13.2)
Hispanic	23	(3.0)	3	(1.6)	1	(2.6)
Non-Hispanic API/other	23	(3.0)	7	(3.7)	0	(0.0)
Prenatal smoke exposure *						
No	452	(60.3)	107	(59.8)	14	(36.8)
Yes	298	(39.7)	74	(40.2)	24	(63.2)
Childhood						
Childhood Household Smoke Exposure						
No	219	(28.4)	46	(24.2)	8	(21.1)
Yes	553	(71.6)	144	(75.8)	30	(78.9)
Age at menarche						
Adulthood	13	(1.7)	13	(1.8)	12	(1.9)
Adult smoking status *						
Never smoked	414	(53.6)	89	(46.8)	11	(28.9)
Former smoker	250	(32.4)	59	(31.1)	15	(39.5)

	Pre-menopause n=773	Menopausal transition n=190	Natural menopause n=38
Mean ± S.D. or n (%)	Mean ± S.D. or n (%)	Mean ± S.D. or n (%)	Mean ± S.D. or n (%)
Current smoker	108 (14.0)	42 (22.1)	12 (31.6)
Alcohol intake at interview			
Nondrinker	283 (36.8)	72 (38.1)	17 (44.7)
<3 drinks/week	241 (31.3)	54 (28.6)	10 (26.3)
3-7 drinks/week	156 (20.3)	35 (18.5)	7 (18.4)
>7 drinks/week	89 (11.6)	28 (14.8)	4 (10.5)
Annual Household Income *			
<\$25,000	48 (6.5)	19 (10.3)	4 (10.8)
\$25,000 - <\$50,000	114 (15.4)	34 (18.4)	12 (32.4)
\$50,000 - <\$75,000	129 (17.4)	35 (18.9)	7 (18.9)
\$75,000 - <\$100,000	157 (21.2)	37 (20.0)	9 (24.3)
\$100,000 - <\$150,000	180 (24.3)	39 (21.1)	4 (10.8)
\$150,000	114 (15.4)	21 (11.4)	1 (2.7)
Education *			
High School graduate or less	135 (17.5)	40 (21.1)	9 (23.7)
Some college/ technical/ trade school	189 (24.5)	61 (32.1)	17 (44.7)
Associate degree	78 (10.1)	20 (10.5)	5 (13.2)
Bachelor's degree	248 (32.1)	49 (25.8)	6 (15.8)
Masters or doctoral degree	122 (15.8)	20 (10.5)	1 (2.6)
BMI (kg/m2) *	27 (5.9)	28 (7.6)	27 (5.9)
Age at interview *	43 (1.8)	44 (1.9)	44 (1.7)
Race			
Non-Hispanic White	605 (78.4)	151 (79.9)	31 (81.6)
Non-Hispanic Black	87 (11.3)	20 (10.6)	6 (15.8)
Hispanic	47 (6.1)	11 (5.8)	1 (2.6)
Non-Hispanic API/other	33 (4.3)	7 (3.7)	0 (0.0)

* p<0.05 for comparison of means by menopausal status for continuous variables, and for comparison of frequencies by menopausal status for categorical variables.

Table 2
Odds ratios (OR) and 95% confidence intervals (CI) relating prenatal smoke exposure to menopausal status

	Menopausal transition		Natural menopause		Combined Transition and Natural Menopause	
	OR (95% CI)	Ref.	OR (95% CI)	Ref.	OR (95% CI)	Ref.
Prenatal smoke exposure						
No		Ref.				
Yes						
Model 1 ^a	1.0 (0.7, 1.4)		2.0 (1.0, 4.1)		1.1 (0.8, 1.5)	
Model 2 ^b	0.9 (0.6, 1.3)		1.7 (0.8, 3.3)		1.0 (0.7, 1.4)	
Adult smoke exposure^c						
Never		Ref.				Ref.
Former	1.0 (0.7, 1.5)		1.3 (0.6, 3.1)		1.1 (0.7, 1.5)	
Current	1.6 (1.0, 2.6)		2.6 (1.0, 6.7)		1.8 (1.2, 2.7)	
Adult smoke exposure^c						
Never		Ref.				Ref.
Former < 12 years duration	1.0 (0.6, 1.7)		1.6 (0.6, 4.4)		1.1 (0.7, 1.8)	
Former 12+ years duration	1.0 (0.6, 1.7)		1.2 (0.4, 3.1)		1.0 (0.7, 1.6)	
Current < 26 years duration	1.1 (0.5, 2.5)		0.7 (0.1, 7.0)		1.1 (0.5, 2.4)	
Current 26+ years duration	1.9 (1.1, 3.1)		3.6 (1.4, 9.0)		2.1 (1.3, 3.4)	
Adult smoke exposure^c						
Never		Ref.				Ref.
Former < 10 cigarettes/day	0.9 (0.6, 1.5)		1.1 (0.4, 3.2)		0.9 (0.6, 1.5)	
Former 10+ cigarettes/day	1.2 (0.7, 1.9)		1.6 (0.6, 4.1)		1.2 (0.8, 1.9)	
Current < 10 cigarettes/day	0.9 (0.4, 1.9)		1.8 (0.4, 7.8)		1.0 (0.5, 2.0)	
Current 10+ cigarettes/day	2.3 (1.3, 3.9)		3.1 (1.1, 8.7)		2.4 (1.5, 3.9)	

