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Effects of maternal smoking during pregnancy on offspring blood pressure in late adolescence

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Abstract

Objectives—Previous studies suggest that maternal smoking during pregnancy is associated with elevated offspring blood pressure during childhood. We aimed to investigate whether this association remained in late adolescence and, if so, whether it could be attributed to an intrauterine effect or to familial confounding.

Methods—We used a national cohort of 87 223 young Swedish men born between 1983 and 1988 with information on both maternal smoking during pregnancy and blood pressure at military conscription. The cohort included 780 full brothers discordant for maternal smoking. Generalized estimation equations were used to estimate regression coefficients (b) with 95% confidence intervals (95% CIs).

Results—We found a small but significant increase in both SBP and DBP for young men whose mothers had been daily smokers during pregnancy compared with sons of nonsmoking mothers: 0.26 (95% CI 0.09 to 0.44) and 0.45mmHg (95% CI 0.31 to 0.59) for SBP and DBP, respectively. In a within-sibling analysis comparing full brothers discordant for maternal smoking exposure, point estimates were similar but not statistically significant: 0.85 (95% CI _0.19 to 1.90) for DBP and 0.81 (_0.56 to 2.19) for SBP.

Conclusion—Maternal smoking during pregnancy is associated with a small but statistically significant increase in offspring blood pressure in late adolescence. Because the association does not appear to be explained by familial confounding, our results support an intrauterine effect of prenatal smoking exposure on blood pressure in late adolescence.

Keywords

adolescent; blood pressure; maternal smoking; prenatal exposure delayed effects; siblings

INTRODUCTION

Maternal smoking during pregnancy is not only a well known risk factor for adverse obstetric outcomes but has also been linked to long-term effects in offspring, such as increased risks of childhood obesity, adult diabetes and increased childhood blood pressure [1]. However, prior studies on offspring blood pressure have presented mixed results. Some

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studies have shown positive effects of maternal smoking on infant and childhood blood pressure, ranging between 0.9 and 5.4mmHg [2–7]. Some studies found no effect [8–11], and one study found an interaction between prenatal smoking exposure and gestational age [12]. Pooled data in a meta-analysis estimated the effect to be 0.62mmHg [13].

Blood pressure is known to track across the lifespan, with children at the higher end of the distribution having higher risks of becoming hypertensive as adults [14,15]. Hence, in a population in which smoking during pregnancy is common, a consequence could be increased prevalence of hypertension and cardiovascular diseases as exposed children grow up and age. However, smoking during pregnancy is more common among women with low socioeconomic position [16] and it has been argued that the relation between smoking during pregnancy and offspring blood pressure is due to socioeconomic confounding that was not adjusted for rather than a true intrauterine effect [13]. There is also a possibility of familial confounding by genetic factors. Both blood pressure [17,18] and smoking during pregnancy [19,20] have been shown to be partly determined by genetic factors.

We used Swedish national registers to link information about maternal smoking during pregnancy to information about offspring blood pressure measurements at mandatory conscription, usually at the age of 18 years. We sought to investigate whether there is an association between maternal smoking during pregnancy and offspring blood pressure in late adolescence and whether a possible association could be attributed to an intrauterine effect of smoking or to familial factors, such as shared genetic and/or environmental factors.

METHODS

Study sample

In this cohort study, we included men born in Sweden between 1983 and 1988 who conscripted for mandatory military service between 2001 and 2006. Of the total 305 896 live-born men recorded in the Swedish Medical Birth Register, 3045 died and 7008 emigrated before estimated age of conscription (i.e. before 18 years). To achieve higher homogeneity within the cohort we also excluded those with mothers born outside the Nordic countries (n=20 322), those with congenital malformations (n=15 092) and multiple births (n=6000). After these exclusions, our sample consisted of 259 515 men of whom 201 701 were drafted for military service up to 2006. Information from blood pressure measurements was available for 92 730 men and data about both maternal smoking during pregnancy and blood pressure were available for 87 223 men.

