Mediation of the association of prenatal maternal smoking with time to natural menopause in daughters by birthweight-for-gestational-age z-score and breastfeeding duration

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Abstract

Background

Maternal smoking during pregnancy, lower birth weight, and shorter breastfeeding duration have all been associated with an earlier age at menopause in the female offspring. This study quantifies the joint mediating effect of birthweight-for-gestational-age z-score and breastfeeding duration in the relationship between maternal smoking during pregnancy and the time to natural menopause in daughters.

Methods

Using pooled data from two prospective birth cohort studies – the 1970 British Cohort Study (n=3,878) followed-up to age 46 years and the 1958 National Child Development Study (n=4,822) followed-up to age 50 years – we perform mediation analysis with inverse odds weighting, implemented in Cox proportional-hazards models.

Results

Maternal smoking during pregnancy was associated with lower birthweight z-scores [β: -0.29; 95% CI -0.34, -0.24] and reduced breastfeeding duration [relative risk ratio (RRR)<1month: 0.90; 95% CI 0.79, 1.02; RRR≥1 month: 0.66; 95% CI 0.59, 0.73], relative to women who were never breastfed. Greater z-score for birthweight [hazard ratio (HR): 0.96; 95% CI 0.91, 1.01] and longer breastfeeding duration [HR≥1 month: 0.84; 95% CI 0.74, 0.96] were associated with lower hazards for earlier age at natural menopause. The total effect of prenatal exposure to cigarette smoke on the time to natural menopause in daughters was estimated as a HR of 1.13 [95% CI 1.02, 1.24]. Birthweight z-score and breastfeeding duration jointly explained 14% of the total effect [HRnatural indirect effect (NIE): 1.02; 95% CI 0.99, 1.05].

Conclusions

The consequences of smoking during pregnancy on the earlier experience of natural menopause in daughters may partly be offset by intrauterine growth and longer breastfeeding duration to the extent that they mediate the risk of earlier menopause.

Keywords

Smoking during pregnancy; Menopause; Birthweight: Breastfeeding; Causal Mediation Analysis; Inverse Odds Weighting; Birth Cohort; Longitudinal.

Key messages

We investigated a pathway whereby maternal smoking during pregnancy influences menopausal age in daughters through fetal growth and breastfeeding duration.

Maternal smoking during pregnancy increased the hazard of earlier menopause by 13%.

Lower birthweight z-score and not being breastfed jointly accounted for about 14% of the increased hazard of earlier menopause.

Maternal focused interventions to prevent and treat suboptimal fetal growth and improve breastfeeding outcomes, in addition to smoking cessation interventions, may partly offset the adverse health consequences of maternal smoking during pregnancy on daughters' reproductive longevity to the extent that they mediate the risk associated with earlier menopause.

Introduction

Natural menopause occurs when the ovarian follicle pool is exhausted. Reaching its peak at around 20 weeks of fetal life, the pool of ovarian follicles declines gradually thereafter. The individual differences in the initial number of ovarian follicles and the rate of ovarian follicle loss are considered to determine menopausal age [1]. Among white women from high-income countries natural menopause occurs on average between 50 and 52 years, though around 10% experience menopause before the age of 45 years. Earlier age at natural menopause has important health implications, such as an increased risk of type 2 diabetes, cardiovascular disease, osteoporosis, and all-cause mortality [2].

Clinical studies have illustrated that toxic agents including cigarette smoke may contribute to the process of ovarian follicle loss before birth and alter the reproductive span of the female offspring [3-4]. In epidemiological studies the association between in utero exposure to cigarette smoke and the timing of menopause in the female offspring is contested [5-10]. Some of the studies show no association, however, present estimates of effect that are adjusted for variables that may be on the causal pathway (mediators). Adjustment for mediators will tend to underestimate the overall effect of maternal smoking during pregnancy and under certain assumptions (e.g. no unmeasured mediator-outcome confounders) the adjusted estimate will represent the part of the effect that is not mediated by the intermediate variable(s) [11]. Understanding the role of mediating factors on the causal pathway in the association between in utero exposure to cigarette smoke and the timing of menopause in the female offspring can offer potential for future intervention and pathways to offset the potentially deleterious effect of in-utero exposure to cigarette smoke [12].

Fetal growth and breastfeeding are two potential mediators. Previous research has suggested that both may be associated with timing of menopause. Restricted fetal growth, generally marked by low birth weight, may adversely affect the peak number of ovarian follicles, and thus affect the timing of the menopause [2]. However, the evidence for a relationship between low birth weight and early menopause has been inconsistent [5, 13-16]. Some studies showed a significant association of low weight at 1 year [16] or at 2 years [15] with early menopause, but not birthweight, pointing to the importance of early life nutrition. Studies have shown that children who were not breastfed or breastfed for short periods [5, 15] may undergo menopause earlier.

Restricted fetal growth is the most consistent effect of prenatal cigarette smoke exposure on the developing offspring. Nicotine interacts with receptors in placental vasculature resulting in decreased placental blood flow and fetal vasoconstriction, which leads to a disruption of the delivery of oxygen and nutrients to the fetus. This reduced blood flow leads to fetal malnutrition and is thought to be a causal mechanism for the effects of prenatal cigarette smoke exposure on poor fetal growth [17]. Birth weight deficits in infants prenatally exposed to cigarette smoke range from 200 to 327 grams, depending on the nicotine dose; it is estimated that 20% of low birthweight and small for gestational age infants are attributable to prenatal exposure to cigarette smoking [18-19].

Maternal smoking during pregnancy also affects lactogenesis and lactation. Women who smoke during pregnancy are less likely to initiate breastfeeding and are more likely to

breastfeed for shorter period [20-22]. Smoking in pregnancy decreases prolactin concentration (an important mediator of normal lactogenesis) which has implications for lactation [23]. It has been proposed that a prolactin measurement between 35th and 38th week of pregnancy could be a good predictor of lactational performance [21, 24]. In addition, low birthweight is associated with delays in (or failure of) early breastfeeding initiation (within the first hours of birth) and reduced duration of exclusive breastfeeding [20]. Hospital practices, baby's health and development, and mother's health and hormone levels [23, 25] have been discussed as reasons for compromised breastfeeding in the immediate postpartum period.

Maternal sociodemographic factors, such as age, parity, ethnicity, and socioeconomic background influence smoking during pregnancy [26]. These factors also influence birthweight and breastfeeding initiation and duration, and age of menopause in daughters, even after adjusting for smoking [27-28, 5].

This study estimates the effect of maternal smoking during pregnancy on the time to natural menopause in daughters that operates through birthweight-for-gestational-age z-score (a marker of fetal growth rate), hereafter birthweight z-score, and breastfeeding duration.

Methodology

Study population

We use data from two British birth cohort studies. The 1970 British Cohort Study (BCS70) follows the lives of 8,655 women (18,037 people) born in a single week in March 1970 [29-31]. This study uses data collected at birth, and ages 5, 42 and 46 [33]. The 1958 National Child Development Study (NCDS) follows the lives of 8,959 women (18,558 people) born in a single week in March 1958 [32]. This study uses information collected at birth and ages 7, 44, and 50 [33]. The proportions of women lost to follow-up by age 46 years in BCS70 and age 50 years in NCDS (due to permanent refusal, inability to trace, emigration, or death) are illustrated in Supplementary material (Figure S1, Supplementary File 1).

