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LIFE COURSE EPIDEMIOLOGY

Maternal smoking during pregnancy and offspring trajectories of height and adiposity: comparing maternal and paternal associations

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Background Maternal smoking during pregnancy is associated with reduced offspring birth length and has been postulated as a risk factor for obesity. Causality for obesity is not established. Causality is well-supported for birth length, but evidence on persistence of height deficits is inconsistent.

Methods We examined the association between maternal smoking during pregnancy and trajectories of offspring height (0–10 years, $N = 9424$), ponderal index (PI) (0–2 years, $N = 9321$) and body mass index (BMI) (2–10 years, $N = 8887$) in the Avon Longitudinal Study of Parents and Children. To strengthen inference, measured confounders were controlled for, maternal and partner smoking associations were compared, dose–response and associations with post-natal smoking were examined.

Results Maternal smoking during pregnancy was associated with shorter birth length, faster height growth in infancy and slower growth in later childhood. By 10 years, daughters of women who smoke during pregnancy are on average 1.11 cm (SE = 0.27) shorter after adjustment for confounders and partner smoking; the difference is 0.22 cm (SE = 0.22) for partner's smoking. Maternal smoking was associated with lower PI at birth, faster PI increase in infancy, but not with BMI changes 2–10 years. Associations were stronger for maternal than partner smoking for PI at birth and PI changes in infancy, but not for BMI changes after 2 years. A similar dose–response in both maternal and partner smoking was seen for BMI change 2–10 years.

Conclusion Maternal smoking during pregnancy has an intrauterine effect on birth length, and possibly on adiposity at birth and changes in height and adiposity in infancy. We do not find evidence of a specific intrauterine effect on height or adiposity changes after the age of 2 years.

Keywords Smoking, growth, obesity, pregnancy, child, ALSPAC

Introduction

It is well established that maternal smoking during pregnancy is associated with lower birth size in offspring.[1–4] The evidence relating to the associations between maternal smoking during pregnancy and offspring post-natal growth is, however, less consistent. Some studies have found that height deficits in children born to mothers who smoke during pregnancy persist,[5–7] whereas others have shown that the gap narrows soon after birth.[8,9]

More recently, there has also been interest in the potential effects of maternal smoking during pregnancy on offspring obesity. A systematic review and meta-analysis ($N = 84\,563$) showed that smoking during pregnancy is associated with increased odds of being overweight in the offspring [pooled odds ratio (OR) 1.50, 95% confidence interval (95% CI) 1.36–1.65],[10] with results not attenuated by adjustment for confounders. However, a recent study comparing siblings for whom maternal smoking during pregnancy was discordant (an approach which can partially control for unmeasured confounders) concluded that observed associations between smoking during pregnancy and offspring obesity are likely to be confounded by shared familial characteristics rather than causally related to intrauterine mechanisms.[11]

Previous publications from the Avon Longitudinal Study of Parents and Children (ALSPAC) have demonstrated associations between maternal smoking during pregnancy and reduced height at the age of 7.5 years,[12] and increased adiposity at the ages of 7 and 9.9 years using single measures of height and adiposity.[13,14] We build on this work to explore associations between maternal smoking during pregnancy and individual trajectories of height and adiposity between birth and the age of 10 years. This will enable us to explore the extent to which differences in height and adiposity at birth between the offspring of smokers and non-smokers are overcome with age, and identify the ages at which any such changes occur. In order to investigate the extent to which any observed associations are due to confounding, we apply several techniques. First, we control for a wide set of socio-economic and familial variables. Secondly, we compare the associations of maternal smoking during pregnancy with those of her partner's smoking during pregnancy in order to explore the existence of any unmeasured familial confounders including socio-economic, behavioural and genetic factors.[15] If the associations of maternal and her partner's smoking with offspring growth trajectories are similar, this is suggestive of confounding by familial factors rather than any causal intrauterine effect of maternal smoking. As proof of principle of the validity of this approach, we have previously shown that the association of maternal smoking in pregnancy with offspring birthweight (an association accepted as causal via intrauterine factors) is considerably stronger than the association of partner smoking with offspring birthweight in ALSPAC.[15] Our third tool to improve inference is to explore whether there is a dose–response for intensity of maternal and partner smoking. Finally, we compare the growth trajectories of offspring of women who smoke during pregnancy with those of women who do not smoke during pregnancy but (re-)start soon after delivery, since if the growth patterns in these two groups are similar then confounding is more likely.

Subjects and Methods

ALSPAC is a prospective birth cohort study in South-West England.[16] Pregnant women resident in one of the three Bristol-based health districts with an expected delivery date between April 1, 1991 and December 31, 1992 were invited to participate. Of these women, 14 541 were recruited; there were 14 062 live-born children, 13 988 of whom were alive at 1 year. Follow-up has included parent- and child-completed questionnaires, links to routine data and clinic attendance. Ethical approval was obtained from the ALSPAC Law and Ethics Committee and the local research ethics committees.

