
Paediatric and Perinatal Epidemiology

50 doi: 10.1111/ppe.12164

Can 'Early Programming' Be Partly Explained by Smoking? Results from a Prospective, Population-Based Cohort Study

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Abstract

Background: Numerous studies have focused the association between low birthweight and later disease. Our objective was to study the association between birthweight and later adult smoking and thereby explore a possible mechanism for the association between low birthweight and later adult disease.

Methods: We studied associations between birthweight of women ($n = 247\,704$) born in 1967–1995 and smoking habits at the end of their pregnancy 13–42 years later in a prospective, population-based cohort study from The Medical Birth Registry of Norway. Similarly, the association between birthweight of men ($n = 194\,393$) and smoking habits of their partners were assessed. Finally, we studied the relation between smoking habits of the participating women and the cause specific death of their mothers ($n = 222\,808$).

Results: Twenty per cent of women with birthweight less than 2000 g were adult daily smokers compared with 11% with birthweight 4000–4499 g [relative risk = 1.8, 95% confidence interval 1.4, 2.2]. Similarly, we found an association between men's birthweight and their partners smoking habits. Mothers of smoking women had doubled risk of dying from lung cancer and from cardiovascular disease compared with mothers of non-smoking women.

Conclusions: Being born with low birthweight is associated with smoking in adulthood. Associations of adult smoking with partners' birthweight and mothers' smoking-related causes of death suggest a shared smoking environment, and may account for some of the established association between birthweight and later cardiovascular disease.

Keywords: *birthweight, fetal origin of adult disease hypothesis, maternal smoking, mortality, pregnancy, tobacco smoking.*

It has been proposed that undernutrition during pregnancy can lead to cardiovascular disease in adult life through early programming.[1] Numerous studies have focused the association between factors in early life, like low birthweight, and later disease.[2–5] The findings of associations between early life environment and later health and disease have evolved into the Developmental Origins of Health and Disease approach.[6]

The relation between low birthweight and adult cardiovascular disease may also be explained by common genetic and/or environmental factors related both to low birthweight and adult cardiovascular disease. Several environmental factors, including smoking, may act in addition to or instead of early programming. Smoking is well known to increase the risk of both low birthweight[7] and cardiovascular disease[8–10] and is, at least in recent decades, closely related to socioeconomic level.[7,10] Although studies claim that the association between low birthweight and adult cardiovascular disease persists even after adjusting for socioeconomic variables, residual confounding cannot be excluded.[2–5,11–13]

The aim of this study was to examine whether women born with low birthweight more often smoke as adults compared with women born with higher birthweights. To examine whether men born with low birthweight more often live in a smoking environment as adults, we also studied their partners' smoking habits in their pregnancies. Since partners often share smoking habits,[14] this would be an indication that also men born with low birthweight are likely to smoke as adults. Finally, we explored the possibility of smoking as a shared environmental exposure across generations, through the relation between

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women's smoking habits and their mothers' cause specific mortality.

We studied birth characteristics of women and men born from 1967 to 1995 who later were registered in The Medical Birth Registry of Norway (MBRN) as mothers and fathers in 1999–2009, when we had information on maternal smoking habits during pregnancy.

Methods

We used data from the MBRN, a population based-registry that has received compulsory notification of all births from at least 16 gestational weeks since 1967.[15] The notification form contains information on demographic variables, the mothers' health before and during pregnancy, complications during pregnancy and delivery, and pregnancy outcomes, as well as mothers', fathers' and infants' national identification numbers. These numbers allow linkage of mother–father–child units in generational data files. Women's smoking habits at the beginning and end of pregnancy have been registered since 1999. We chose to focus on smoking at the end of pregnancy since these women are more likely to stay lifelong smokers.[16] Smoking was dichotomised as non-smoking and daily smoking.

