Smoking, body mass index, socioeconomic status and the menopausal transition in a British national cohort

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Background	This study investigates whether cigarette smoking, body mass index (BMI) and socioeconomic status are independently associated with age at menopausal transition.
Methods	Menopausal status and risk factor information were collected prospectively from 1572 British women followed up since their birth in 1946, so far until 50 years. Cox's regression models were used to investigate the relationships of interest.
Results	Cigarette smokers started the perimenopause and reached the menopause earlier than ex-smokers and non-smokers. The relative risk for smokers compared with non-smokers was 1.31 (95% CI : 1.09–1.56) for perimenopause and 1.63 (95% CI : 1.17–2.27) for menopause. Body mass index was associated with the age at inception of the perimenopause only among smokers and ex-smokers, with underweight women having the earliest perimenopause. No association was observed between BMI and age at menopause. Smokers and underweight women were more likely than others to start hormone replacement therapy (HRT) before becoming postmenopausal. There was no effect of education or social class on age at inception of the perimenopause or age at menopause. Single women had an earlier perimenopause but the effect was confounded by parity.
Conclusions	Smoking was independently related to an earlier menopausal transition, although the effect on inception of the perimenopause was particularly observed among underweight women. There was no independent effect of socioeconomic status. The popularity of HRT use in this cohort may have had an impact on the findings.
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Estimates of the median age of menopause in western industrialized countries have ranged between 48 and 52 years[1] while the median age at inception of the perimenopause has been estimated at 47–48 years.[2,3] The investigation of potential risk factors which affect the timing of the menopause and perimenopause (the period prior to menopause when biological and endocrinological changes associated with ovarian failure take place) is of clinical importance in relation to future disease risk. Increased risk of osteoporosis is associated with an early

menopause,[4–6] while a later age at menopause may be associated with an increased risk of breast cancer[7,8] and endometrial cancer.[9]

There is consistent evidence that cigarette smoking increases risk of earlier menopause,[10–19] whereas parity decreases risk.[16,20–22] In the few studies which have investigated the timing of inception of the perimenopause, the same relationships have been observed with smoking[2] and parity.[3] Other potential risk factors such as socioeconomic status[2,10,15,17–20,22] and body mass index (BMI)[2,13,16,22,23] show more inconsistent results.

The MRC National Survey for Health and Development (NSHD), a nationally representative cohort of men and women from the general population of Britain, born in one week in March 1946, provides a unique opportunity to investigate factors effecting the timing of both the inception of the perimenopause and the menopause. Having looked at the effects of reproductive factors in a previous paper,[3] this paper investigates the effects of

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smoking, relative body weight and socioeconomic status in childhood and adult life on the risk of inception of perimenopause and menopause in women by age 50 years.

Methods

The NSHD is a socially stratified birth cohort of 2548 women and 2814 men, followed up 19 times between their birth in 1946 and age 43 years.[24,25] The population interviewed at the age of 43 years were, in most respects, representative of the native population of that age.[26] Since 1993 when cohort members were 47 years old, a postal questionnaire about health during the middle years of life has been sent annually to 1778 women study members with whom there was still contact.[27] Of the original cohort of women 6% had died (n = 154), 9% were living abroad (n = 232) and were not in contact with the study, 12% had refused to participate (n = 296) and 3% could not be traced (n = 88). Data from the first 4 years of the survey are currently being analysed, during which 1572 (88%) women have returned at least one postal questionnaire and the response rates in each year have varied from 84% to 90%.

Definition of menopausal status

Definition of menopausal status (premenopausal, perimenopausal and postmenopausal) was based on the criteria used in the Massachusetts Women's Health Study.[14,28] Date of menopause was defined retrospectively following 12 months of amenorrhoea. The date of inception of the perimenopause was defined either as the date of last period if periods had stopped for between 3 and 12 months, or as the date when a woman reported that her menstrual cycle length had become more irregular in the preceding 12 months. The definitions mean that menopause was defined to the month, whereas inception of the perimenopause was defined to the year.