Data sources

Data were obtained by interlinking information from the Swedish Medical Birth, Conscript, Education (in 1990) and Multi-Generation Registers. This register linkage was possible through the unique personal identity number given to each Swedish resident at birth or immigration. The Swedish Medical Birth Register holds information about more than 98% of all births in Sweden since 1973. Registration is required by law and information is collected and documented by midwives at the pregnant woman’s first visit to antenatal care. In more than 95% of all pregnancies, this takes place before the 15th week of gestation [21]. Selfreported data about maternal smoking during pregnancy have been routinely collected since 1983. Smoking habits were registered in standardized antenatal records using check boxes and categorized as nonsmoking, smoking one to nine cigarettes daily or smoking at least 10 cigarettes daily. These categories have previously been associated with cotinine levels [22]. Information about birth weight, gestational age, parity, maternal diseases during pregnancy and whether the parents-to-be were living together in early pregnancy were also derived from the Medical Birth Register. Maternal diagnoses during pregnancy and at

delivery are coded according to the International Classification of Diseases (ICD). The eighth revision (ICD-8) was used up to 1986, and the ninth revision (ICD-9) was used from 1987 to 1996. Blood pressure disease during pregnancy refers to hypertensive disorders of all causes (including pregnancy-induced hypertensive disorders; ICD-8 code 637; and ICD-9 code 642). Birth weight was standardized according to Swedish reference standards for weight at birth, given gestational ages between 28 and 42 weeks of gestation [23]. We excluded 159 observations with less than 28 or more than 42 weeks of gestation in the adjusted analyses. Gestational age was determined by ultrasound examination or, if not available, dates of last menses. During the study period, ultrasound examinations became increasingly common.

Information about parents' education was obtained from the Register of Education in 1990. If parents were cohabiting at the time of the pregnancy, we used the highest education for either of the parents, otherwise the mother's education was used.

Up to 2010, conscription was forced by law upon all Swedish men aged 18, but already in 2007, the number of conscripts fell dramatically. Psychological and physical examinations were performed to optimally recruit and place young men for military service. Only those with severe handicaps, congenital malformations or chronic disease were excluded from conscription. However, over the past decades, drafting to complete military service has become less common, and in 2000 only 37% were selected for military service compared with 90% in 1986 [24]. Only men considered physically and mentally suitable for military service proceeded to additional tests, which included measurement of blood pressure. The men we have blood pressure data for, should therefore be healthier than the overall cohort. Blood pressure measurements were performed by nurses working at enrollment offices in Sweden. One single blood pressure measurement was performed after 5 min of rest on the right arm in supine position. Both automatic and manual sphygmomanometers were used and, in case of an uncertain reading, an additional measurement was performed using a manual sphygmomanometer after further rest. Information about the young men's age, height and weight at the time of conscription was also obtained from the Conscript Register. Almost all men were between 17 and 19 years at conscription (97%). Weight was recorded in kilograms (in light indoor clothes) and height was measured in centimeters (without shoes). The BMI was calculated as the ratio between weight and squared height (kg/m2) and classified according to WHO criteria [25]. Underweight was defined as BMI of 18.5 kg/m2 or less, normal weight as BMI of 18.5–24 kg/m2, overweight as BMI 25–29 kg/m2 and obesity as BMI of at least 30 kg/m2. Within the cohort, 9448 men were identified as full brothers through the Multi-Generation Register, of whom 780 were discordant for maternal smoking during pregnancy and, hence, informative in a within-sibling analysis. For this analysis, we categorized smoking as absent (nonsmoker) or present (smoker).

Statistical analyses

We used generalized estimating equation (GEE) models to estimate regression coefficients (b) and 95% confidence intervals (CIs) for SBP and DBP levels in late adolescence as a function of maternal smoking during pregnancy. The reason to use GEE instead of a plain linear regression model was the correlated structure of our data (siblings). We performed both univariate and multivariate analyses in different models. In the first model, we adjusted for age, height and BMI at conscription. In the second model, we adjusted for parents' education and whether the parents were living together during pregnancy, this could be seen as a measure of family social position. In a third model, we included all these characteristics and added parity and maternal blood pressure disease during pregnancy. Finally, we wanted to investigate whether a possible effect of maternal smoking on offspring blood pressure was explained (mediated) through effects on birth weight and/or gestational age. We, therefore,

also present a fourth model in which we also include birth weight for gestational age and gestational age.