^a Adjusted for age at interview and site

^b Adjusted for age at interview, site and maternal education

^c Adjusted for age at interview, site, maternal education and BMI

Table 3
Models of the association between number of cigarettes per day smoked by the mother during pregnancy and menopausal status

Number of maternal cigarettes per day	Model 1 ^a		Combined Transition and Natural Menopause		Model 2 ^b		Combined Transition and Natural Menopause	
	Menopausal transition	Natural menopause	OR (95% CI)	OR (95% CI)	Menopausal transition	Natural menopause	OR (95% CI)	OR (95% CI)
None								
0 + to <1/2 pack/day	0.8 (0.5, 1.5)	1.7 (0.7, 4.3)		1.0 (0.6, 1.6)	0.7 (0.4, 1.3)	1.6 (0.6, 4.4)		0.8 (0.5, 1.4)
1/2 pack to < 1 pack/day	0.9 (0.6, 1.5)	1.6 (0.6, 4.3)		1.0 (0.7, 1.6)	0.9 (0.6, 1.6)	1.5 (0.5, 4.1)		1.0 (0.6, 1.6)
1 pack/day	0.9 (0.6, 1.6)	1.7 (0.7, 4.0)		1.0 (0.7, 1.7)	0.9 (0.6, 1.6)	1.6 (0.7, 3.9)		1.0 (0.7, 1.7)

^a Adjusted for age at interview, site and maternal education

^b Adjusted for age at interview, site, maternal education, adult smoking status and BMI

Table 4
Multivariable models of patterns of smoke exposure across the lifecycle in different life periods and menopausal status

	Percentage of Combined Group	Model 1 ^a		
		Menopausal transition	Natural menopause	Combined Transition and Natural Menopause
		OR (95% CI)	OR (95% CI)	OR (95% CI)
<i>Prenatal and Childhood Household Smoke Exposure (CHSE) and menopausal status</i>				
No smoke	25%	Ref.	Ref.	Ref.
Prenatal only	2%	1.0 (0.7, 1.6)	0.5 (0.2, 1.5)	1.0 (0.6, 1.5)
Childhood Smoke Exposure (CHSE)	34%	0.4 (0.1, 1.8)	1.2 (0.1, 11.4)	0.5 (0.1, 1.8)
Prenatal + CHSE	39%	1.0 (0.6, 1.5)	1.1 (0.5, 2.7)	1.0 (0.7, 1.6)
<i>Prenatal and adult smoke exposure and menopausal status</i>				
Model 2 ^b				
	Percentage of Combined Group	Menopausal transition	Natural menopause	Combined Transition and Natural Menopause
		OR (95% CI)	OR (95% CI)	OR (95% CI)
No prenatal, no current	35%	Ref.	Ref.	Ref.
Prenatal, no current	16%	1.1 (0.6, 1.8)	2.7 (0.8, 9.4)	1.2 (0.7, 2.0)
No prenatal, current smoking	24%	1.4 (0.9, 2.2)	2.8 (0.9, 9.0)	1.5 (1.0, 2.3)
Prenatal smoke exposure & current smoking	24%	1.1 (0.7, 1.7)	3.4 (1.1, 10.3)	1.3 (0.8, 2.0)

^a Adjusted for age at interview, site and maternal education; P for interaction of menopausal transition = 0.28; P for interaction of natural menopause = 0.65; P for interaction of combined = 0.26.

^b Adjusted for age at interview, site and maternal education; P for interaction of menopausal transition = 0.29; P for interaction of natural menopause = 0.47; P for interaction of combined = 0.24.