Outcome: Age at natural menopause

At age 42 and 46 surveys in BCS70 and age 44 and 50 surveys in NCDS information was collected on menstrual irregularity, month and year of last menstrual period, any surgery to remove the uterus or both ovaries, and use of hormonal therapy (HT). Natural menopause, taken as the date of the final menstrual period (FMP), was defined retrospectively after 12 consecutive months of amenorrhea not due to surgery or other medical treatment [1]. Peri-menopausal women were those with 3 to 11 months of amenorrhea or whose periods became less regular in the absence of amenorrhea. Pre-menopausal women reported menstruation within the last 3 months. Women who were premenopausal, perimenopausal or had undergone natural or surgical menopause, or started HT before their FMP were included in this analysis. Women whose periods stopped for other reasons (e.g. pregnancy, contraceptives, chemotherapy, or radiotherapy) or there was no sufficient information to determine their menopause status, were excluded. Details about the classification of menopause status are provided in Supplementary material (Table S1, Supplementary file 1).

Exposure: Maternal cigarette smoking during pregnancy

At birth mothers of cohort children in both studies were asked whether they smoked during the pregnancy. Maternal smoking during pregnancy was categorised as non-smokers (women who never smoked or stopped smoking before becoming pregnant) and smokers (women who smoked during part or throughout the whole pregnancy).

Mediators: Birthweight-for-gestational-age z-score and breastfeeding duration

Information on birthweight and gestational age in both studies was recorded by a midwife at cohort member's birth. In each cohort separately, birthweight (in kilograms), adjusted for gestational age (in weeks), was transformed to standard deviation scores (z-scores), using the LMS method [34]. Z-scores, calculated according to the British 1990 Growth Reference [35], were obtained using the egen zanthro() function in Stata [36].

At the first major survey following the birth sweep, mothers in both studies were asked if the cohort child was breastfed partly or wholly even for a few days. The available data was categorised as never breastfed, breastfed for less than 1 month, and breastfed for 1 month or longer.

Potential confounding variables: Maternal education, maternal age and father's social class at birth, previous live births

To control for confounders of the exposure, mediators, and outcome (Figure 1), we included the following preexposure characteristics: whether the mother remained in school after minimum school leaving age of 15 years (yes, no); father's social class at birth (non-manual, manual, no father figure), maternal age at birth (years), and previous live births (number). The choice of covariates was based on the literature and previous research by our research group [5].

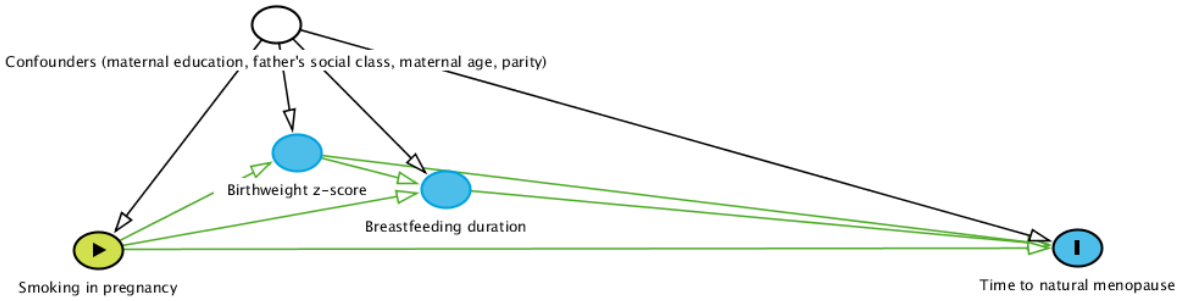

Fig 1. A causal diagram of the association between maternal smoking in pregnancy and time to natural menopause in daughters

Statistical analysis

We first present descriptive statistics for all variables included in the analysis for each cohort separately (means and standard deviations (SDs) for continuous variables, percentages for categorical variables) for both the imputed sample (see 'Missing data' section) and sample with complete cases (Table 1).

We next assess the associations between maternal smoking during pregnancy and birthweight z-scores and breastfeeding duration using linear and multinomial regression models and assess the associations between birthweight z-scores and breastfeeding duration and time of natural menopause using Cox proportional hazards models (Table 2). Follow-up time in the Cox proportional hazards models was in years since age 11 (the average age for start of puberty in girls) until the earliest of natural menopause, surgery, HT, or end of study period). Follow-up was treated as censored if the event was not natural menopause (surgery, HT, or end of study period). We present adjusted linear regression coefficients, relative risk ratios (RRRs) and hazard ratios (HRs), and corresponding 95% confidence intervals (CIs), for both pooled and study specific analyses of multiply imputed samples (Table 2). The pooled analysis incorporated a dummy variable identifying the cohort (NCDS or BCS70).

We then decompose the total effect (TE) of maternal cigarette smoking during pregnancy on the timing of natural menopause in daughters into natural direct effects (NDE) and natural indirect effects (NIE) through birthweight z-scores and breastfeeding duration (Table 3). We use sequential causal multiple mediator analysis with inverse odds weighting (IOW) [37-38], implemented in Cox proportional-hazards models. The odds are obtained using logistic regression model for the exposure given the mediators and confounding variables. The

weights are computed by taking the inverse of the predicted odds for each observation in the exposed group; the unexposed group is assigned an IOW of 1. We estimate the TE using an unweighted Cox proportional hazards model of the outcome conditional on the exposure and confounding variables. We estimate the NDE via a weighted Cox proportional hazards model of the outcome conditional on the exposure and confounding variables, using the IOW. We calculate the NIE via the mediators by subtracting the NDE from the TE and 200 bootstrap replications are used to derive bias-corrected CIs for TE, NDE and NIE. We present pooled and study specific results from multiply imputed samples. In secondary analysis we restrict the follow-up period in the pooled sample until age 46 years (i.e. the follow-up period in the younger BCS70 cohort) to allow better comparison between the cohorts in terms of follow-up time. In this analysis NCDS women were censored at age 46.

Results from complete case analyses are presented in Supplementary material (Table S2 and S3, Supplementary file 1).

Missing data

Missing data in the dates of menopause, surgery, or HT initiation was approached as follows: 1) for all events, if the year was available but the month was missing: between 4.2 to 13.6% in BCS70 and 5.1 to 22.0% in NCDS – the missing months were replaced with mid-year (July); 2) for natural menopause, if neither month nor year was available: 11.6% in BCS70 and 5.1% in NCDS – the missing date was replaced with the date of interview minus 12 months; 3) for surgery or HT initiation, if neither month nor year was available: between 2.7 to 9.1% in BCS70 and 3.0 to 5.2% in NCDS – the missing date was replaced with the date of interview. Details about missing data in menopause status and timing of first event are available in Supplementary material (Tables S1 and S1a, Supplementary file 1).

We used multiple imputation (MI) with chained equations, performed in each cohort separately, to address the missingness in the confounders, mediators, and exposure [39]. The imputation model included the exposure, all mediators, and confounders, as well as the outcome; though as outcomes were fully observed missing values were only imputed on exposure, mediators, and confounders [40]. The proportion of missing observations for each variable ranged between 5.2 to 17.3% in NCDS and 6.9 to 18.2% in BCS70 (Table 1). We created 20 imputed datasets for each cohort and conducted the analyses using each of the 20 imputed datasets; the estimates from each imputed dataset were combined to obtain overall estimates using Rubin’s rules [41].

All analyses were conducted using Stata 17.

Results

The study sample comprised 8,700 women: 3,878 women in the BCS70 cohort and 4,822 women in the NCDS cohort. By the 9th follow-up of BCS70 at age 46, 8.9% of women had experienced natural menopause, and by the 9th follow-up of NCDS at age 50, 24.4% had undergone natural menopause. 44.3% of women in BCS70, and 41.7% in NCDS had mothers who smoked at any time during the pregnancy. Z-scores for birthweight were lower in NCDS [mean -0.36 (SD 1.10)] compared to BCS70 [mean -0.21 (SD 1.11)]. 40.4% of women in BCS70 and 69.5% in NCDS received breastmilk - partly or wholly even for a few days (Table 1). In both cohorts, maternal sociodemographic factors were strongly associated with the exposure, mediators, and outcome (Table S4, Supplementary file 1).