We included 293 237 singleton women born 1967–1995 and linked them to their first registered birth from 1999 to 2009. Women who were registered in the MBRN with more than one infant in this period were thus only counted once. We excluded 29 168 (9.9%) women with missing smoking habits and 3837 (1.3%) occasional smokers as well as women with missing birthweight ($n = 306$), birthweight less than 500 g or more than 6000 g ($n = 6$) and 11 918 (4.1%) women with missing gestational age. Gestational age was based on the first day of the last menstrual period and ranged from 13 to 48 weeks. To avoid mixing reduced birthweight due to growth restriction with that due to preterm delivery, we focused on women born at term (≥37 weeks) when studying absolute birthweight. Smoking has been shown to affect fetal growth in weight primarily in the third trimester of pregnancy.[17]

Z-scores for birthweight by gestational age were computed by applying Norwegian standards for birthweight by sex and gestational age.[18] We excluded absolute z-score values of 5 or more ($n = 298$) as misclassified gestational age. For z-score analyses, the remaining values were categorised into nine groups: from –4.9 to 4.99 as shown in Tables 1 and 2, with 0.50–1.49 as the reference group. A total of 247 704 singleton born women and 238 488 singleton term born women were thus the final study populations for birthweight z-score analyses and absolute birthweight analyses, respectively.

Table 1. Relative risks for women's daily smoking status at the end of pregnancy by their own birthweight by gestational age z-score among 247 704 singleton born women (both term and preterm), delivered in 1967–1995 and followed to their own pregnancy between 1999 and 2009 in Norway

Women's birthweight z-score	Total	Daily smoking by the end of pregnancy		Unadjusted model		Adjusted model[a]	
	No.	No.	%	RR	[95% CI]	RR	[95% CI]
–4.9, –3.51	214	50	23.4	2.02	[1.58, 2.57]	1.81	[1.42, 2.31]
–3.5, –2.51	2013	398	19.8	1.71	[1.56, 1.87]	1.61	[1.47, 1.76]
–2.5, –1.51	17 001	2970	17.5	1.51	[1.45, 1.57]	1.43	[1.37, 1.49]
–1.5, –0.51	69 785	10 102	14.5	1.25	[1.21, 1.29]	1.23	[1.19, 1.27]
–0.5, 0.49	94 669	12 046	12.7	1.10	[1.07, 1.13]	1.10	[1.07, 1.14]
0.5, 1.49	49 234	5702	11.6	1.00	Reference	1.00	Reference
1.5, 2.49	12 247	1 396	11.4	0.98	[0.93, 1.04]	0.96	[0.91, 1.02]
2.5, 3.49	2082	253	12.2	1.05	[0.93, 1.18]	0.99	[0.88, 1.11]
3.5, 4.99	459	64	13.9	1.20	[0.96, 1.51]	1.09	[0.86, 1.37]
Total	247 704	32 981	13.3				

[a]Adjusted for the women's mothers' education (low: <11 years, medium 11–14 years, high (reference): >14 years) and women's birth order (first born (reference), second born, third born, fourth or later born) and women's year of birth (1967–1976 (reference), 1977–1986, 1987–1995).

CI, confidence interval; RR, relative risk.

Table 2. Relative risks for men having a smoking partner at the end of her pregnancy by the men's birthweight z-score among 194 393 singleton men delivered in 1967–1994 and followed to their partners' pregnancy between 1999 and 2009 in Norway

Men's birthweight z-score	Total	Partners daily smoking by the end of pregnancy		Unadjusted model	
	No.	No.	%	RR	[95% CI]
–4.9, –3.51	126	21	16.7	1.38	[0.94, 2.05]
–3.5, –2.51	966	158	16.4	1.36	[1.18, 1.57]
–2.5, –1.51	7428	1179	15.9	1.32	[1.25, 1.40]
–1.5, –0.51	38 117	5427	14.2	1.18	[1.14, 1.22]
–0.5, 0.49	73 434	9543	13.0	1.08	[1.05, 1.11]
0.5, 1.49	52 820	6359	12.0	1.00	Reference
1.5, 2.49	17 441	2063	11.8	0.98	[0.94, 1.03]
2.5, 3.49	3417	416	12.2	1.01	[0.92, 1.11]
3.5, 4.99	644	89	13.8	1.15	[0.95, 1.39]
Total	194 393	25 255	13.0		

CI, confidence interval; RR, relative risk.