Women experiencing cessation of periods other than by a natural menopause were identified from the health questionnaires where dates of hysterectomy or bilateral oophorectomy operations were given. A complete record of hormone replacement therapy (HRT) use was also collected. The use of the majority of such preparations cause bleeding, meaning that, according to the definitions of menopausal status used here, it was not possible to define age at inception of perimenopause or age at menopause if HRT was started before changes to the regularity, or cessation of, menstrual cycles were reported.

Definition of explanatory factors

Smoking status and measured height and weight were obtained at home interviews by trained nurses when the survey members were 36 years of age. The information was thus given prior to the beginning of the perimenopause for all but four woman. Women were categorized into lifelong non-smokers (34%), ex-smokers (35%) and current smokers (31%) and the number of cigarettes smoked per day by current smokers was also considered. The BMI (weight/height^2) was calculated as a measure of body composition and women allocated to one of four groups representing underweight ($\leqslant$20.00 kg/m^2) (16%), normal weight (20.01–25.00 kg/m^2) (61%), overweight (25.01–30.00 kg/m^2) (17%) and obese (>30.00 kg/m^2) (6%).

Social class of the survey member herself and of her spouse or partner were derived from current occupations at 36 years of age. Socioeconomic status during childhood was assigned from father's occupation when the survey member was 11 years old, or if this was unknown, a measure at 4 or 15 years. Marital status at 36 years was split into three categories, those single and never married (15%), those married or living with a partner (89%) and those divorced, separated or widowed and not living with a partner (6%). Educational training level achieved by the age of 26 years was categorized into no qualifications (35%), below secondary qualifications (9%), ordinary secondary qualifications ('O' level or equivalent) (26%), advanced secondary qualifications ('A' level or equivalent) (24%) and higher qualifications (degree or equivalent) (6%).

Definition of confounders

Parity, updated at each follow-up and self-reported shortest and longest menstrual cycle length in the preceding year, obtained at 43 years, were considered as potential confounding factors.[3,29,30]

Statistical methods

Cox's proportional hazard models[31] were used to obtain estimates of the unadjusted and adjusted relative risk (RR) for each risk factor. Potential interactions between risk factors were also investigated. Follow-up time was in years since age 25 for the perimenopause analysis and in months since age 25 for the menopause analysis. The assumption of proportional hazards was checked and found to be reasonable in all cases.

For the analysis with perimenopause as the outcome, follow-up was until inception of the perimenopause (n = 852) or until the first of the following events: hysterectomy (or bilateral oophorectomy) (n = 271), start of HRT use (n = 143) or last returned questionnaire (n = 281). Follow-up was treated as censored if the event was not perimenopause. As women often start HRT because they are experiencing health symptoms associated with the perimenopause[32–34] suggesting that censoring may not be independent of the outcome of interest, analyses using a competing risks framework[35,36] were carried out. All analyses were repeated taking first event (either inception of the perimenopause or start of HRT use) as the outcome and then taking HRT use as the outcome while censoring the follow-up of women who reached perimenopause at the age of inception.

The small number of women (n = 17) whose periods stopped for other surgical reasons (usually endometrial ablation) or medical treatment (for example, chemotherapy) before the inception of the perimenopause, and those who were taking oral contraceptives (n = 2) or for whom data were not complete (n = 6) were omitted.

Comparable analyses were carried out with menopause (n = 243) as the outcome of interest. The follow-up time for women who did not have a natural menopause was censored at the first of the following events: hysterectomy (n = 288), start of HRT use (n = 289) or last returned questionnaire (n = 724). Twenty-two women whose periods stopped due to surgery or medical treatments, two taking oral contraceptives and four with incomplete information were omitted.

Results

Missing data

Women with missing risk factor information (n = 178) did not differ in the rate at which they reached the perimenopause

from those with complete information (log rank test: $P = 0.93$). There was a suggestion that those with missing information reached the menopause earlier than others, but the difference was not significant at the 5% level (log rank test: $P = 0.13$).

Risk factors for age at inception of the perimenopause

The unadjusted proportional hazard models indicate increased rates of entry to the perimenopause at any given age, or equivalently an earlier inception, for women who were smokers at 36 years of age compared with those who had never smoked (RR = 1.28, 95% CI : 1.07–1.53) (Table 1). A trend of increasing rates with increasing number of cigarettes smoked per day was observed (Table 1) (test for trend in analysis with ex-smokers and non-smokers combined as the baseline category: $P = 0.002$).