Dichotomous indicators of any/no smoking during pregnancy were based on self-report data, the details of which are found in the Supplementary Data, available as Supplementary data at *IJE* online.

In addition to the dichotomous variables, a three-category measure of smoking dose was created for both mothers and their partners; individuals were classified as non-smokers, light smokers ($\leqslant$10 cigarettes/day) and heavy smokers (>10 cigarettes/day). A three-category indicator of maternal post-natal smoking status was created: did not smoke during pregnancy and had not (re-)started smoking by 8 weeks post delivery, did not smoke during pregnancy but had (re-)started smoking by 8 weeks post delivery, or smoked during pregnancy.

Height and weight data were available for ALSPAC participants from several sources; measurement methods and number of measures per child are detailed in the Supplementary Data, available as Supplementary data at *IJE* online**.** Within ALSPAC, the only measures of adiposity repeated across the whole of childhood were those based on height and weight. Body mass index (BMI, kg/m^2) is the most common way of adjusting weight for height. Patterns of BMI change in early childhood are extremely complicated. Given this, we decided not to model BMI from birth. Rather, ponderal index (PI, kg/m^3) was used as the measure of adiposity from birth to the age of 2 years. BMI was modelled from the age of 2–10 years.

Individual trajectories of height between the ages 0 and 10 years, PI between the ages 0 and 2 years and BMI between the ages 2 and 10 years were estimated using random-effects linear spline models[17] (two

levels: measurement occasion and individual). These models allow for the change in scale and variance of growth measures over time and use all available data from all eligible children under a missing at random assumption. They allow for individual variation in trajectories, since random effects allow each individual to have different intercepts and slopes (rates of growth in each linear spline period). Trajectories were modelled separately for boys and girls, and not beyond the age of 10 years since puberty would necessitate individual spline points due to variation in age at puberty onset. Full statistical methodology is in the Supplementary Data, available as Supplementary data at *IJE* online.

Variables considered as potential confounders were maternal education, household occupational social class, parity, maternal age, maternal height, maternal BMI, gestational age at birth and breastfeeding. Measurements are detailed in the Supplementary Data, available as Supplementary data at *IJE* online. Associations between maternal/partner smoking during pregnancy and confounders were assessed by tabulations and logistic regressions.

Analyses were restricted to children alive at the age of 1 year, with at least one measure of height/adiposity between the ages 0 and 10 years, data on maternal and her partner's smoking during pregnancy and all confounders. Where relevant, analyses were further restricted to those with dose/maternal post-natal smoking data.

Associations between growth trajectories and (i) maternal/partner smoking during pregnancy, (ii) maternal/partner smoking dose and (iii) maternal post-natal smoking were modelled by including interaction term(s) in the random-effects models between the smoking variables and the intercept (birth length, PI at birth, or BMI at the age of 24 months) and each growth coefficient (rate of height growth, PI change or BMI change in each linear spline period). An example model is shown in the Supplementary Data, available as Supplementary data at *IJE* online. Heterogeneity tests were performed in Stata using the 'metan' command to assess the statistical evidence for differences between maternal and partner coefficients.

Analyses were carried out using the statistical packages Stata11,[18] MLwiN v2.24[19] and the Stata command 'runmlwin'.[20]

Results

The eligible sample for the main analysis was 9424 offspring for height models, 9321 for PI models and 8887 for BMI models (64–67% of the cohort members alive at the age of 1 year). Of the mothers included in our analysis, 20.5% of them and 36.1% of their partners smoked during the pregnancy. Overall, 3471 (39%) of households were discordant for parental smoking (further details in Supplementary Data, available as Supplementary data at *IJE* online). Sample sizes and prevalences for dose–response and post-natal smoking analysis are detailed in Supplementary Data and Supplementary Tables S1 and S2, available as Supplementary data at *IJE* online.

Although the participants included in our analyses were of higher socio-economic position than those excluded (Supplementary Table S3, available as Supplementary data at *IJE* online), the association between maternal smoking during pregnancy and birth length did not differ between participants included in our analyses and those excluded due to missing data on confounders (Supplementary Table S4, available as Supplementary data at *IJE* online). Women who smoked during pregnancy tended to be of lower socio-economic position, higher parity, younger age and shorter height than those who did not (Supplementary Table S5, available as Supplementary data at *IJE* online); similar associations with these characteristics were observed for partner smoking (Supplementary Table S6, available as Supplementary data at *IJE* online). There was some evidence that associations with maternal education, age and height and breastfeeding were stronger for partner smoking than maternal smoking; the reverse was true for household social class and no differences were observed for parity, gestational age or maternal BMI (Supplementary Table S7, available as Supplementary data at *IJE* online).