The women's and their mothers' highest achieved educational level was obtained from Statistics Norway in 2009. Education was divided in three levels, low (<11 years), medium (11–14 years) and high (college or university level: >14 years). There was missing information on education for 348 (0.14%) of the women and 907 (0.37%) of their mothers.

Our data also contained information on men born 1967–1994. We linked a total of 228 163 singleton born men to their first registered infant delivered in 1999–2009 to study the relation between the men's birthweights and their partners' smoking habits at the end of their pregnancies. We excluded 21 623 (9.5%) men whose partners had missing smoking habits and 2889 (1.4%) whose partners were occasional smokers. We further excluded men with missing birthweight ($n = 259$), birthweight more than 6000 g ($n = 4$) (none had birthweight less than 500 g) and missing gestational age ($n = 8736$; 3.8%), as well as 259 men whose birthweight by gestational age z-scores were 5 or more (absolute values). The final study populations were 194 393 singleton born men for birthweight z-score analyses, and 186 039 singleton, term born men for absolute birthweight analyses.

Our primary objective was to investigate the association between birthweight and later adult smoking. To examine if women's smoking was related to the smoking habits of their mothers, we looked at the association between women's smoking habits in pregnancy and smoking-related deaths in their mothers. We had information on cause-specific death of mothers to 222 808 women whose smoking habits at the end of pregnancy were registered. A secondary objective was therefore to study the cause-specific mortality among these mothers in relation to the smoking habits of their daughters, for deaths occurring at least 1 year after delivery. Data on cause of death were retrieved from the national Cause of Death Registry from 1969 until December 2009. Detailed description of this linkage has recently been published.[19] The study was approved by the regional ethics committee, REK VEST (2009/1868) and by the internal review board of the MBRN.

Statistical analyses

Analyses were carried out using STATA, version 12.1 (StataCorp, College Station, TX, USA) and IBM SPSS Statistics for Windows version 20 (IBM Corp., Armonk, NY, USA). Relative risks (RR) with 95% confidence intervals (CI) and *P*-values where calculated by using generalised linear models for the binominal family in STATA. Our data material consists of generations, and this warrants a restrictive attitude regarding adjustment for conventional confounding variables. We chose to adjust for the women's mothers' education as well as the women's year of birth and birth order, as these variables could be potential common causes for both the women's birthweight as well as the women's own smoking habits. Mothers who themselves where first born have been shown to smoke less than mothers who were later born.[20]

We used Cox proportional hazards model in STATA to study the hazard ratios for women's mothers' death in strata of the women's smoking habits at the end of pregnancy. The proportionality assumption was verified by a log-log survival plot. We used the mothers' age as the underlying time variable with mothers entering follow-up at their daughters' year of birth. Outcomes were death from any causes, cardiovascular death (International Classification of Diseases (ICD) version 8 and 9: 410–414, 430–438; ICD-10: I20-I25, G45, I60-I65, I67, I69), death from lung cancer (ICD-8 and ICD-9: 162; ICD-10: C33-34) and death from all others causes combined. We adjusted for the mothers' education as a possible confounder.

Results

Among our study population of 247 704 singleton born women, 32 981 (13%) smoked daily at the end of their pregnancy. A comparison of the population of non-smoking and daily smoking women is provided in Table 3. Daily smoking women were more likely to be young, multiparous, less educated and more likely to be of higher birth order. The daily smoking prevalence decreased during the study period from 17% in 1999–2003 to 9.5% in 2004–2009. Women whose mothers were less educated were more often smokers.

Figure 1a shows smoking habits at the end of pregnancy by birthweight of singleton, term born women. Women born with birthweight less than 2000 g had a 75% higher risk of smoking daily at the end of their pregnancies than women whose birthweight was 4000–4499 g [RR = 1.8, 95% CI 1.4, 2.2]. There was a statistically significant trend between women's decreasing birthweight and increasing prevalence of adult smoking ($P < 0.001$).