The rate of inception of perimenopause decreased linearly with each increase in BMI category, although the effect was not significant at the 5% level ($P = 0.14$) (Table 1). Women who were single at 36 years of age had an earlier age at inception than those who were married or cohabiting ($P = 0.001$) (Table 1). This relationship also accounted for the association between spouse's social class and inception of the perimenopause. There was no evidence of an effect of educational qualifications or any of the other social class variables (Table 1).

The estimates of RR from a model including smoking status, BMI and marital status remained comparable with the unadjusted ones in a restricted sample consisting of all women with complete risk factor information (Table 2). Subsequent investigation of interactions revealed that an interaction between smoking status and BMI was significant at the 10% level ($P = 0.06$). This term indicated that there was a decreasing risk across categories of BMI among smokers and ex-smokers, but not non-smokers (Figure 1). This leads to an estimated RR for smokers compared with non-smokers among underweight women of 1.64 (95% CI : 1.20–2.25), compared with no effect (RR = 1.05, 95% CI : 0.79–1.39) among overweight women.

The effects of BMI and smoking status remained unchanged on addition of parity to the model, but the effect of marital status was confounded. The RR for those women who were never married compared with married women was reduced to 0.75 (95% CI : 0.52–1.07). The further addition of shortest menstrual cycle length to the model in an analysis restricted to the subgroup of women who were still premenopausal at 43 years of age ([n = 1033], the age at which women were asked about menstrual cycles), was found to marginally reduce the effect of smoking, although no difference in the level of statistical significance was observed.

The model with first event as the outcome (either inception of the perimenopause or HRT use) yielded very similar estimates to those for age at inception of the perimenopause and there was evidence of an interaction between smoking status and BMI ($P = 0.06$). The effect of smoking status on the outcome was slightly stronger due to current smokers having over double the rate of HRT uptake compared with non-smokers.

Risk factors for age at menopause

Smokers had a higher risk of reaching menopause than non-smokers with the RR after adjustment for BMI and marital status being 1.65 (95% CI : 1.19–2.29), but there was no difference in

risk between non-smokers and ex-smokers (Table 3). The estimates for the effect of marital status indicated that single women tended to reach menopause earlier than other women, but the effect did not reach conventional significance levels (Table 3). There was no evidence of a relationship between age at menopause and BMI, education or social class or of smoking by BMI interaction ($P > 0.1$ in each case). Menstrual cycle length slightly reduced the effect of smoking in the relevant subgroup of women (n = 1029).

The effect of smoking status on the first event outcome (either menopause or HRT use) was stronger (RR = 1.91, 95% CI : 1.52–2.41 after adjustment for BMI and marital status) than its effect on menopause, as was the effect of BMI (RR = 0.91 for normal against underweight, 95% CI : 0.80–1.03 after adjustment for smoking and marital status). These strengthened effects were due to smokers and underweight women being more likely than others to start HRT use prior to the menopause.

Discussion

The study found that women who were smokers at 36 years of age reached the inception of the perimenopause and subsequently the menopause earlier than ex-smokers and lifelong non-smokers. These associations were independent of socioeconomic status, BMI and parity. These findings were consistent with those from previous studies.[2,10–19] Previously, women who smoke have been found to have a median age of menopause 1–2 years earlier than those who do not smoke.[10] The median age at menopause has not yet been reached in the NSHD cohort, but the RR observed is consistent with previous studies where a comparable effect has been presented,[17] with long-term smokers compared with non-smokers[19] and for younger ages.[13] A different effect of smoking status may exist at older ages and this possibility will be investigated as further data become available. Median age at inception of the perimenopause was 48 years for all smoking status groups with non-smokers reaching the perimenopause within a year of smokers. Since smokers have been found to have a shorter perimenopause than non-smokers[2] the effect of smoking on age at menopause may be expected to be stronger than the effect on inception of the perimenopause.