To examine whether a possible effect of maternal smoking on offspring blood pressure in early adulthood was influenced by unmeasured familial (genetic and/or shared environmental) factors, we estimated the effects of maternal smoking during pregnancy on blood pressure within fullbrother pairs discordant for maternal smoking during pregnancy [26]. As we only had information on 174 half-brothers, these were excluded from the family analysis. Full siblings share, on average, 50% of their cosegregating genes and, to a large extent, childhood environment. Maternal smoking during pregnancy was decomposed into a withinfamily effect, which estimated the expected change in offspring SBP by a one-unit change in maternal smoking behavior between pregnancies with male fetuses. A withinfamily score was assigned to each son, defined as the difference between smoking status at the index pregnancy and the mean value of maternal smoking status across the two pregnancies [26]. For example, if a mother smoked in one pregnancy but not the other, the exposed sibling would have a within-score of 0.5 and the unexposed would have a within-score of _0.5. Only discordant pairs were used because they provide the information for the estimation of a within component. This within score compares exposure to maternal smoking during pregnancy relative to their sibling's exposure. If confounding familial factors are important, these factors would make family members more alike. Hence, we would expect the within-full brother estimates to be smaller than those found for the cohort. Analyses were done with PROC MIXED in SAS version 9.2 (SAS Institute Inc., Cary, North Carolina, USA). This study was approved by the regional research ethics committee at Karolinska Institutet, Stockholm, Sweden.

RESULTS

Table 1 shows number of conscripts and their mean SBP and DBP in relation to parental, pregnancy and conscript characteristics. The mean SBP in the cohort was 130.7mmHg and mean DBP was 69.3mmHg. There was a positive linear trend among maternal smoking during pregnancy, conscripts' height, BMI and mean blood pressure. Birth weight for gestational age (a measure of fetal growth) and gestational age showed inverse associations with blood pressure; that is, those born small for gestational age (<2 standard deviations below the mean) and those born preterm (_36 weeks of gestation) had higher mean blood pressure.

Among conscripts without blood pressure measurements (N=108 971), the prevalence of maternal smoking during pregnancy was higher than among conscripts with such measurements (29.2 vs. 26.2%), the parents had lower education, the mothers were less often cohabiting with the fathers during pregnancy and information about height and BMI at conscription was lacking to a larger extent (data not shown). Among conscripts who had information about blood pressure but lacked information on maternal smoking during pregnancy (N=5507), the same pattern with lower parental education and parents not cohabiting was noted. Further, among those with missing information about maternal smoking during pregnancy, preterm birth was more common and hypertensive disorders during pregnancy less common (data not shown). In general, our cohort of conscripts, with information on both blood pressure measurement and maternal smoking during pregnancy, appeared to have higher socioeconomic background and to have been less exposed to maternal smoking than the conscripts with missing information. Mean height in our cohort was 180.6 cm, mean weight was 74.4 kg and mean BMI was 22.8 kg/m2. Ninety-five percent of the conscripts in our cohort had a BMI of less than 30.0 kg/m2. The prevalence of prenatal exposure to maternal smoking during pregnancy in the overall cohort was 26.2% (16.8% of the mothers smoked one to nine cigarettes daily, and 9.3% smoked _10 cigarettes

daily). Table 2 shows regression coefficients for the association between maternal smoking during pregnancy and SBP and DBP in offspring at conscription. Maternal smoking of one to nine cigarettes daily was not associated with significantly increased offspring SBP (b=0.18, 95% CI _0.02 to 0.39). However, maternal smoking of at least 10 cigarettes daily (vs. nonsmoking) exhibited a small but significant effect (b=0.64, 95% CI 0.38 to 0.90). Adjustment for potential confounders slightly attenuated the association (b=0.53, 95% CI 0.26 to 0.80) in the fully adjusted model. Additional adjustment for standardized birth weight and gestational age attenuated the association yet some more (b=0.44, 95% CI 0.17 to 0.71). The association between maternal smoking during pregnancy and DBP was statistically significant in both smoking categories and point estimates were slightly higher than for SBP. Adjustment for potential confounders slightly attenuated the results and the strongest attenuation was seen after adjustment for BMI (especially SBP) and parental education.