Similarly, Figure 1b shows the relation between birthweight of singleton, term born men and smoking habits of their partners at the end of their pregnancies.

Table 3. Daily smoking at the end of pregnancy (13%) by various characteristics for 247 704 women born[a] in 1967–1995 and followed to their own year of delivery between 1999 and 2009 in Norway

	Non-smoking women		Daily smoking women		Total
Characteristic	No.	%	No.	%	No.
Total	214 723	87	32 981	13	247 704
Women's year of birth					
1967–1976	136 408	87	20 223	13	156 631
1977–1986	73 320	87	11 341	13	84 661
1987–1995	4995	78	1417	22	6412
Women's year of delivery					
1999–2003	109 125	83	21 845	17	130 970
2004–2009	105 598	90	11 136	9.5	116 734
Women's birth order					
First born	89 602	88	12 601	12	102 203
Second born	72 571	87	10 992	13	83 563
Third or later born	52 091	85	9300	15	61 391
Parity					
0	145 332	89	17 849	11	163 181
1	48 375	84	9446	16	57 821
2+	21 016	79	5686	21	26 702
Women's education					
Low (<11 years)	25 119	65	13 372	35	38 491
Middle (11–14 years)	76 494	84	14 745	16	91 239
High (>14 years)	112 903	96	4723	4.0	117 626
Women's mothers' education					
Low (<11 years)	57 962	80	14 875	20	72 837
Middle (11–14 years)	112 694	88	15 119	12	127 813
High (>14 years)	43 357	94	2790	6.1	46 147

[a]The women's birth order and education and the women's mothers' education were missing for 547, 348 and 907 individuals, respectively.

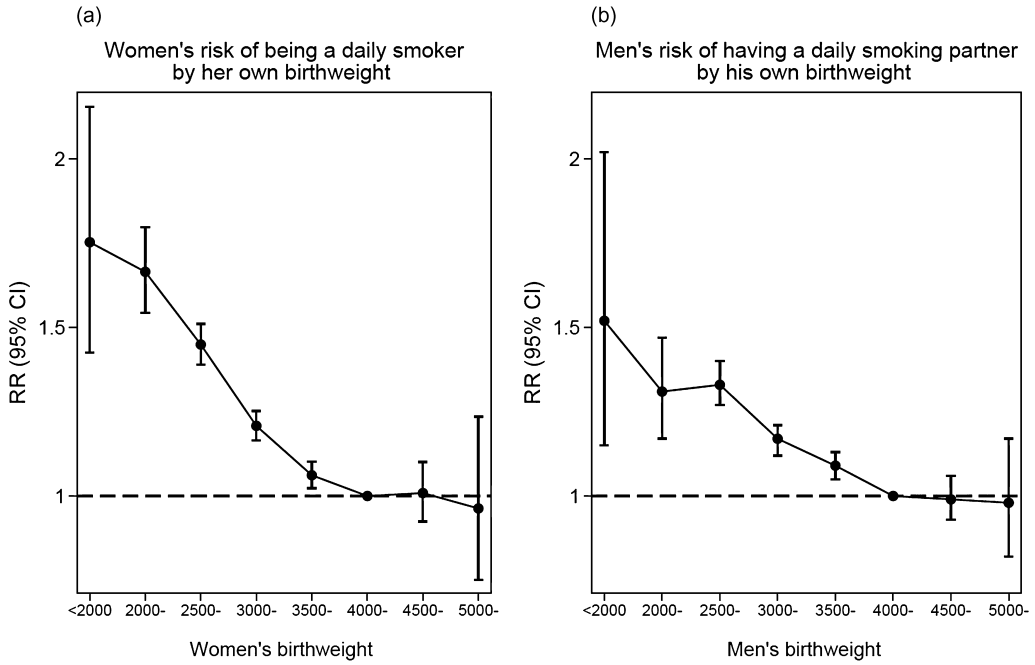

Figure 1. Relative risk (RR) of smoking status at the end of pregnancy by women's own birthweight among 238 488 term, singleton women (a) and among partners to 186 039 term, singleton men by the men's birthweight (b). Shown for women and men delivered in 1967–1995 and followed to the delivery of their own children from 1999 until 2009.