Table 1. Characteristics of the study sample(s)

Characteristic	**BCS70 (n=3,878, followed-up to age 46 years)**				**NCDS (n=4,822, followed-up to age 50 years)**		
	N	**% complete cases**	**% imputed sample**		**N**	**% complete cases**	**% imputed sample**
Natural menopause							
No	3,533	91.10			3,645	75.59	
Surgical menopause	331	8.54			534	11.07	
HT before FMP	174	4.49			542	11.24	
Pre- and peri- menopause	3,028	78.07			2,569	53.28	
Yes	345	8.90			1,177	24.41	
Smoking in pregnancy							
No	2,001	55.66	55.69		2,632	58.29	58.24
Yes (incl. stopped during pregnancy)	1,594	44.34	44.31		1,883	41.71	41.76
Missing	283	7.30			307	6.37	
Birthweight (kg) (mean, SD)	3,607	3.26 (0.50)			4,423	3.26 (0.51)	
Missing	180	4.75			399	8.27	
Gestational age (weeks) (mean, SD)[1]	3,392	39.78			4,117	40.16 (1.73)	
Missing	395	10.43			705	14.62	
Birthweight z-score (mean, SD)	3,379	-0.21 (1.11)	-0.21 (1.19)		3,987	-0.36 (1.10)	-0.37 (1.20)
Missing	499	12.87			835	17.32	
Breastfeeding							
Never	1,877	59.63	59.74		1,285	30.48	30.51
Up to 1 month	507	16.11	16.14		1,031	24.45	24.55

More than 1 month	764	24.27	24.11		1,900	45.07	44.94
Missing	730	18.82			606	12.57	
In school after age 15							
Yes	1,342	37.47	37.42		1,229	26.96	27.01
No	2,240	62.53	62.58		3,330	73.04	72.99
Missing	296	7.63			263	5,45	
Social class at birth							
Non-manual	1,131	31.47	31.42		1,248	27.30	27.26
Manual	2,209	61.46	61.48		3,088	67.54	67.57
No father in HH/Other	254	7.07	7.10		236	5.16	5.17
Missing	284	7.32			250	5.18	
Maternal age at birth (mean, SD)	3,609	25.94 (5.32)	25.95 (5.54)		4,568	27.49 (5.67)	27.48 (5.89)
Missing	269	6.94			258	5.27	
Previous live births (mean, SD)	3,608	1.09 (1.29)	1.09 (1.32)		4572	1.26 (1.53)	1.26 (1.59)
Missing	270	6.96			254	5.18	

Note:
[1] 167 (4.92% of) women in BCS70 and 168 (4.08%) in NCDS were born before 37 weeks of gestation (preterm).
The imputation model included birthweight z-score rather than birthweight (kg) and gestational age (weeks).

Table 2 illustrates the associations between maternal smoking during pregnancy, birthweight z-scores and breastfeeding duration, as well as their relationships with the timing of menopause in the pooled and study specific samples. Maternal cigarette smoking during pregnancy was strongly associated with lower birthweight z-score [β: -0.29; 95% CI -0.34, -0.24] and lower likelihood for longer breastfeeding [RRR<1month: 0.90; 95% CI 0.79, 1.02; RRR≥1 month: 0.66; 95% CI 0.59, 0.73], relative to no breastfeeding. The likelihood for being breastfed for longer, compared to not being breastfed, increased with an increase in birthweight z-score. One standard deviation higher birthweight z-score corresponded to 5% higher odds for being breastfed for less than one month (RRR<1month: 1.05; 95% CI 0.98, 1.12;) and 6% increased odds for being breastfed for 1 month or longer (RRR≥1 month: 1.06; 95% CI 1.00, 1.12). An increase in the z-score for birthweight was associated with lower hazard for earlier age at natural menopause (HR: 0.96, 95% CI 0.91, 1.01). Women who were breastfed for 1 month or longer had a lower hazard of earlier menopause (HR: 0.84, 95% CI 0.74, 0.96) compared to women who never received breastmilk. The patterns of these associations were similar in the study specific analyses, though the evidence for an association between breastfeeding and age at menopause in NCDS was weaker (Table 2).

Table 2. Associations between maternal smoking during pregnancy, birthweight z-scores, breastfeeding duration, and time to natural menopause in daughters (imputed sample)

Pooled (n=8,700, followed-up to age 50 years)	**Birthweight z-score**	**Breastfed <1 month** reference: (never)	**Breastfed 1+months** reference: (never)	**Daughter's experience of natural menopause** reference: no (incl. pre-, peri-, surgical menopause, HT)
	β (95% CI)	**RRR (95% CI)**	**RRR (95% CI)**	**HR (95% CI)**
Maternal smoking in pregnancy (reference: no smoking)	-0.29 (-0.34, -0.24) [1]	0.90 (0.79, 1.02)	0.66 (0.59, 0.73) [1]	1.13 (1.01, 1.26) [1]
Birthweight z-score		1.05 (0.98, 1.12)	1.06 (1.00, 1.12) [2]	0.96 (0.91, 1.01) [2]
Breastfed <1 month (reference: never)				0.99 (0.86, 1.15) [3]
Breastfed 1month + (reference: never)				0.84 (0.74, 0.96) [3]
BCS70 (n=3,878, followed-up to age 46 years)	**Birthweight z-score**	**Breastfed <1 month** reference: (never)	**Breastfed 1+months** reference: (never)	**Daughter's experience of natural menopause** reference: no (incl. pre-, peri-, surgical menopause, HT)
	β (95% CI)	RRR (95% CI)	RRR (95% CI)	HR (95% CI)
Maternal smoking in pregnancy (reference: no smoking)	-0.32 (-0.40, -0.24) [1]	0.82 (0.66, 1.01)	0.62 (0.51, 0.75) [1]	1.21 (0.97, 1.51) [1]
Birthweight z-score		1.03 (0.93, 1.14)	1.07 (0.98, 1.17) [2]	1.00 (0.90, 1.10) [2]
Breastfed <1 month (reference: never)				0.91 (0.66, 1.27) [3]
Breastfed 1month + (reference: never)				0.47 (0.33, 0.68) [3]
NCDS (n=4,822, followed-up to age 50 years)	**Birthweight z-score**	**Breastfed <1 month** reference: (never)	**Breastfed 1+months** reference: (never)	**Daughter's experience of natural menopause** reference: no (incl. pre-, peri-, surgical menopause, HT)
	β (95% CI)	RRR (95% CI)	RRR (95% CI)	HR (95% CI)
Maternal smoking in pregnancy (reference: no smoking)	-0.27 (-0.34, -0.20) [1]	0.99 (0.84, 1.17)	0.71 (0.61, 0.83) [1]	1.10 (0.97, 1.24) [1]
Birthweight z-score		1.06 (0.98, 1.16)	1.06 (0.98, 1.13) [2]	0.95 (0.89, 1.00) [2]
Breastfed <1 month (reference: never)				1.06 (0.90, 1.25) [3]
Breastfed 1month + (reference: never)				0.96 (0.83, 1.11) [3]

Note:
Model adjusted for:
[1] maternal education, social class and maternal age at birth, previous live births (and cohort in pooled sample)
[2] maternal education, social class and maternal age at birth, previous live births, maternal smoking in pregnancy (and cohort in pooled sample)
[3] maternal education, social class and maternal age at birth, previous live births, maternal smoking in pregnancy, birthweight z-score (and cohort in pooled sample).
Results from complete cases are presented in Supplementary material (Table S2, Supplementary file 1).