The findings are consistent with studies showing higher rates of infertility among smokers compared with non-smokers.[37,38] A possible explanation for earlier menopause of smokers is that smoking has a toxic effect on ovarian function, and accelerates the rates of follicular atresia.[39,40] The fact that there are increased rates of inception of perimenopause with increased number of cigarettes smoked also supports this theory. However, the lack of effect when comparing ex-smokers with non-smokers may provide evidence against an irreversible toxic effect of smoking.

The current study showed only a weak relationship between BMI and age at the inception of the perimenopause and no such relationship between BMI and age at menopause. The finding in relation to the perimenopause, that the effect was observed particularly among smokers and that there was no relationship among lifelong non-smokers was consistent with the findings of Willett *et al.*[13] in relation to menopause. These findings suggest that the effect of smoking is particularly marked among underweight women.

Table 1 Unadjusted relative risks for inception of the perimenopause by potential risk factors obtained from Cox's proportional hazard models

	No. (%)	Relative risk (95% CI)	P-value[a]
Smoking status at 36 years			
Non-smoker	476 (34.4)	1	0.02
Ex-smoker	481 (34.8)	1.07 (0.90–1.27)	
Current smoker	425 (30.8)	1.28 (1.07–1.53)	
Smoking status at 36 years			
Non-smoker	476 (34.4)	1	0.03
Ex-smoker	481 (34.9)	1.07 (0.90–1.27)	
Smoker			
1–14 cigs/day	149 (10.8)	1.12 (0.87–1.44)	
15–24 cigs/day	209 (15.2)	1.37 (1.10–1.70)	
25+ cigs/day	65 (4.7)	1.42 (0.99–2.02)	
BMI[b] at 36 years (linear effect)			
Underweight	212 (15.5)	1	0.14
Normal	834 (60.9)	0.93 (0.85–1.03)	
Overweight	237 (17.3)	0.87 (0.71–1.05)	
Obese	87 (6.4)	0.80 (0.60–1.08)	
Marital status at 36 years			
Single	74 (15.3)	1	0.001
Married	1228 (88.8)	0.65 (0.49–0.86)	
Divorced/widowed	81 (5.9)	0.95 (0.65–1.39)	
Educational qualifications by age 26 years			
None	513 (35.1)	1	0.36
Below 'O' level	130 (8.9)	0.82 (0.62–1.09)	
'O' level	382 (26.2)	0.89 (0.75–1.07)	
'A' level	350 (24.0)	1.04 (0.86–1.24)	
Degree	85 (5.8)	1.01 (0.75–1.35)	
Social class at 36 years			
I	25 (1.8)	1	0.97
II	256 (18.6)	1.10 (0.63–1.90)	
III non-manual	317 (23.1)	1.10 (0.64–1.89)	
III manual	64 (4.7)	1.21 (0.65–2.24)	
IV	151 (11.0)	1.18 (0.67–2.08)	
V	47 (3.4)	0.98 (0.51–1.86)	
Not working	513 (37.4)	1.14 (0.66–1.95)	
Social class of spouse at 36 years			
I	133 (12.0)	1	0.01
II	298 (26.8)	1.03 (0.79–1.34)	
III non-manual	109 (9.8)	1.00 (0.72–1.41)	
III manual	288 (25.9)	0.94 (0.71–1.23)	
IV	113 (10.2)	0.94 (0.67–1.34)	
V	16 (1.4)	1.02 (0.52–2.02)	
No spouse	155 (13.9)	1.49 (1.12–1.99)	
Childhood social class			
I	100 (6.8)	1	0.92
II	298 (20.4)	1.12 (0.83–1.52)	
III non-manual	248 (16.9)	1.07 (0.78–1.46)	
III manual	450 (30.8)	1.11 (0.83–1.48)	
IV	289 (19.8)	1.10 (0.81–1.49)	
V	78 (5.3)	0.95 (0.63–1.44)	

[a] P-value for the likelihood ratio test for the model including the risk factor compared with the null model.

[b] Body mass index.