The multi-level models identified (Supplementary Figures S1–S3, available as Supplementary data at *IJE* online):

(i) four periods of length/height growth (boys: birth to 3, 3–10, 10–29, 29–120 months; girls: birth to 2, 2–11, 11–32, 32–120 months);
(ii) two periods of PI change in boys (birth to 2 and 2–24 months);
(iii) three periods of PI change in girls (birth to 1, 1–4 and 4–24 months); and
(iv) six periods of BMI change (boys: 24–56, 56–67, 67–73, 73–79, 79–105 and 105–120 months; girls: 24–60, 60–65, 65–75, 75–81, 81–103 and 103–120 months).

Maternal smoking during pregnancy is associated with lower birth length (Tables 1 and 2) and this association remains after adjustment for confounders and after mutual adjustment for partner's smoking. In fully adjusted models, maternal smoking is associated with a 0.67 cm (SE = 0.09) lower birth length in girls and 0.63 cm (SE = 0.08) in boys. In unadjusted models, partner's smoking is also associated with lower birth length, but this is attenuated by adjustment for confounders and maternal smoking (Table 3). There is strong evidence for a statistical difference between the coefficients of maternal and partner's smoking for birth length ($P < 0.001$) (Tables 1 and 2). For girls, there is evidence of a

Table 1 The associations between maternal and partner smoking during pregnancy and trajectories of height, PI and BMI in female offspring

		Maternal smoking during pregnancy			Partner smoking during pregnancy			*P* value
	Mean (SD) growth rate per month	Crude coefficient[a] (SE)	Adjusted coefficient (SE)[b]	Adjusted coefficient with further adjustment for paternal smoking (SE)	Crude coefficient[a] (SE)	Adjusted coefficient[b] (SE)	Adjusted coefficient with further adjustment for maternal smoking (SE)	Maternal–partner hetero-geneity[c]
Height, *N* = 4592								
Birth length, cm	49.8 (1.1)	−0.7644 (0.0910)	−0.6555 (0.0837)	−0.6680 (0.0888)	−0.2375 (0.0759)	−0.1440 (0.0693)	0.0367 (0.0731)	<0.001
Growth 1, cm/month	3.9 (0.2)	0.0403 (0.0473)	0.0375 (0.0470)	0.0281 (0.0502)	0.0308 (0.0392)	0.0301 (0.0389)	0.0220 (0.0416)	0.93
Growth 2, cm/month	1.8 (0.2)	0.0450 (0.0136)	0.0467 (0.0136)	0.0430 (0.0145)	0.0214 (0.0113)	0.0212 (0.0113)	0.0083 (0.0121)	0.07
Growth 3, cm/month	0.9 (0.09)	−0.0124 (0.0063)	−0.0125 (0.0063)	−0.0117 (0.0068)	−0.0058 (0.0052)	−0.0055 (0.0052)	−0.0018 (0.0056)	0.26
Growth 4, cm/month	0.5 (0.04)	−0.0066 (0.0024)	−0.0068 (0.0024)	−0.0073 (0.0026)	−0.0009 (0.0020)	−0.0010 (0.0020)	0.0012 (0.0021)	0.01
PI, *N* = 4544								
PI at birth, kg/m^3	26.7 (1.4)	−0.0680 (0.1094)	−0.0723 (0.1102)	−0.0888 (0.0966)	0.0007 (0.0904)	−0.0001 (0.0907)	0.0339 (0.0966)	0.37
PI change 1, kg/m^3/month	−0.4 (1.7)	0.3285 (0.1592)	0.3338 (0.1591)	0.3813 (0.1712)	0.0077 (0.1320)	0.0085 (0.1320)	−0.1079 (0.1419)	0.03
PI change 2, kg/m^3/month	0.2 (0.6)	0.0252 (0.0589)	0.0243 (0.0589)	0.0264 (0.0634)	0.0023 (0.0486)	0.0024 (0.0486)	−0.0048 (0.0523)	0.70
PI change 3, kg/m^3/month	−0.4 (0.07)	−0.0052 (0.0088)	−0.0053 (0.0088)	−0.0071 (0.0094)	0.0022 (0.0073)	0.0022 (0.0073)	0.0043 (0.0078)	0.35
BMI, *N* = 4353 (kg/m^2/month**)**								
BMI change 1	−0.01 (0.02)	−0.0026 (0.0040)	−0.0024 (0.0040)	−0.0041 (0.0043)	0.0019 (0.0033)	0.0022 (0.0033)	0.0034 (0.0036)	0.18
BMI change 2	−0.06 (0.1)	−0.0236 (0.0380)	−0.0240 (0.0381)	0.0032 (0.0408)	−0.0555 (0.0300)	−0.0570 (0.0300)	−0.0583 (0.0323)	0.24
BMI change 3	−0.02 (0.08)	0.0375 (0.0319)	0.0372 (0.0319)	0.0142 (0.0340)	0.0540 (0.0247)	0.0543 (0.0247)	0.0503 (0.0264)	0.40
BMI change 4	0.01 (0.1)	0.0108 (0.0352)	0.0107 (0.0353)	0.0273 (0.0375)	−0.0291 (0.0272)	−0.0293 (0.0272)	−0.0367 (0.0290)	0.18
BMI change 5	0.07 (0.03)	−0.0008 (0.0036)	−0.0006 (0.0036)	−0.0027 (0.0038)	0.0042 (0.0028)	0.0043 (0.0028)	0.0049 (0.0030)	0.12
BMI change 6	0.04 (0.03)	0.0095 (0.0043)	0.0096 (0.0043)	0.0078 (0.0046)	0.0064 (0.0034)	0.0064 (0.0034)	0.0042 (0.0036)	0.54