Men born at term with birthweight less than 2000 g had a 1.5 RR [95% CI 1.2, 2.0] of having a partner who smoked daily at the end of her pregnancy, compared with men whose birthweight was 4000–4499 g. There was a statistically significant trend between men's decreasing birthweight and increasing prevalence of adult smoking among partners ($P < 0.001$).

Daily smoking among pregnant women has decreased during the last decades.[21] We therefore repeated the analyses in two consecutive periods. During the first 5-year period (1999–2003), the RR of daily smoking was 1.6 [95% CI 1.2, 2.0] for women born at term with birthweight <2000 vs. 4000–4499 g, while in the last 6-year period (2004–2009), the corresponding RR was 2.0 [95% CI 1.4, 2.9].

Including preterm women, Table 1 shows the percentage of daily smoking at the end of pregnancy by women's own birthweight by gestational age z-scores. Among women in the lowest z-score category (–4.9 to –3.51), 23% were daily smokers as adults, compared with 12% of women in the reference category [z = 0.5 –1.49; RR = 2.0, 95% CI 1.6, 2.6]. Adjusting for the education of the women's mothers as well as the women's birth order and the women's year of birth slightly attenuated the results but did not change the pattern. Including women who reported daily smoking at the beginning of the pregnancy gave similar but weaker RR estimates.

The education level of the women's mothers did not seem to modify the results: In the highest level of mothers' education, women with birthweight z-scores –2 or less had a 1.41 RR [95% CI 0.96, 2.05] of being daily smokers as adults compared with women with z-score 0 or higher. In the lowest level of mothers' education, the corresponding RR was 1.5 [95% CI 1.3, 1.6]. However, the education level for the women and their mothers was associated with the women's smoking habits at the end of pregnancy. Even when women themselves had high education, their mothers' education level was associated with her smoking habits: Among women with high education, the proportions who smoked daily at the end of pregnancy was 2.8% and 6.1% when their mothers had high and low education, respectively, while the corresponding proportions among women with low education were 25% and 38%.

The relation between men's birthweight z-scores and smoking habits of their partners at the end of pregnancy is presented in Table 2. Among men in the lowest z-score category, 17% had a daily smoking partner, compared with 12% of men in the reference z-score category [RR = 1.4, 95% CI 0.9, 2.1].

Table 4. Hazard ratios for death of mothers by comparing mothers who had smoking daughters to mothers with non-smoking daughters (reference) among 222 808 mothers followed from 1967–2009

	Women's smoking habits by the end of pregnancy									
	Non-smoking women			Daily smoking women						
	Maternal deaths		Total	Maternal deaths		Total	Unadjusted model		Adjusted model[a]	
Mothers' cause of death	No.	%	No.	No.	%	No.	HR	[95% CI]	HR	[95% CI]
Death from any causes	11 073	5.8	191 836	2617	8.5	30 972	1.7	[1.6, 1.7]	1.5	[1.4, 1.6]
Cardiovascular death	1453	0.76	191 836	423	1.4	30 972	2.1	[1.9, 2.3]	1.8	[1.6, 2.0]
Death from lung cancer	990	0.52	191 836	321	1.0	30 972	2.3	[2.1, 2.7]	2.0	[1.7, 2.2]
Death from all other causes combined	8647	4.5	191 836	1881	6.1	30 972	1.5	[1.5, 1.6]	1.4	[1.3, 1.5]

[a]Adjusted for the women's mothers' education (low <11 years, medium 11–14 years, high (reference) >14 years).
CI, confidence interval; HR, hazard ratio.

We observed a statistically significant trend between birthweight z-scores and adult smoking habits for women and between birthweight z-scores and partners' adult smoking habits for men ($P < 0.001$). The correlation between women's and men's birthweight was low and could not explain this similarity [Pearson correlation coefficient 0.023, 95% CI 0.018, 0.027]. Among singleton men born at term with low birthweight the RR of having a partner who also was born singleton, at term with low rather than high birthweight was 1.2 [95% CI 0.9, 1.7]. When excluding partners with birthweight less than 2500 g, the relation between men's birthweight and partners' smoking habits remained similar.