Table 2 Unadjusted and adjusted relative risks for inception of the perimenopause by smoking status, body mass index (BMI) and marital status for a sample of 1369 women obtained from Cox's proportional hazard models

	Unadjusted		Adjusted[a]	
	Relative risk (95% CI)	P-value[b]	Relative risk (95% CI)	P-value[c]
Smoking status at 36 years				
Non-smoker	1	0.01	1	0.02
Ex-smoker	1.08 (0.91–1.28)		1.08 (0.91–1.29)	
Current smoker	1.31 (1.09–1.56)		1.29 (1.08–1.54)	
BMI[d] at 36 years (linear effect)				
Underweight	1	0.14	1	0.12
Normal	0.93 (0.85–1.03)		0.93 (0.84–1.02)	
Overweight	0.86 (0.71–1.05)		0.86 (0.71–1.04)	
Obese	0.80 (0.60–1.08)		0.80 (0.60–1.06)	
Marital status at 36 years				
Single	1	0.002	1	0.003
Married	0.66 (0.50–0.88)		0.65 (0.49–0.87)	
Divorced/widowed	0.97 (0.66–1.42)		0.91 (0.62–1.33)	

[a] Results obtained from model including all risk factors presented in Table.

[b] P-value for the likelihood ratio test for the model including the risk factor compared with the null model.

[c] P-value for the likelihood ratio test comparing the model including all terms with models excluding each in turn.
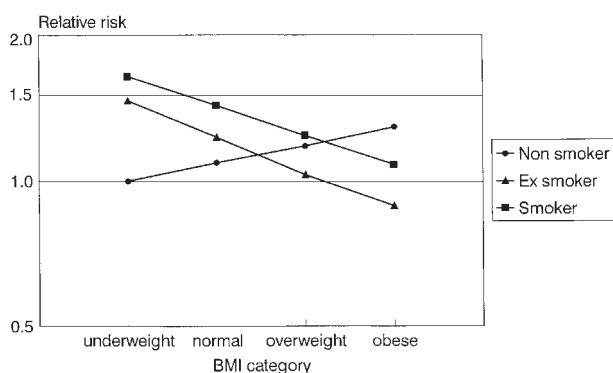
[d] Body mass index.

Figure 1 Relative risks for inception of the perimenopause for categories of women defined by a cross-tabulation of body mass index (BMI) at 36 years (fitted as a linear effect) and smoking status at 36 years

Smokers and ex-smokers had a higher rate of HRT use at all ages than non-smokers. This may be because smokers reached the menopausal transition earlier and hence, because of menopausal symptoms, went onto HRT earlier. It has also been suggested that smokers may suffer more severely from menopausal symptoms than non-smokers[32] and may therefore be more likely to use HRT during the perimenopause. The association between smoking status and stages of the menopause may, therefore, have been weakened by this selective removal of women from the natural menopause transition. The results of the analysis taking either inception of the perimenopause or start of HRT use as the outcome, indicated that the median age at first event among smokers was 47 years compared with 48 years for non-smokers. Hence, this analysis would provide estimates of the effect on age at start of perimenopause if first use of HRT were assumed to be an indicator of the inception of the perimenopause. Alternatively, smokers may be more likely to take HRT due to other individual characteristics, irrespective of whether they are nearing the menopause. The increased use of HRT among smokers in this cohort is similar to other British studies[32,41] but contrasts to most American studies.[34,42,43] More generally, there is evidence[44–46] that the social and behavioural characteristics of HRT use in younger cohorts may differ from those of older cohorts where a healthy user effect was commonly observed.[34,44] A self-selection for HRT use, similar to that seen among smokers, also occurred in relation to BMI, particularly during the perimenopause where underweight women were more likely to be users. The main effect of BMI on age at first event (menopause or HRT use) was similar to that observed for age at inception of the perimenopause where a relative risk of around 0.90 for each category increase in BMI was observed.

Marital status was the only socioeconomic indicator related to the timing of the menopausal transition and this association was confounded by parity. Single women were more likely to be nulliparous than married women. Nulliparous women have been found to have an earlier age at inception of the perimenopause[3] and an earlier age at menopause[16,20–22] than parous women which may be due to an accelerated depletion in oocyte numbers among nulliparous women because of continuous ovulation uninterrupted by pregnancy. There is no clear mechanism, unrelated to parity, which could explain any possible remaining effect of marital status.