Table 3 shows analyses within full brothers. The regression coefficients present the expected change in offspring SBP (mmHg) for a one-unit change in maternal smoking behavior between pregnancies (that is going from smoker to nonsmoker or the other way around). Among full siblings, the expected changes in SBP and DBP were 0.69 (95% CI _0.67 to 2.04) and 1.14mmHg (95% CI 0.10 to 2.17), respectively, if the mother had smoked when pregnant compared with if she had not. Adjustment for potential confounders only slightly changed these estimates.

DISCUSSION

In the cohort analysis, we found that maternal smoking during pregnancy increased offspring blood pressure in late adolescence. In the analysis within full brothers, we found similar point estimates, albeit not statistically significant. These results indicate that there may be an intrauterine effect of maternal smoking on offspring blood pressure.

Previous studies of the association between maternal smoking during pregnancy and offspring blood pressure have yielded mixed results. Eight studies report a positive association [2–7,27,28], eight studies a null association [8–11,29–32] and one study reports an interaction with gestational age [12]. The study by Brion et al. [8] found that adjusting for social position attenuated the association between maternal smoking and offspring blood pressure toward the null. Further, similar effects of paternal and maternal smoking during pregnancy were found, indicating familial confounding rather than an intrauterine effect [8]. In a review by the same authors, a meta-analysis with pooled data showed an effect of maternal smoking on offspring blood pressure of 0.62mmHg [13]. In a prior study of offspring in late adolescence, a significant positive effect of maternal smoking of 1.95mmHg on SBP and a nonsignificant effect of 1.15mmHg on DBP was found [7]. Although we also found a positive association, our estimated effect was smaller and closer to the effects reported from the meta-analysis.

Some strengths of this study are the large sample size, prospectively collected information, and the ability to control for effects of important covariates. Further, we are only aware of one previous study assessing the relationship between maternal smoking and late adolescent offspring blood pressure [7]. Importantly, this is also the first study to assess familial confounding by studying the association in differentially exposed siblings.

Study limitations include that information on smoking during pregnancy was self-reported and limited to the first trimester (i.e. at the time of the first visit to prenatal care). Although self-reported smoking is considered to have acceptable validity [22], smoking habits could change during pregnancy. In the 1980s, 11% of women who reported smoking in the first

trimester stopped smoking later during pregnancy [33]. Heavy smokers, women who were exposed to passive smoking in their homes, low educated women and women who did not live with the baby's father were more likely to continue smoking throughout the pregnancy [34,35]. We, therefore, adjusted for parental education and if the mother was cohabiting with the child's father during pregnancy. Also, women who smoke during pregnancy most often continue to smoke when the baby is born. Hence, we cannot distinguish between effects of prenatal and postnatal maternal smoking. As information about maternal smoking during pregnancy was collected at the antenatal clinics recall bias could be excluded. However, there could be reporting bias in which women underestimate the amount smoked, which would lead to an underestimation of our results. Another limitation is that we only had outcome data for young men who were considered suitable for military service and most often willing to engage in military training (29% of the age cohort). Naturally, this increases the likelihood of selection bias. Men with recorded blood pressure measurements had parents with higher education and mothers who less often smoked while pregnant, indicating a higher socioeconomic background compared with those without outcome data. However, this selection should have resulted in a more homogenous population with higher internal validity; this could be the explanation to why results changed very little after adjustment for potential confounders. Further, we only had data on men in this study and, hence, the findings are not generalizable to women. We had only one blood pressure measurement for each participant, which may lead to decreased precision but not cause any systematic errors. In addition, blood pressure measurements were conducted in a nonstandardized fashion by different nurses using different devices; however, this is unrelated to the exposure and could, if anything, lead to a nondifferential measurement error.