The estimated total causal effects, direct and indirect effects, and the corresponding bias-corrected bootstrap confidence intervals, in the pooled and study specific samples, are shown in Table 3. Maternal smoking during pregnancy, compared to non-smoking, increased the hazard of menopause by 13% (HRTE=1.13, 95% CI 1.02, 1.24). Birthweight z-score alone mediated 5.8% of the TE (HRNIE= 1.01, 95% CI 0.99, 1.04), and jointly birthweight z-score and breastfeeding mediated 14.4% (HRNIE=1.02, 95% CI 0.99, 1.05). Maternal smoking in pregnancy was associated with menopause timing independent of (the mediating role of) birthweight z-score only (HRNDE 1.12, 95% CI 1.02, 1.24) and birthweight z-score and breastfeeding jointly (HRNDE=1.11, 95% CI 1.01, 1.23).

The pattern of results was similar across the cohorts, but all effects were stronger in BCS70 than in NCDS (Table 3). In BCS70, maternal smoking during pregnancy increased the hazard of menopause by 21% (HRTE=1.21, 95% CI 0.97, 1.52). Birthweight z-score alone mediated 4.1% of this association (HRNIE= 1.01, 95% CI 0.94, 1.08), while jointly birthweight z-score and breastfeeding mediated 22.1% (HRNIE=1.04, 95% CI 0.96, 1.13). Maternal smoking in pregnancy was associated with menopause timing independent of (the mediating role of) birthweight z-score only (HRNDE 1.20, 95% CI 0.94, 1.58) and birthweight z-score and breastfeeding jointly (HRNDE=1.16, 95% CI 0.90, 1.52). In NCDS, prenatal cigarette smoking increased the hazard of menopause by only 10% (HRTE=1.10, 95% CI 0.99, 1.22) and birthweight z-score mediated a smaller percentage of the association at 1.7% (HRNIE=1.00 95% CI 0.98, 1.04). The joint mediation with breastfeeding was also less than for BCS70 at 6.4% (HRNIE=1.01, 95% CI 0.98, 1.05). As in BCS70, prenatal cigarette smoking was associated with daughter's menopause timing independent of (the mediating role of) birthweight z-score only (HRNDE 1.10, 95% CI 0.99, 1.22) and birthweight z-score and breastfeeding duration jointly (HRNDE=1.09, 95% CI 0.99, 1.23).

Table 3. Mediation of the association between maternal smoking in pregnancy and time to natural menopause by birthweight z-scores and breastfeeding (imputed sample)

Pooled sample (n=8,700, followed-up to age 50 years)	Natural menopause		
	HR	95% CI[1]	
Mediation by birthweight z-score			
Total	1.13	1.02	1.24
Indirect (acting through the mediators)	1.01	0.99	1.04
Direct (unexplained by these mediators)	1.12	1.02	1.24
proportion mediated (%)[2]	**5.83**		
Mediation by birthweight z-score + breastfeeding duration			
Total	1.13	1.02	1.24
Indirect	1.02	0.99	1.05
Direct	1.11	1.01	1.23
proportion mediated (%)[2]	**14.39**		
BCS70 (n=3,878, followed-up to age 46 years)	Natural menopause		
	HR	95% CI	
Mediation by birthweight z-score			
Total	1.21	0.97	1.52
Indirect	1.01	0.94	1.08
Direct	1.20	0.94	1.58
proportion mediated (%)[2]	**4.05**		
Mediation by birthweight z-score + breastfeeding duration			
Total	1.21	0.97	1.52
Indirect	1.04	0.96	1.13
Direct	1.16	0.90	1.52
proportion mediated (%)[2]	**22.05**		
NCDS (n=4,822**,** follow-up to age 50 years)	Natural menopause		
	HR	95% CI	
Mediation by birthweight z-score			
Total	1.10	0.99	1.22
Indirect	1.00	0.98	1.04
Direct	1.10	0.99	1.22
proportion mediated (%)[2]	**1.73**		
Mediation by birthweight z-score + breastfeeding duration			
Total	1.10	0.99	1.22
Indirect	1.01	0.98	1.05
Direct	1.09	0.99	1.23
proportion mediated (%)[2]	**6.42**		

Note:

[1] Bias-corrected 95% CIs, bootstrapping based on 200 replications.

[2] The proportion mediated was calculated using the formula: {HRNDE (HRNIE− 1)/(HRNDE * HRNIE− 1)}*100.

Results from complete cases are presented in Supplementary material (Table S3, Supplementary file 1).

Secondary analysis

We repeated the analysis restricting the follow-up time in the pooled sample to the follow-up period in the younger BCS70 cohort (up to age 46 years) and observed only small increases in the proportions mediated by birthweight z-score and jointly with breastfeeding. Birthweight z-score alone mediated 12.9% (HRNIE= 1.01, 95% CI 0.98, 1.05) and jointly with breastfeeding mediated 20.5% (HRNIE=1.02, 95% CI 0.99, 1.06) (Table S5, Supplementary material).

Discussion

Our results supported a hypothesised pathway whereby maternal smoking during pregnancy influences menopausal age in daughters partially through fetal growth and breastfeeding duration. We showed that prenatal exposure to cigarette smoke is related to increasing hazard of earlier menopause, and that lower birthweight z-score and lack of breastfeeding account for about 14% of the increased hazard of earlier menopause. After accounting for the effect of birthweight z-score and breastfeeding, there remained evidence of a direct effect of maternal smoking during pregnancy on the timing of daughters' menopause. This leaves room for unmeasured mediators or other interlinked mediating pathways including a direct influence of toxic chemical exposure during pregnancy. The pattern of results was similar across the cohorts though some differences in the effect sizes were noticeable, possibly due to different confounding structures.

To our knowledge the role of intermediate factors in the association between prenatal exposure to cigarette smoking and time to natural menopause in female offspring has not been quantified previously. Consistent with previous research, we illustrated that fetal growth and breastfeeding duration are both influenced by maternal smoking in pregnancy, and that breastfeeding duration is influenced by fetal growth [22, 42]. We also showed that greater birthweight z-score and breastfeeding duration are associated with lower hazards for earlier menopause [13, 15]. These relationships laid the foundation for the hypothesised mediation in this study.

There are several possible pathways through which fetal growth may influence the time to menopause. Restricted fetal growth has been associated with adverse environment in fetal life and suboptimal fetal development [43], which in turn may increase the rate of follicle atresia during fetal life and reduce the ovarian follicle reserve at birth [44]. Restricted fetal growth may also contribute to permanent changes in physiology and metabolism, which in turn may increase the risk of a number of diseases in later life (e.g. disorders of the reproductive system, coronary heart disease or related disorders) [45-46] and contribute to follicle loss after birth. Low birthweight has also been related to suboptimal breastfeeding outcomes, for which aspects of childbirth hospital care (e.g. NICU admission, feeding protocols, protocols around mother-infant separation, lengths of stay), infant (e.g. physiologic immaturity) and maternal factors (e.g. comorbidities, obstetrical complications, hormonal imbalances) [23, 25] may play a role. Breast milk activates several metabolic processes influencing microanatomy development, growth, metabolism, gut microbiological colonisation and maturation, immunological and brain systems development [47]. Disease protection, optimal growth and improved cognitive development may in turn constitute some of the possible pathways through which breastfeeding may influence the timing of the menopause (e.g. by shaping subsequent life circumstances that may influence menopausal age). For example, it has been suggested that breast milk may offer protection against several autoimmune conditions (e.g. diabetes mellitus, Crohn's disease, rheumatoid arthritis) [47]. Studies have also shown that women with these or related conditions have an earlier onset of menopause [48-50]. It has also been suggested that breastfeeding may prevent the development of overweight and obesity and may benefit child's cognitive development [51]. Weight gain during childhood is a risk factor for early age at menarche [52] and early menarche has been associated with earlier menopause [53]. Studies have also shown that women with lower cognitive ability in childhood are more likely to reach menopause earlier than women with higher cognitive ability [5, 54].