The current study found no association between socioeconomic status (measured by level of education, adult social class and childhood social class) and age at either menopause transition. Social class, education, household income, marital status and location of residence have been used as indicators of socioeconomic status in previous studies on timing of the menopause, and findings have been mixed.[2,10,15,17–20,22] Discrepancies may be due to the confounding of different measures of socioeconomic status and also of confounding with smoking status.[10,19]

Table 3 Unadjusted and adjusted relative risks for menopause by smoking status, body mass index (BMI) and marital status for a sample of 1365 women obtained from Cox's proportional hazard models

	Unadjusted		Adjusted[a]	
	Relative risk (95% CI)	*P*-value[b]	Relative risk (95% CI)	*P*-value[c]
Smoking status at 36 years				
Non-smoker	1	0.002	1	0.002
Ex-smoker	0.98 (0.69–1.38)		0.98 (0.69–1.39)	
Current smoker	1.64 (1.19–2.28)		1.65 (1.19–2.29)	
BMI[d] at 36 years (linear effect)				
Underweight	1	0.87	1	0.84
Normal	1.02 (0.85–1.21)		1.02 (0.85–1.22)	
Overweight	1.03 (0.72–1.47)		1.04 (0.73–1.48)	
Obese	1.05 (0.61–1.78)		1.06 (0.62–1.80)	
Marital status at 36 years				
Single	1	0.27	1	0.30
Married	0.66 (0.40–1.08)		0.66 (0.40–1.08)	
Divorced/widowed	0.75 (0.37–1.52)		0.67 (0.33–1.36)	

[a] Results obtained from model including all risk factors presented in Table.

[b] *P*-value for the likelihood ratio test for the model including the risk factor compared with the null model.

[c] *P*-value for the likelihood ratio test comparing the model including all terms with models excluding each in turn.

[d] Body mass index.

The differences in findings between the perimenopause and menopause in this study may be due to the characteristics of women starting HRT during the perimenopause who are thus included as an event in the perimenopause model but censored in the menopause model. Furthermore, the results for age at menopause relate to relatively young ages and relationships may change as more women reach the menopause. The smaller number of menopause events, compared with perimenopause, and small numbers of women in some risk factor categories, means lower power to detect effects, particularly interactions. Age at menopause is, however, easier to define than age at inception of the perimenopause. The definition of perimenopause used here may not identify the inception of the perimenopause in all women since perimenopause may not always affect the regularity of menstruation.

Since the NSHD is a prospective study, risk factor and confounding variable information was obtained at follow-ups prior to menopause and hence was less subject to recall bias than if collected concurrently with menopausal status, as has been the case in many previous studies. We were also able to consider lifetime social class as the NSHD has measures of childhood as well as adult social class. The outcomes are subject to recall bias only for the 155 women who reached the inception of the perimenopause and 56 women who reached the menopause more than a year before the first postal questionnaire was sent.

Compared with most previous studies, a greater proportion of women were taking HRT in the NSHD as it is a younger cohort of women. This increased popularity in HRT use will be a constant problem in epidemiological investigation of the natural menopause if menstrual change is the indicator of menopausal status.[3,47] It may be that the results presented in this paper can only be interpreted under the conditions existing in the study and may not be generalizable to populations with different patterns of HRT use. The use of the competing risks analysis does, however, provide valuable additional information and can be considered as a sensitivity analysis.

In conclusion, the study suggests that smokers have an earlier inception of perimenopause and earlier menopause than non-smokers. The size of the effects estimated here may have been weaker than in samples with less HRT use, since smokers were more likely to start taking HRT than non-smokers before inception of, or during the perimenopause. There was weak evidence that women with lower BMI at 36 years reached inception of the perimenopause earlier than those with higher BMI, and this applied particularly to smokers. Of the socio-economic indicators, only marital status had any effect on age at either menopausal transition, but the association was confounded by parity. As more women reach the menopause, further analyses will be carried out to assess whether the effects of these risk factors on rates of menopause vary with age.

Acknowledgements

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