It can be argued that BMI, and perhaps also height, might be both mediators and confounders in this analysis because smoking during pregnancy has been suggested to cause increased BMI in offspring. However, a previous study, also using this cohort, suggested that the effect of maternal smoking on offspring BMI was confounded by familial factors [36]. We suspect that BMI in this case might be more of a confounder than a mediator and we have, therefore, chosen to adjust for it in some of the analyses. Maternal smoking causes fetal growth restriction [37], which is often measured through birth weight adjusted for gestational age and sex. Low birth weight has consistently been associated with hypertension and cardiovascular disease later in life and this has been suggested to happen through fetal programming [38]. One hypothesis is, hence, that maternal smoking could affect offspring blood pressure through fetal growth restriction. Proposed mechanisms are increased arterial resistance, endothelial dysfunction, altered renal structure and function and altered composition and amount of perivascular adipose tissue, which can be a modulator of vascular function [29,39]. The effect of maternal smoking on offspring blood pressure found in this study is small, and other risk factors, predominantly the rapid increase in overweight and obesity, probably constitute a much larger threat toward public health. However, it is possible that changes caused by prenatal exposure to maternal smoking or other adverse fetal conditions may cause an increased vulnerability to other risk factors over the lifespan. In this study, we found a larger effect on offspring DBP than on SBP. In the young age groups (<50 years old), DBP has been shown to be the best predictor of future cardiovascular disease, that is, better than both SBP and pulse pressure [40].

In conclusion, our results suggest that maternal smoking during pregnancy can have a small long-term effect on late adolescent/young adult offspring blood pressure. Further, the results indicate that this effect might not be attributed to confounding familial factors. However, the found effect is small and it is uncertain whether this association persists later in life; therefore, the public health importance of this finding is uncertain. Future studies focusing on underlying mechanisms as well as studies investigating whether there is an association

between maternal smoking during pregnancy and adult hypertension and cardiovascular disease risk would be further warranted.

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Abbreviations

b	regression coefficient
CI	confidence interval
GEE	generalized estimating equation
ICD	International Classification of Diseases

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Table 1

Parental, birth and conscript characteristics and blood pressure in late adolescence among 92 730 Swedish men born in 1983–1988

	N	Systolic Mean (SD)	Diastolic Mean (SD
Overall cohort	92 730	130.7 (11)	69.3 (9)
Maternal smoking during pregnancy			
Nonsmoker	64 414	130.6 (11)	69.1 (9)
Daily smoker	22 809	130.9 (11)	69.7 (9)
One to nine cigarettes per day	14 655	130.7 (11)	69.5 (9)
_10 cigarettes per day	8154	131.2 (11)	69.9 (9)
Missing	5507	131.0 (11)	69.4 (9)
Parity			
1	39 227	130.8 (11)	69.3 (9)
2	33 344	130.7 (11)	69.3 (8)
3	15 141	130.5 (11)	69.2 (9)
_4	5018	130.3 (11)	68.9 (9)
Parental education			
9-year compulsory school	6824	131.1 (11)	70.0 (8)
Secondary school 1–2 years	34 076	130.6 (11)	69.3 (9)
Secondary school 3 years	12 187	130.6 (11)	69.3 (9)
Higher education <3 years	19 518	130.7 (11)	69.1 (9)
Higher education _3 years	19 955	130.8 (11)	69.1 (8)
Missing	170	131.9 (11)	71.5 (8)
Parents living together			
Yes	85 765	130.7 (11)	69.2 (9)
No	3843	131.0 (11)	69.8 (9)
Missing	3122	130.8 (11)	69.5 (8)
Birth weight for gestational age			
<_2 SD	1865	131.5 (11)	70.2 (9)
_2 to 2 SD	86 858	130.7 (11)	69.3 (9)
>2 SD	3136	130.4 (11)	68.8 (9)
Missing	871	130.7 (11)	69.7 (8)
Gestational age (weeks)			
28–31	237	134.0 (12)	70.7 (9)
32–36	3363	132.0 (11)	69.5 (9)
37–41	76 790	130.7 (11)	69.2 (9)
41–42	12 062	130.1 (11)	69.3 (8)
Missing	278	130.2 (12)	69.1 (9)
Blood pressure disease during pregnancy			