Finally, we looked at cause-specific death among 222 808 of the women's mothers in strata of the women's smoking habits at the end of their pregnancies (Table 4). For lung cancer, cardiovascular, total death and death from all other causes combined, the respective hazard ratios of cause specific death were 2.3 [95% CI 2.1, 2.7], 2.1 [95% CI 1.9, 2.3], 1.7 [95% CI 1.6, 1.7] and 1.5 [95% CI 1.5, 1.6] if the women were daily smokers rather than non-smokers at the end of pregnancies. Adjusting for the mothers' education slightly weakened the results. When dividing the period into 1999–2003 and 2004–2009, the hazard ratio estimates for all four cause-of-death categories increased from the first to the second period but CIs were overlapping.

Comment

In this cohort study, we have shown that women who were born at term with a low birthweight are more often smokers at the end of their pregnancies than women with higher birthweights. The same was true for growth restricted women at all gestational ages. Similar associations were found between men's birthweight and their partners' smoking habits in their pregnancies. Further, mothers whose daughters smoked throughout pregnancy had approximately twice the risk of dying from both lung cancer and cardiovascular disease compared with mothers whose daughters did not smoke as adults.

Strengths and weaknesses of the study

An important strength of the present study is the large size of the cohort, enabling detailed birthweight by gestational age stratification, which showed a dose–response relation between birthweight by gestation and later daily smoking. Also, due to the prospective design, there was no retrospective recall bias of birthweight, gestational age or smoking habits. The population-based compulsory notification of births made selection bias minimal. In Tables 1 and 2, we use the complete material (term and preterm born women and men), while in Figure 1, we use only data for term born women and men. Gestational age itself was, however, hardly related to later smoking (results not shown). Preterm birth is associated with maternal smoking, but not as strongly as low birthweight is. Smoking-related risks for preterm birth have been shown to be in the range 1.2–1.6 while risks for small-for-gestational-age has been shown to be 1.5–2.9.[22]

Our population had a relatively high proportion of missing smoking habits (9.9%). However, missing smoking habits was only weakly associated with low birthweight [RR = 1.1, 95% CI 1.03, 1.2].

Among women where smoking information was missing, mean birthweight of their singleton infants was reported to be 114 g lower than among non-smoking women, compared with 229 g lower among daily smoking women, which indicates that approximately half of the women with missing smoking habits were smokers.[21] In a sensitivity analysis, we assigned all women with missing information on smoking habits to be daily smokers. This reclassification did not change the dose–response pattern although it attenuated the results. We excluded occasional smokers from analyses as a previous study found that 66% of women reporting occasional smoking had cotinine values suggesting daily smoking.[23]

Maternal smoking during pregnancy has only been registered in the MBRN since 1999. Therefore, we could not study the smoking habits of the women's mothers directly. However, previous studies have shown that maternal smoking is linked through generations.[24–26] A recent Norwegian study found an inverse association between offspring birthweight and grandparental cardiovascular mortality, but this was considerably weakened after adjusting for maternal smoking during pregnancy.[27] They also showed an inverse association between birthweight and lung cancer and chronic obstructive pulmonary disease. Recently, Smith *et al*.[28] concluded that so far there is no study that includes medical records of birthweight and gestational age, that appropriately takes life style habits and socioeconomic status into account and that includes disease incidence or cause of death as end points. We have focused a factor that has not been available when studying the relation between low birthweight and adult cardiovascular disease: smoking habits passed on through generations. By using smoking-related mortality among mothers as a proxy for their smoking habits, we suggest that maternal smoking is a common cause of offspring low birthweight as well as offspring's smoking habits in adulthood. The latter will be an important risk factor for cardiovascular disease, and accordingly, transgenerational smoking habits could explain parts of the association between low birthweight and later cardiovascular disease. Thus, studies describing this relation need to be able to adjust appropriately for smoking habits.