Implications

Our analysis suggests that part of the harmful effect of cigarette smoking during pregnancy on the reproductive longevity of the female offspring may partly be offset through maternal focused interventions to improve birth and breastfeeding outcomes. There has been a marked increase in the rates of breastfeeding in the UK in recent years [55], however, mothers who smoke are less likely to breastfeed [56]. According to qualitative studies, mothers who smoke base their intentions to breastfeed on how they perceive the health risks that smoking poses to their newborn. Many smoking mothers think that formula is better for their newborn than their milk, which contains nicotine and other tobacco toxins [57-58]. Public health advice provided by the NHS, CDC, La Leche League and others [59-61] already recommends that mothers breastfeed even if they cannot stop smoking; further efforts to promote the benefits of breastfeeding among smokers could be beneficial. Women who smoke are also more likely to have low milk supply which limits their ability to breastfeed [56]. Women facing these difficulties should also receive further support [23].

As breastfeeding and birth weight did not fully mediate the association between maternal smoking and daughters' reproductive longevity, there may be other pathways involved. Therefore, more research is needed on the factors that mediate this effect, especially those that are modifiable. It also may be that cigarette smoking during pregnancy has a direct impact (i.e. not via any previously hypothesised mediators) on the reproductive health of the female offspring. While the epidemiological evidence of this direct effect is inconclusive, one possible explanation is the adjustment for variables that may mediate the effect of smoking during pregnancy on the age of menopause in the female offspring in previous studies. We therefore recommend further research takes into account the temporal sequence of factors adjusted.

Strengths and limitations

Our findings need to be interpreted while bearing in mind the limitations. We define as 'smokers' women who smoked at any time during the pregnancy, and we do not have information about the time women stopped smoking or smoking during lactation. We included women who smoked at any time because clinical research has illustrated irreversible effect of prenatal cigarette smoke exposure on germ and somatic cells in female gonads as early as the first trimester [4]. Neither do we have information on 'exclusive' breastfeeding; our information on breastfeeding relates to any breastfeeding. This means that the breastfed groups in our analysis may include those who have received formula milk (or other complementary foods) alongside breast milk (i.e. received mixed feeding rather than exclusive breastfeeding). Our data also do not allow us to explore the effects of specific breastfeeding lengths longer than 1 month (e.g. breastfeeding for 6 months and beyond). Nonetheless, to better understand the impact of breastfeeding duration, we treated women who were breastfed for periods shorter and longer than one month in separate categories. Smoking during pregnancy and infant feeding behaviours were self-reported by the cohort women's mothers, and there is the potential for misclassification in our analysis which (if differential) may distort the exposure-outcome associations. However, we consider the potential for misclassification due to socially desirable response small as both smoking and formula feeding were considered 'normative' in the late 50s and early 70s [62]. Measurement error in the exposure and mediator variables can also contribute to bias in the causal mediation analysis and

underestimate the indirect effect and therefore the proportion mediated [63-64]. Other limitations include the retrospective collection of information on breastfeeding and menopause and potential for recall bias although recall was not over a long period.

Like other counterfactual-based approaches to mediation, the IOW method assumes no unmeasured confounding of the exposure-outcome effect, the mediator-outcome effect, and the exposure-mediator effect. Further, the IOW method assumes that there are no confounders of the mediator-outcome effect that are affected by the exposure (i.e. no intermediate confounding) [37-38]. Despite our best attempts to account for important determinants of maternal smoking, fetal growth, breastfeeding, and menopausal age, unmeasured confounding cannot be ruled out. We addressed the assumption for 'no intermediate confounding' by investigating the role of potential mediators operating in period of life which is close to the exposure; such an assumption becomes less plausible for mediators operating in later life (i.e. longer periods between the exposure and mediators). Another limitation of the IOW method is that the variances of estimates can be wider than those of traditional parametric mediation methods, making it more difficult to detect small indirect effects. Coefficients and effect sizes in causal mediation analysis are often small due to attrition, measurement error, and use of multiple mediators. These limitations are thought to be best handled by increasing the statistical power of the analysis, as well as optimising the temporal interval between the exposure and mediators, and using bootstrap confidence intervals [64], as in our analysis.

The strengths of our analysis are the use of prospective birth cohort studies, following people throughout life, which offer advantages for studying intergenerational transmission of disadvantage in health. NCDS and BCS70 provide a unique opportunity to study the effect of maternal smoking during pregnancy on the time to menopause in daughters, which younger cohort studies cannot yet offer. The comparable study designs, measures, and follow up periods, allow us to combine the data from the two cohorts and perform pooled analysis on imputed data with increased statistical power. By increasing the size of our analytical sample, we also address constraints in the performance of causal mediation analysis highlighted previously [64]. The rates of smoking during pregnancy in the studied cohorts are considerably higher than those in recent years in the UK (less than 10% of mothers smoked during pregnancy in 2021/22) [55]. The rates of breastfeeding were also low [65] compared to recent figures (about 72% of babies had a first feed of maternal or donor breast milk in 2022/23) [66]; though the data are not exactly comparable due to differences in breastfeeding definitions. This could be considered a further methodological advantage for this analysis as it may help in detecting an effect, though this can also be a potential issue for generalisability to contemporary cohorts. Although it has limitations, the IOW method offers the advantage to estimate causally interpretable effects in the context of multiple mediators irrespective of their measurement scale, in a time-to-event setting, and with imputed datasets; and further, in the presence of exposure-mediator interactions. Weighting treats the exposure and mediators as independent by deactivating indirect pathways of the mediators. IOW is agnostic with regards to effects of interactions and thus is valid regardless of interactions between any set of covariates, exposure, or mediators on the outcome, without the need to specify them (i.e. account for interaction between the exposure) [37-38].

Conclusion

Birthweight-for-gestational-age-z-score and breastfeeding jointly mediated about 14% of the effect of prenatal exposure to maternal cigarette smoking on the timing of menopause in the female offspring. This points to factors in early life that may have the potential to offset the deleterious effects of maternal smoking during pregnancy to the extent that they mediate the risk associated with earlier menopause. Alongside smoking cessation interventions, breastfeeding education and breastfeeding support in the early postnatal period may be beneficial for women's reproductive longevity.