[a]Coefficients are for interactions between smoking during pregnancy and the intercept (birth length, PI at birth or BMI at the age of 2 years) or slope (growth rate in each linear spline period), that is they represent the additive effect of maternal or partner smoking during pregnancy on the intercept or growth rate. Slopes are centimetre per month for height growth, kilograms per cubic metre per month for PI and kilograms per square metre per month for BMI.

[b]Adjusted for maternal education, household social class, parity, maternal age, maternal height, maternal BMI, gestational age at birth and breastfeeding.

[c]*P*-values are for heterogeneity tests of the difference of maternal–partner coefficients, with mutual adjustment for maternal/partner smoking.

Height growth period 1: birth to 2 months; height growth period 2: 2–11 months; height growth period 3: 11–32 months; height growth period 4: 32–120 months; PI change period 1: birth to 1 month; PI change period 2: 1–4 months; PI change period 3: 4–24 months; BMI change period 1: 24–56 months; BMI change period 2: 56–67 months; BMI change period 3: 67–73 months; BMI change period 4: 73–79 months; BMI change period 5: 79–105 months; BMI change period 6: 105–120 months.

Table 2 The associations between maternal and partner smoking during pregnancy and trajectories of height, PI and BMI in male offspring

		Maternal smoking during pregnancy			Partner smoking during pregnancy			*P*-value
	Mean (SD) growth rate per month	Crude coefficient[a] (SE)	Adjusted coefficient (SE)[b]	Adjusted coefficient with further adjustment for paternal smoking (SE)	Crude coefficient[a] (SE)	Adjusted coefficient[b] (SE)	Adjusted coefficient with further adjustment for maternal smoking (SE)	Maternal–partner hetero-geneity[c]
Height, $N = 4832$								
Birth length, cm	50.7 (1.2)	−0.6849 (0.0891)	−0.5865 (0.0785)	−0.6275 (0.0830)	−0.0873 (0.0765)	−0.0590 (0.0664)	0.1095 (0.0698)	<0.001
Growth 1, cm/month	3.8 (0.2)	0.0155 (0.0401)	0.0198 (0.0396)	0.0262 (0.0424)	−0.0098 (0.0339)	−0.0078 (0.0335)	−0.0152 (0.0358)	0.46
Growth 2, cm/month	1.7 (0.2)	0.0497 (0.0183)	0.0504 (0.0183)	0.0476 (0.0196)	0.0199 (0.0155)	0.0210 (0.0155)	0.0063 (0.0166)	0.11
Growth 3, cm/month	1.0 (0.1)	−0.0054 (0.0065)	−0.0055 (0.0065)	−0.0033 (0.0069)	−0.0053 (0.0055)	−0.0063 (0.0055)	−0.0052 (0.0059)	0.83
Growth 4, cm/month	0.5 (0.04)	−0.0027 (0.0022)	−0.0025 (0.0023)	−0.0020 (0.0024)	−0.0019 (0.0018)	−0.0018 (0.0019)	−0.0012 (0.0020)	0.80
PI, $N = 4777$								
PI at birth, kg/m^3	26.2 (1.2)	−0.2557 (0.1013)	−0.2296 (0.1022)	−0.2059 (0.1087)	−0.1298 (0.0865)	−0.1233 (0.0867)	−0.0569 (0.0921)	0.30
PI change 1, kg/m^3/month	0.5 (0.8)	0.2482 (0.0678)	0.2494 (0.0678)	0.2311 (0.0726)	0.1125 (0.0580)	0.1145 (0.0580)	0.0436 (0.0621)	0.05
PI change 2, kg/m^3/month	−0.4 (0.08)	−0.0055 (0.0076)	−0.0053 (0.0076)	−0.0048 (0.0081)	−0.0026 (0.0065)	−0.0027 (0.0065)	−0.0011 (0.0069)	0.73
BMI, $N = 4534$ (kg/m^2/month)								
BMI change 1	−0.01 (0.05)	0.0118 (0.0156)	0.0114 (0.0156)	0.0117 (0.0169)	0.0035 (0.0120)	0.0031 (0.0119)	−0.0003 (0.0130)	0.57
BMI change 2	−0.03 (0.02)	−0.0081 (0.0092)	−0.0091 (0.0092)	−0.0079 (0.0101)	−0.0054 (0.0072)	−0.0054 (0.0072)	−0.0027 (0.0078)	0.68
BMI change 3	−0.03 (0.04)	−0.0108 (0.0153)	−0.0087 (0.0153)	−0.0154 (0.0164)	0.0108 (0.0120)	0.0103 (0.0120)	0.0144 (0.0129)	0.15
BMI change 4	−0.02 (0.04)	0.0171 (0.0174)	0.0163 (0.0174)	0.0095 (0.0186)	0.0179 (0.0132)	0.0180 (0.0132)	0.0153 (0.0141)	0.80
BMI change 5	−0.02 (0.03)	−0.0012 (0.0043)	−0.0017 (0.0043)	0.0006 (0.0045)	−0.0049 (0.0033)	−0.0049 (0.0033)	−0.0050 (0.0035)	0.33
BMI change 6	0.05 (0.03)	0.0054 (0.0024)	0.0057 (0.0024)	0.0043 (0.0026)	0.0044 (0.0020)	0.0045 (0.0020)	0.0033 (0.0021)	0.77