Comparisons to other studies

It has been argued that the early programming hypothesis is too general and has inconsistent support.[29] Also, it has been suggested that socioeconomic factors and smoking are possible mediators that may explain the association.[30,31] Low birthweight is related to socioeconomic level both at birth[32] and later in life[33] and adjusting for adult deprivation have been shown to weaken the relation between infant and adult mortality rates.[34] Low childhood socioeconomic position has been shown to predict later smoking, an association partly explained by educational level.[35] However, several 'early origin studies' state that adjustment for smoking has been done.[2–5,12,13,36] Besides the Nurses' Health Study,[3] these studies have below 1500 participants. In the Nurses' Health Study with 70 297 participants, the authors adjust for smoking as a confounding factor both for the nurse and the nurse's mother without a considerable change in the inverse association between the extremes of self-reported birthweight and cardiovascular disease.[3] However, adjusting for an intermediate variable using traditional statistical models is questionable and biased associations cannot be excluded.[37,38]

In our study, we found that birthweight was related to adult smoking habits both directly and indirectly through partners' smoking habits in pregnancy. A previous study from the MBRN showed low correlation between mothers' and fathers' birthweight.[39] Given this low correlation and the persistent association after excluding partners whose own birthweight was very low, this may reflect spousal selection on smoking status.[14] Since smoking in pregnancy is associated with intrauterine growth restriction, these findings indicate that children born with low birthweight seem to share environmental risk factors that are culturally dependent. This suggests smoking as a shared environmental exposure across generations, and that the mothers' smoking contributed to low birthweight in their offspring. The birthweight–smoking association among women was observed in both the highest and the lowest level of their mothers' education, and indicates that smoking habits are 'inherited' irrespective of socioeconomic status. In an adjusted model where we consider women's own education as a proxy for their socioeconomic status and included it as an adjustment variable, the RRs somewhat attenuated, but the pattern remained evident (data not shown).

Some studies have claimed no association between birthweight and adult smoking.[3,12,13] However, the association between birthweight[40] and weight at 1 year of age[41] and later adult smoking habits has previously been mentioned. Some of these studies are commenting on the association between birthweight and smoking habits among men only.[12,41] Others have information on birthweight only from self-report[3] and do not have data on gestational age.[13,40] The relation between birthweight and adult smoking is influenced by different overall smoking prevalences between populations as well as different time periods within a population. Different birth cohorts appear to have dissimilar patterns of smoking habits[42] and Great Britain and the US experienced both an earlier tobacco epidemic as well as higher consumptions than Norway.[43]

We studied women born in 1967–1995 and their smoking habits between 1999 and 2009. Thus, our cohort of women is younger than women in most other studies.[3,4,13,40,44–46] Among pregnant women in the Norwegian Mother and Child Cohort Study, 20% of those born in 1954–1965 reported being exposed to cigarette smoke in utero, compared with 32% among those born in 1981–1992.[47] For the general female population in Norway, the peak smoking prevalence was 10% for the early 1890s cohort, 52% for the early 1940s cohort and 41% for the early 1960s cohort.[42]

In this study, we had the opportunity to quantify the association between z-scores for birthweight by gestational age and adult smoking habits in a large material. This study shows that birthweight is associated with smoking habits in adulthood. It is therefore essential that research relating birthweight to later health outcomes provide a proper control for smoking habits both of the mother during pregnancy and in adulthood for the individual under study. The women in our study were too young to allow us to study the relation between their birthweight and their own long-term cardiovascular morbidity and mortality with adequate power. Future studies will be able to look at a person's whole lifetime and could study how birthweight and later smoking habits are related to cardiovascular disease.

Conclusion

In conclusion, being born with low birthweight is associated with smoking in adulthood. Associations of adult smoking with partners' birthweight and mothers' smoking-related causes of death suggest a shared smoking environment, and may account for some of the established association between birthweight and later cardiovascular disease.

Conflict of interest: The authors declare that they have no conflict of interests.

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