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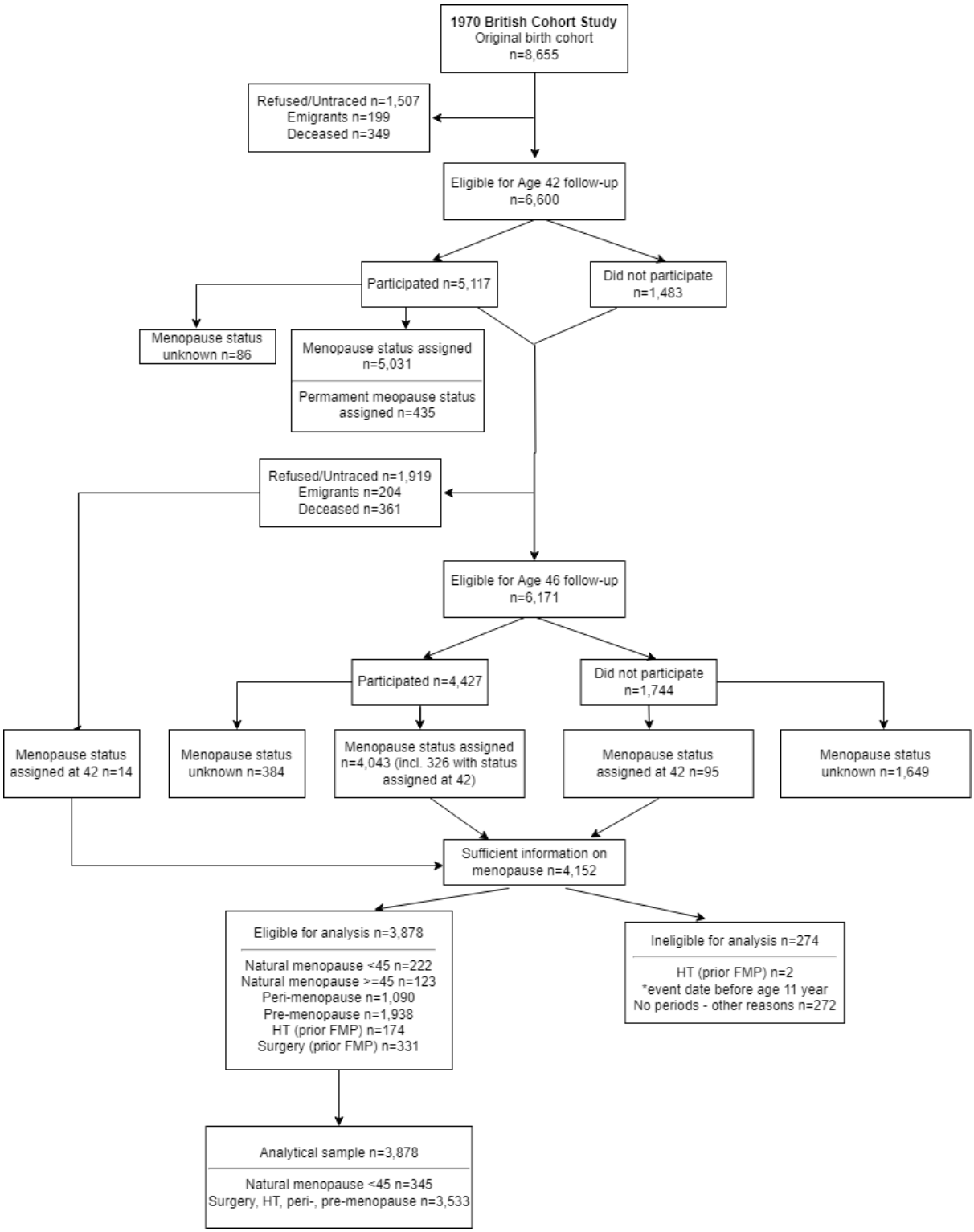
Supplementary Material

Supplementary File 1

Fig. S1 Participation and attrition in the 1970 British Cohort Study (A) and 1958 National Child Development Study (B)

A)



B)

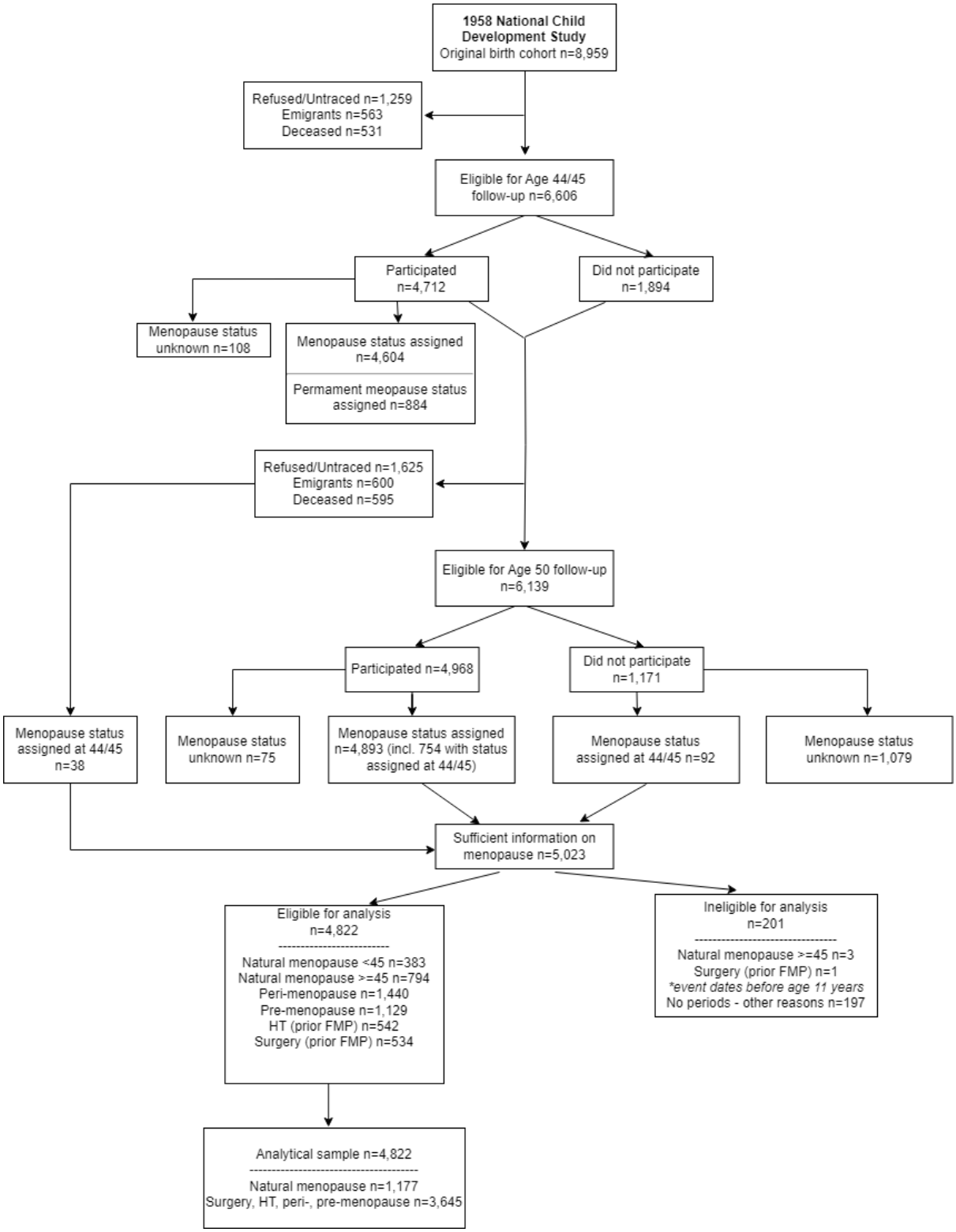

1958 National Child Development Study
Original birth cohort n=8,959
Refused/Untraced n=1,259
Emigrants n=563
Deceased n=531
Eligible for Age 44/45 follow-up n=6,606
Participated n=4,712
Did not participate n=1,894
Menopause status unknown n=108
Menopause status assigned n=4,604
Permament meopause status assigned n=884
Refused/Untraced n=1,625
Emigrants n=600
Deceased n=595
Eligible for Age 50 follow-up n=6,139
Participated n=4,968
Did not participate n=1,171
Menopause status assigned at 44/45 n=38
Menopause status unknown n=75
Menopause status assigned n=4,893 (incl. 754 with status assigned at 44/45)
Menopause status assigned at 44/45 n=92
Menopause status unknown n=1,079
Sufficient information on menopause n=5,023
Eligible for analysis n=4,822
Natural menopause <45 n=383
Natural menopause >=45 n=794
Peri-menopause n=1,440
Pre-menopause n=1,129
HT (prior FMP) n=542
Surgery (prior FMP) n=534
Ineligible for analysis n=201
Natural menopause >=45 n=3
Surgery (prior FMP) n=1
*event dates before age 11 years
No periods - other reasons n=197
Analytical sample n=4,822
Natural menopause n=1,177
Surgery, HT, peri-, pre-menopause n=3,645