[a]Coefficients are for interactions between smoking during pregnancy and the intercept (birth length, PI at birth or BMI at the age of 2 years) or slope (growth rate in each linear spline period), i.e. they represent the additive effect of maternal or partner smoking during pregnancy on the intercept or growth rate. Slopes are centimetre per month for height growth, kilograms per cubic metre per month for PI, and kilograms per square metre per month for BMI.

[b]Adjusted for maternal education, household social class, parity, maternal age, maternal height, maternal BMI, gestational age at birth and breastfeeding.

[c]*P*-values are for heterogeneity tests of the difference of maternal–partner coefficients, with mutual adjustment for maternal/partner smoking.

Height growth period 1: birth to 3 months; height growth period 2: 3–10 months; height growth period 3: 10–29 months; height growth period 4: 29–120 months; PI change period 1: birth to 2 months; PI change period 2: 2–24 months; BMI change period 1: 24–60 months; BMI change period 2: 60–65 months; BMI change period 3: 65–75 months; BMI change period 4: 75–81 months; BMI change period 5: 81–103 months; BMI change period 6: 103–120 months.

Table 3 Predicted differences in height and adiposity between the offspring of smokers and non-smokers

	Predicted measurement for offspring of non-smokers (SE)	Predicted change (SE) comparing offspring of smokers with non-smokers	
		Maternal smoking	Partner smoking
Girls			
Height (cm)			
Birth	50.75 (0.11)	−0.67 (0.09)	+0.04 (0.07)
Age 2 years	86.52 (0.12)	−0.37 (0.12)	+0.13 (0.10)
Age 10 years	140.67 (0.16)	−1.11 (0.27)	+0.22 (0.22)
Adiposity			
PI at birth (kg/m^3)	26.37 (0.12)	−0.09 (0.10)	+0.03 (0.10)
BMI at age 2 years) (kg/m^2)	16.55 (0.10)	+0.14 (0.10)	+0.05 (0.08)
BMI at age 10 years	17.79 (0.11)	+0.39 (0.14)	+0.35 (0.11)
Boys			
Height (cm)			
Birth	51.55 (0.10)	−0.63 (0.08)	+0.11 (0.07)
Age 2 years	88.33 (0.11)	−0.26 (0.12)	+0.04 (0.10)
Age 10 years	141.53 (0.15)	−0.46 (0.26)	−0.10 (0.22)
Adiposity			
PI at birth (kg/m^3)	25.86 (0.10)	−0.21 (0.11)	−0.06 (0.09)
BMI at age 2 years	16.85 (0.19)	−0.14 (0.48)	+0.07 (0.37)
BMI at age 10 years	16.22 (0.08)	+0.24 (0.08)	+0.10 (0.07)

Values are predicted from the multi-level models, based on models adjusted for confounders and mutually adjusted for both maternal and partner's smoking. Height/lengths are in centimetres, PI is in kilograms cubic per metre, BMI is in kilograms per square metre.

dose–response in the relationship between maternal smoking and offspring birth length, with the lower birth length among smokers compared with non-smokers being twice the magnitude for heavy smokers (−1.02 cm) compared with light smokers (−0.53 cm); in boys there was no dose–response, with differences in comparison with non-smokers being the same for heavy and light smokers (both −0.64 cm) (Table 4). There is no reduction in birth length for the offspring of women who do not smoke during pregnancy but (re-)start within 8 weeks of delivery in either girls or boys (Table 5).