	N	Systolic Mean (SD)	Diastolic Mean (SD
Yes	3674	132.4 (11)	70.7 (9)
No	89 056	130.6 (11)	69.2 (9)
Age (years)			
<17.5	904	130.7 (11)	68.9 (8)
17.5–18.5	79 697	130.6 (11)	69.1 (9)
>18.5	12 129	131.3 (11)	70.3 (8)
Height (cm)			
<175	15 662	129.6 (11)	69.2 (9)
175–179	24 617	130.3 (11)	69.2 (9)
180–184	27 203	130.8 (11)	69.3 (8)
>185	24 958	131.5 (11)	69.3 (9)
Missing	290	133.5 (11)	72.4 (9)
BMI (kg/m2)			
<18.5	3679	126.6 (11)	69.3 (8)
18.5–24.5	70 682	130.2 (11)	69.1 (8)
25–30	14 891	133.0 (11)	69.5 (9)
_30	3188	134.7 (11)	70.9 (9)
Missing	290	133.5 (11)	72.4 (9)

Table 2

Regression coefficients for the association of maternal smoking during pregnancy on offspring blood pressure in late adolescence in a cohort of Swedish men born in 1983–1988

	Adjusted Models b (95% CI)				
	Crude	**Model 1**	**Model 2**	**Model 3**	**Model 4**
SBP					
Maternal smoking					
Nonsmoker	Reference	Reference	Reference	Reference	Reference
Daily smoker	0.35 (0.17 to 0.52)	0.20 (0.03 to 0.37)	0.37 (0.19 to 0.55)	0.26 (0.09 to 0.44)	0.20 (0.03 to 0.38)
One to nine cigarettes per day	0.18 (_0.02 to 0.39)	0.06 (-0.14 to 0.26)	0.21 (0.00 to 0.42)	0.12 (_0.09 to 0.33)	0.08 (_0.13 to 0.29)
_10 cigarettes per day	0.64 (0.38 to 0.90)	0.45 (0.19 to 0.71)	0.66 (0.39 to 0.93)	0.53 (0.26 to 0.80)	0.44 (0.17 to 0.71)
DBP					
Maternal smoking					
Nonsmoker	Reference	Reference	Reference	Reference	Reference
Daily smoker	0.57 (0.44 to 0.70)	0.50 (0.37 to 0.63)	0.48 (0.34 to 0.61)	0.45 (0.31 to 0.59)	0.44 (0.30 to 0.57)
One to nine cigarettes per day	0.43 (0.27 to 0.58)	0.38 (0.22 to 0.53)	0.35 (0.19 to 0.51)	0.33 (0.17 to 0.49)	0.33 (0.17 to 0.49)
_10 cigarettes per day	0.82 (0.62 to 1.02)	0.72 (0.53 to 0.92)	0.71 (0.51 to 0.92)	0.67 (0.47 to 0.88)	0.64 (0.43 to 0.85)
Total	87 223	86 954	85 705	85 438 8	4 570

CI, confidence interval.

Model 1Adjusted for conscript characteristics (age, height and BMI).

Model 2 Adjusted for parental characteristics (education and cohabitation status).

Model 3 Adjusted for conscript, parental and pregnancy characteristics (parity and maternal blood pressure disease during pregnancy).

Model 4 Adjusted for the same characteristics as model 3 and additionally adjusted for birth weight for gestational age and gestational age.

Table 3

Crude and adjusted estimates of the expected change in blood pressure in male full siblings discordant for maternal smoking during pregnancy following a change in smoking status between pregnancies

	Crude, b (95% CI)	Adjusted, b (95% CI)
SBP (mmHg)	0.69 (_0.67 to 2.04)	0.81 (_0.56 to 2.19)
DBP (mmHg)	1.14 (0.10 to 2.17)	0.85 (_0.19 to 1.90)
Total number of discordant brothers	780	758

CI, confidence interval.

Adjusted for age at conscription, height, BMI, parental cohabitation status at time of pregnancy, parity and maternal blood pressure disease during pregnancy.