Table S1. Classification of women into menopause status in the 1970 British Cohort Study (A) and 1958 National Child Development Study (B)

A)

1970 BCS cohort				
Menopause status	**Age 42**		**Age 46**	
	n	%	n	%
Menopause <40 years (premature menopause)	44	0.9	53	1.2
Menopause 40-44 years (early menopause)	86	1.7	169	3.7
Menopause 45 or more years	n.a.		123	2.7
Peri-menopause	812	15.9	1,090	24.0
Pre-menopause	3,390	66.2	1,938	42.7
Hormone therapy (before FMP)	72	1.4	176	3.9
Hysterectomy/Bilateral oophorectomy (before FMP)	182	3.6	331	7.3
No periods (other reasons)	414	8.1	241	5.3
Never had a period	31	0.6	31	0.7
Insufficient information	86	1.7	384 [1]	8.5
(Age 42 participants) Not in age 46 survey			878	
Total	5,117	100.0	4,536	100.0

Notes:
If a woman had gone through natural menopause or a surgery (hysterectomy/bilateral oophorectomy) or had initiated HT prior to the FMP, their menopausal status remained unchanged for the subsequent survey (i.e. figures at age 46 include women with permanent menopause status at age 42).

Overall number of women (and denominator) excludes cases non-participating in subsequent sweep (i.e. 878 women who took part at age 42 but not age 46).

Women whose periods stopped for other obvious reasons (e.g. pregnancy, contraceptives, chemotherapy or radiotherapy) were excluded from this analysis.

Analytical sample further excludes 2 women (on HT prior FMP) with reported event date before age 11 years.

Due to an error, women at age 46 in the 1970 cohort who at age 42 reported no periods in the past 12 months for reasons different from natural menopause, including pregnancy and contraceptive use, were not asked whether they had periods in the past 12 months, resulting in insufficient information to determine their menopause status at age 46 survey.

B)

1958 NCDS cohort				
Menopause status	**Age 44/45**		**Age 50**	
	n	%	n	%
Menopause <40 years (premature menopause)	131	2.8	176	3.5
Menopause 40-44 years (early menopause)	106	2.2	207	4.1
Menopause 45 or more years	23	0.5	797	15.6
Peri-menopause	841	17.8	1,440	28.2
Pre-menopause	2,833	60.1	1,129	22.1
Hormone therapy (before FMP)	268	5.7	542	10.6
Hysterectomy/Bilateral oophorectomy (before FMP)	294	6.2	535	10.5
No periods (other reasons)	108	2.3	197	3.9
Never had a period	-		-	
Insufficient information	108	2.3	75	1.5
(Age 44 participants) Not in age 50 survey			411	
Total	4,712	100.0	5,098	100.0

Notes:
If a woman had gone through natural menopause or a surgery (hysterectomy/bilateral oophorectomy) or had initiated HT prior to the FMP, their menopausal status remained unchanged for the subsequent survey (i.e. figures at age 50 include women with permanent menopause status at age 44/45).

Overall number of women (and denominator) excludes cases non-participating in subsequent sweep (i.e. 411 women who took part at age 44/45 but not age 50).

Women whose periods stopped for other obvious reasons (e.g. pregnancy, contraceptives, chemotherapy or radiotherapy) were excluded from this analysis.

Analytical sample further excludes 4 women with reported event date before age 11 years (3 with natural menopause >=45 years and 1 with surgical menopause).

Due to an error, women in the 1958 cohort who reported natural menopause in the age 44/45 survey were not asked about their age at their FMP; they were asked about this subsequently at the age 50 follow-up.

Table S1a. Missing data in the dates of menopause, surgery, or HT initiation in the 1970 British Cohort Study (A) and 1958 National Child Development Study (B)

A)

1970 BCS cohort						
Menopause status Missing data	**Age 42**			**Age 46**		
	n	n missing	% missing	n	n missing	% missing
Menopause	110			345		
Missing month of FMP		32	29.1		40	11.6
Missing month and year of FMP		55	50.0		71	20.1
Hormone therapy (before FMP)	72			176		
Missing month of HT initiation		20	27.8		24	13.6
Missing month and year of HT initiation		14	19.4		16	9.1
Hysterectomy/Bilateral oophorectomy (before FMP)	182			331		
Missing month of surgery		13	7.1		14	4.2
Missing month and year of surgery		7	3.8		9	2.7

Notes: N at age 46 includes n at age 42 (i.e. n at 46 is cumulative).

B)

1958 NCDS cohort						
Menopause status Missing data	**Age 44/45**			**Age 50**		
	n	n missing	% missing	n	n missing	% missing
Menopause	260			1,180		
Missing month of FMP		6	2.3		60	5.1
Missing month and year of FMP		38	14.6		52	4.4
Hormone therapy (before FMP)	268			542		
Missing month of HT initiation		106	39.6		119	22.0
Missing month and year of HT initiation		10	3.7		16	3.0
Hysterectomy/Bilateral oophorectomy (before FMP)	294			535		
Missing month of surgery		66	22.4		75	14.0
Missing month and year of surgery		23	7.8		28	5.2

Notes: N at age 50 includes n at age 44/45 (i.e. n at 50 is cumulative).

Table S2. Associations between maternal smoking during pregnancy, birthweight z-scores, breastfeeding duration, and time to natural menopause in daughters (complete case sample)

Pooled (n=6,354, followed-up to age 50 years)	**Birthweight z-score**	**Breastfed <1 month** reference: (never)	**Breastfed 1+months** reference: (never)	**Daughter's experience of natural menopause** reference: no (incl. pre-, peri-, surgical menopause, HT)
	β (95% CI)	**RRR (95% CI)**	**RRR (95% CI)**	**HR (95% CI)**
Maternal smoking in pregnancy (reference: no smoking)	-0.28 (-0.33, -0.22) [1]	0.92 (0.80, 1.05)	0.66 (0.59, 0.75) [1]	1.19 (1.06, 1.35) [1]
Birthweight z-score		1.06 (0.99, 1.12)	1.05 (1.00, 1.11) [2]	0.95 (0.90, 1.00) [2]
Breastfed <1 month (reference: never)				0.97 (0.83, 1.14) [3]
Breastfed 1month + (reference: never)				0.82 (0.71, 0.94) [3]
BCS70 (n=2,826, followed-up to age 46 years)	**Birthweight z-score**	**Breastfed <1 month** reference: (never)	**Breastfed 1+months** reference: (never)	**Daughter's experience of natural menopause** reference: no (incl. pre-, peri-, surgical menopause, HT)
	β (95% CI)	RRR (95% CI)	RRR (95% CI)	HR (95% CI)
Maternal smoking in pregnancy (reference: no smoking)	-0.29 (-0.38, -0.21) [1]	0.85 (0.68, 1.05)	0.64 (0.52, 0.77) [1]	1.34 (1.04, 1.73) [1]
Birthweight z-score		1.03 (0.93, 1.14)	1.06 (0.97, 1.16) [2]	1.00 (0.89, 1.12) [2]
Breastfed <1 month (reference: never)				0.90 (0.64, 1.27) [3]
Breastfed 1month + (reference: never)				0.41 (0.27, 0.62) [3]
NCDS (n=3,528, followed-up to age 50 years)	**Birthweight z-score**	**Breastfed <1 month** reference: (never)	**Breastfed 1+months** reference: (never)	**Daughter's experience of natural menopause** reference: no (incl. pre-, peri-, surgical menopause, HT)
	β (95% CI)	RRR (95% CI)	RRR (95% CI)	HR (95% CI)
Maternal smoking in pregnancy (reference: no smoking)	-0.26 (-0.33, -0.19) [1]	1.01 (0.84, 1.21)	0.71 (0.61, 0.84) [1]	1.15 (1.01, 1.32) [1]
Birthweight z-score		1.07 (0.99, 1.17)	1.05 (0.98, 1.13) [2]	0.94 (0.88, 1.00) [2]
Breastfed <1 month (reference: never)				1.04 (0.87, 1.24) [3]
Breastfed 1month + (reference: never)				0.93 (0.79, 1.09) [3]