In the first year of life, the offspring of women who smoke during pregnancy grow faster than the offspring of non-smokers (growth periods 1 and 2 in Tables 1 and 2). In girls, the association between partner's smoking and offspring growth in the first few months of life (growth period 1 in Tables 1 and 2) is similar to the association with maternal smoking after mutual adjustment (*P*-value for heterogeneity is 0.93); in boys, the coefficients are in opposite directions with maternal smoking associated with faster growth and partner's smoking associated with slower growth, but there is no statistical evidence of heterogeneity ($P = 0.46$) and the coefficients have large standard errors in both girls and boys. The positive association between maternal smoking in pregnancy and growth in later infancy (growth period 2 in Tables 1 and 2) is not attenuated by adjustment for measured confounders or mutual adjustment for partner's smoking. A positive association for growth in this period is also seen for partner's smoking, but the magnitude is ∼4-fold weaker than for maternal smoking, with some evidence of statistical heterogeneity between the maternal and partner coefficients ($P = 0.07$ for girls, 0.11 for boys).

Later in childhood, between the ages ∼1 and 10 years, the offspring of women who smoke grow more slowly in height than those of non-smokers. This association is weak but not attenuated by measured confounders. In boys, the associations with growth between the ages 1 and 10 years are approximately similar for maternal and partner's smoking; in girls, there is some indication of maternal smoking being more strongly associated with slower growth than partner smoking in the final growth period only (growth period 4 in Table 1); *P*-value for heterogeneity is 0.01.

By the age of 10 years, the daughter of a woman who smoked during pregnancy is on average 1.11 cm (SE = 0.27) shorter than the daughter of a non-smoker once measured confounders and partner's

Table 4 Dose–response in predicted differences in height and adiposity between the offspring of smokers and non-smokers

		Predicted change (SE) comparing offspring of smokers with non-smokers			
	Predicted measurement for offspring of non-smokers (SE)	Light maternal smoking: ⩽10 cigarettes/day	Heavy maternal smoking: >10 cigarettes/day	Light partner smoking: ⩽10 cigarettes/day	Heavy partner smoking: >10 cigarettes/day
Girls					
Height (cm) $N = 3351$					
Birth	50.39 (0.14)	−0.53 (0.12)	−1.02 (0.15)	+0.04 (0.11)	+0.11 (0.10)
Age 2 years	86.23 (0.15)	−0.21 (0.17)	−0.31 (0.22)	−0.08 (0.16)	−0.01 (0.15)
Age 10 years	140.55 (0.20)	−0.74 (0.38)	−1.70 (0.51)	−0.31 (0.34)	−0.19 (0.33)
Adiposity $N = 3189$					
PI at birth (kg/m^3)	26.25 (0.15)	+0.01 (0.17)	−0.53 (0.21)	−0.06 (0.15)	+0.08 (0.14)
BMI at age 2 years (kg/m^2)	16.49 (0.12)	+0.29 (0.14)	−0.15 (0.17)	+0.10 (0.13)	+0.05 (0.11)
BMI at age 10 years	17.73 (0.13)	+0.22 (0.19)	+0.47 (0.25)	+0.29 (0.17)	+0.43 (0.17)
Boys					
Height (cm) $N = 3544$					
Birth	51.11 (0.15)	−0.64 (0.12)	−0.64 (0.16)	+0.18 (0.11)	+0.03 (0.11)
Age 2 years	87.94 (0.15)	−0.06 (0.17)	−0.27 (0.23)	+0.09 (0.16)	−0.26 (0.15)
Age 10 years	141.26 (0.20)	−0.24 (0.36)	−0.73 (0.50)	−0.04 (0.33)	−0.33 (0.32)
Adiposity $N = 3288$					
PI at birth (kg/m^3)	25.83 (0.14)	−0.07 (0.15)	−0.37 (0.20)	+0.04 (0.14)	−0.09 (0.14)
BMI at age 2 years	16.89 (0.25)	+0.40 (0.67)	−2.10 (1.02)	+0.45 (0.58)	+0.24 (0.52)
BMI at age 10 years	16.23 (0.11)	+0.09 (0.11)	+0.14 (0.16)	−0.08 (0.10)	+0.21 (0.10)

Values are predicted from the multi-level models, based on models adjusted for confounders and mutually adjusted for both maternal and partner's smoking. Height/lengths are in centimetres, PI is in kilograms per cubic metre, BMI is in kilograms per square metre. Maternal smoking dose calculated from the highest smoking level reported from three antenatal questionnaires. Partner smoking dose calculated from reported smoking behaviour in a questionnaire at 18 weeks' gestation.

smoking have been adjusted for; the difference is 0.22 cm (SE = 0.22) for partner's smoking (Table 3). The equivalent differences in boys are 0.46 cm (SE = 0.26) for maternal smoking and 0.10 cm (SE = 0.22) for partner smoking. The offspring of women who (re-)started smoking within 8 weeks of delivery show a much smaller height deficit than those whose mothers smoked during pregnancy (Table 5).

The offspring of women who smoke during pregnancy have a PI at birth 0.09 kg/m^3 (girls, SE = 0.10) or 0.21 kg/m^3 (boys, SE = 0.11) lower than offspring of women who do not smoke in pregnancy (Tables 1 and 2) in adjusted models. For both boys and girls, this association is not attenuated by adjustment for measured confounders. In mutually adjusted models, the negative association of maternal smoking with PI at birth is stronger for maternal than partner smoking. However, the standard errors of coefficients for both maternal and partner smoking and PI at birth are large, and there is little statistical evidence of a difference between the associations of maternal and partner's smoking with PI at birth (P-values for heterogeneity of maternal and partner coefficients 0.30 for boys, 0.37 for girls). There is, however, an indication of a dose–response, with the reduction in PI at birth being much greater in the offspring of women who smoke heavily during pregnancy compared with the reduction association with light smoking (Table 4). The associations with post-natal smoking and PI at birth are qualitatively different for boys and girls (formal interaction tests were not performed); in girls both maternal smoking during pregnancy and post-natal smoking are associated with a reduced PI at birth, whereas in boys the reduction in PI at birth is confined to maternal smoking during pregnancy (Table 5).

Male offspring of women who smoke have faster rates of PI increase in the first 2 months of life, and female offspring have slower rates of PI decrease in the first 1 month of life and faster rates of PI increase between the ages 1 and 4 months. Among girls, the associations with PI changes are in opposite directions for maternal and partner's smoking, although there is only statistical evidence of a difference between the coefficients for the first 1 month of life ($P = 0.03$).

Table 5 Differences in predicted differences in height and adiposity between the offspring of women who do not smoke during or after pregnancy, those who stop smoking during pregnancy but restart soon afterwards, and those who smoke during pregnancy

		Predicted change (SE) comparing offspring with those whose mothers are non-smokers	
	Predicted measurement for offspring of non-smokers (SE)	Restarters: no smoking during pregnancy but resumed within 8 weeks of delivery	Pregnancy smokers
Girls			
Height (cm) $N=4302$			
Birth	50.55 (0.13)	+0.20 (0.20)	−0.66 (0.08)
Age 2 years	86.31 (0.13)	+0.17 (0.30)	−0.27 (0.12)
Age 10 years	141.04 (0.17)	−0.08 (0.69)	−0.96 (0.27)
Adiposity $N=4095$			
PI at birth (kg/m^3)	26.25 (0.13)	−0.10 (0.28)	−0.05 (0.12)
BMI at age 2 years (kg/m^2)	16.53 (0.11)	−0.25 (0.24)	+0.15 (0.10)
BMI at age 10 years	17.83 (0.12)	−0.11 (0.35)	+0.54 (0.14)
Boys			
Height (cm) $N=4503$			
Birth	51.21 (0.13)	+0.33 (0.20)	−0.55 (0.08)
Age 2 years	87.96 (0.13)	+0.08 (0.29)	−0.26 (0.12)
Age 10 years	141.20 (0.16)	−0.23 (0.62)	−0.60 (0.25)
Adiposity $N=4245$			
PI at birth (kg/m^3)	25.92 (0.12)	+0.25 (0.27)	−0.17 (0.11)
BMI at age 2 years	16.84 (0.20)	+0.19 (1.05)	−0.26 (0.47)
BMI at age 10 years	16.22 (0.10)	+0.26 (0.20)	+0.24 (0.08)

Values are predicted from the multi-level models, based on models adjusted for confounders and mutually adjusted for both maternal and partner's smoking. Height/lengths are in centimetres, PI is in kilograms per cubic metre, BMI is in kilograms square per. Non-smokers are those who reported no smoking in any of the three antenatal questionnaires. Restarters are those who reported no smoking in any of the three antenatal questionnaires but who reported that they had (re-)started smoking since the birth in a questionnaire at ~8 weeks after delivery. Pregnancy smokers are those who reported smoking at any time during pregnancy in the three antenatal questionnaires.

Among boys, the associations with PI changes in the first 2 months are ~5-fold stronger for maternal smoking than for partner's smoking (*P*-value for heterogeneity of coefficients is 0.05). All of these associations, however, are of small magnitude when compared with the mean and standard deviation of average PI change rates, and have large standard errors.

There is little evidence of differences in PI changes later in infancy and BMI changes between the ages 2 and 10 years between the offspring of smokers and non-smokers. Some of the coefficients are of greater magnitude for maternal smoking and others are stronger for partner's smoking, but all effect sizes are very small with large standard errors and there is no statistical evidence of maternal–partner differences in any of the coefficients.