Note:

Model adjusted for:
[1] maternal education, social class and maternal age at birth, previous live births (and cohort in pooled sample)
[2] maternal education, social class and maternal age at birth, previous live births, maternal smoking in pregnancy (and cohort in pooled sample)
[3] maternal education, social class and maternal age at birth, previous live births, maternal smoking in pregnancy, birthweight z-score (and cohort in pooled sample).

Table S3. Mediation of the association between maternal smoking in pregnancy and time to natural menopause by birthweight z-scores and breastfeeding (complete case sample)

Pooled sample (n=6,354, followed-up to age 50 years)	Natural menopause		
	HR	95% CI[1]	
Mediation by birthweight z-score			
Total	1.19	1.06	1.34
Indirect (acting through the mediators)	1.01	0.98	1.05
Direct (unexplained by these mediators)	1.18	1.03	1.33
proportion mediated (%)[2]	**8.42**		
Mediation by birthweight z-score + breastfeeding duration			
Total	1.19	1.06	1.34
Indirect	1.03	0.99	1.07
Direct	1.16	1.02	1.31
proportion mediated (%)[2]	**17.37**		
BCS70 (n=2,826 followed-up to age 46 years)	Natural menopause		
	HR	95% CI	
Mediation by birthweight z-score			
Total	1.34	1.03	1.74
Indirect	1.03	0.95	1.12
Direct	1.29	0.99	1.70
proportion mediated (%)[2]	**13.33**		
Mediation by birthweight z-score + breastfeeding duration			
Total	1.34	1.03	1.74
Indirect	1.08	0.99	1.18
Direct	1.24	0.94	1.63
proportion mediated (%)[2]	**30.20**		
NCDS (n=3,528**,** follow-up to age 50 years)	Natural menopause		
	HR	95% CI	
Mediation by birthweight z-score			
Total	1.15	1.00	1.32
Indirect	1.00	0.96	1.04
Direct	1.15	1.00	1.33
proportion mediated (%)[2]	**2.09**		
Mediation by birthweight z-score + breastfeeding duration			
Total	1.15	1.00	1.32
Indirect	1.01	0.97	1.06
Direct	1.14	0.99	1.32
proportion mediated (%)[2]	**7.27**		

Note:

[1] Bias-corrected 95% CIs, bootstrapping based on 10,000 replications.

[2] The proportion mediated was calculated using the formula: {HRNDE (HRNIE− 1)/(HRNDE * HRNIE− 1)}*100.

Table S4. Crude associations between maternal smoking during pregnancy, birthweight z-scores, breastfeeding duration, time to natural menopause in daughters, and potential confounders (imputed samples)

BCS70 (n=3,878, followed-up to age 46 years)	**Maternal smoking in pregnancy** (reference: no smoking)	**Birthweight z-score**	**Breastfed <1 month** reference: (never)	**Breastfed 1+months** reference: (never)	**Daughter's experience of natural menopause** reference: no (incl. pre-, peri-, surgical menopause, HT)
	OR (95% CI)	β (95% CI)	RRR (95% CI)	RRR (95% CI)	HR (95% CI)
Mother in school after minimum school leaving age of 15 years (yes, no)	0.47 (0.41, 0.55)	0.10 (0.02, 0.18)	1.50 (1.21, 1.85)	3.15 (2.62, 3.79)	0.67 (0.52, 0.85)
Father's social class at birth - manual (reference: non-manual)	1.79 (1.54, 2.08)	-0.16 (-0.24, -0.08)	0.70 (0.56, 0.87)	0.41 (0.34, 0.49)	1.47 (1.13, 1.90)
Father's social class at birth - no father figure (reference: non-manual)	2.59 (1.97, 3.42)	-0.28 (-0.45, -0.12)	1.11 (0.73, 1.70)	0.41 (0.28, 0.61)	1.55 (0.99, 2.42)
Maternal age at birth (in years)	0.97 (0.96, 0.98)	0.02 (0.01, 0.03)	0.99 (0.97, 1.00)	1.02 (1.01, 1.04)	0.98 (0.96, 1.00)
(Number of) previous live births	1.05 (1.00, 1.11)	0.09 (0.06, 0.12)	0.81 (0.74, 0.89)	0.90 (0.84, 0.97)	1.04 (0.96, 1.13)
NCDS (n=4,822, followed-up to age 50 years)	**Maternal smoking in pregnancy** (reference: no smoking)	**Birthweight z-score**	**Breastfed <1 month** reference: (never)	**Breastfed 1+months** reference: (never)	**Daughter's experience of natural menopause** reference: no (incl. pre-, peri-, surgical menopause, HT)
	OR (95% CI)	β (95% CI)	RRR (95% CI)	RRR (95% CI)	HR (95% CI)
Mother in school after minimum school leaving age of 15 years (yes, no)	0.59 (0.51, 0.67)	0.08 (0.00, 0.16)	1.16 (0.94, 1.42)	2.01 (1.70, 2.37)	0.71 (0.62, 0.82)
Father's social class at birth - manual (reference: non-manual)	1.60 (1.39, 1.83)	-0.15 (-0.23, -0.08)	1.12 (0.92, 1.37)	0.65 (0.55, 0.76)	1.46 (1.27, 1.68)
Father's social class at birth - no father figure (reference: non-manual)	2.19 (1.65, 2.89)	-0.30 (-0.48, -0.12)	0.91 (0.62, 1.35)	0.38 (0.27, 0.54)	1.63 (1.24, 2.13)
Maternal age at birth (in years)	1.02 (1.01, 1.03)	0.02 (0.02, 0.03)	0.95 (0.94, 0.96)	0.97 (0.96, 0.98)	1.00 (0.99, 1.01)
(Number of) previous live births	1.09 (1.05, 1.13)	0.10 (0.07, 0.12)	0.86 (0.82, 0.91)	0.86 (0.81, 0.90)	1.09 (1.06, 1.13)

Table S5. Mediation of the association between maternal smoking in pregnancy and time to natural menopause by birthweight z-scores and breastfeeding (imputed sample)

Pooled sample (n=8,700, followed-up to age 48 years)	**Natural menopause**		
	HR	95% CI[1]	
Mediation by birthweight z-score			
Total	1.10	0.99	1.22
Indirect (acting through the mediators)	1.01	0.98	1.05
Direct (unexplained by these mediators)	1.09	0.98	1.22
proportion mediated (%)[2]	**12.87**		
Mediation by birthweight z-score + breastfeeding duration			
Total	1.10	0.99	1.22
Indirect	1.02	0.99	1.06
Direct	1.08	0.96	1.21
proportion mediated (%)[2]	**20.51**		

Note:

[1] Bias-corrected 95% CIs, bootstrapping based on 200 replications.

[2] The proportion mediated was calculated using the formula: {HRNDE (HRNIE− 1)/(HRNDE * HRNIE− 1)}*100.