By the age of 2 years, the male offspring of women who smoked during pregnancy remain slightly less adipose than the offspring of non-smokers; their BMI is on average $0.14\,kg/m^2$ (SE = 0.48) lower than the offspring of smokers. In girls, however, maternal smoking during pregnancy is associated with higher BMI by the age of 2 years of $0.14\,kg/m^2$ (SE = 0.10) (Table 3). When the cumulative effect of all adiposity changes up to the age of 10 years is calculated, maternal smoking during pregnancy has a similar association with offspring adiposity compared with partner's smoking for girls; but for boys, there is a stronger association for maternal smoking. After adjustment for confounders, maternal smoking in pregnancy is associated with higher BMI at the age of 10 years by an average $0.39\,kg/m^2$ (SE = 0.14) in girls and $0.24\,kg/m^2$ (SE = 0.08) in boys. The observed increases in BMI by the age of 10 years for partner's smoking during pregnancy are $0.35\,kg/m^2$ (SE = 0.11) for girls and $0.10\,kg/m^2$ (SE = 0.07) for boys (Table 3). The difference in BMI at the age of 10 years compared with the baseline group of non-smokers is greater for the offspring of women who smoked heavily during

pregnancy than for the offspring of women who smoked lightly (Table 4). However, a similar difference between heavy and light smokers is observed for partner smoking. In girls, the difference in BMI at the age of 10 years compared with the baseline group of non-smokers is greater for the offspring of women who smoked during pregnancy than for women who (re-)started smoking within 8 weeks of delivery, but in boys these groups have a similar elevation in BMI at the age of 10 years (Table 5).

Discussion

Our data are consistent with maternal smoking reducing offspring birth length through a causal intrauterine effect; this association was strong, resistant to adjustment for observed confounding factors, not observed for partner's smoking during pregnancy and not observed in the offspring of women who (re-)started smoking within 8 weeks of delivery. This is consistent with the large body of literature suggesting a causal effect of maternal smoking during pregnancy on birth size.[1–4,21,22] Several potential mechanisms for the causal effect of smoking on birth size have been postulated, including the vasoconstrictive action of nicotine and fetal hypoxia,[23,24] and it is possible that these mechanisms could result in lasting changes to the infant that would affect post-natal growth. In our study, there was some indication of different post-natal growth patterns in the offspring of maternal smokers compared with non-smokers, with children of smokers growing more rapidly in infancy but more slowly later in childhood. However, differences in post-natal height growth rates between the offspring of smokers and non-smokers are relatively small, and could be explained by chance. Thus the height differential, which persists across childhood as previously observed in this cohort,[12] appears to be largely due to smaller birth length rather than to different post-natal height growth patterns.

Animal studies have suggested an association between maternal nicotine exposure and changes in adipose tissue and glucose metabolism, which would be consistent with maternal smoking during pregnancy having a causal effect on greater offspring adiposity.[25–27] Although many observational studies in human populations have also demonstrated an association between maternal smoking during pregnancy and increased offspring adiposity,[10,11,28–31] including one showing stronger maternal than paternal effects[32] and another carried out on a cohort born between 1959 and 1966, when smoking during pregnancy was more common and less socio-economically confounded, and average BMI levels were lower,[31] the degree to which this association is causal via intrauterine mechanisms is uncertain, with confounding by familial factors potentially very important.[11] In our data, the offspring of women who smoke during pregnancy have a slightly lower PI at birth, and faster rates of adiposity change in the first few months of life. By the age of 2 years, male children born to women who smoked during pregnancy remain of slightly lower BMI than those born to non-smokers or to women whose partners smoked, but female offspring of smokers have slightly higher BMI. By the age of 10 years, children of both genders born to women who smoked during pregnancy have greater BMI. Associations between maternal smoking during pregnancy and adiposity changes were not attenuated by adjustment for measured confounders. For PI at birth, we did not demonstrate statistical heterogeneity between the coefficients for maternal and partner's smoking, indicating that this observed maternal–partner difference may be due to chance, although a dose–response was observed such that the reduction in PI at birth was largely restricted to the offspring of women who smoked heavily (>10 cigarettes/day). For PI changes in the first months of life, there is some evidence that the coefficients for maternal and partner's smoking are different, indicating a possible effect of maternal smoking during pregnancy on adiposity changes in the early months of life. However, the coefficient sizes were small with large standard errors, thus the associations could be due to chance and require replication in other studies. For PI changes in later infancy and BMI changes between the ages 2 and 10 years, however, the associations with maternal and partner's smoking are equivalent, suggesting that any associations between smoking during pregnancy and adiposity changes after early infancy may be due to either confounding by unmeasured familial factors. These findings contrast with results from a recent publication, which reported that in Brazilian children born either in 1993 or 2004, maternal smoking in pregnancy was associated with greater offspring BMI at ages 12 and 48 months, with no association with partner's smoking and statistical evidence for differences between maternal and paternal smoking.[32] The population differences between the two studies and the inability of the Brazilian study to examine associations into later childhood might explain these differences. Although we found a dose–response such that the offspring of women who smoke heavily (>10 cigarettes/day) have a higher BMI at the age of 10 years than the offspring of light smokers, a similar dose response is observed for partner's smoking. At least in boys, the increase in BMI at the age of 10 years is also similar for the offspring of women who (re-)started smoking within 8 weeks of delivery. Together, these observations suggest that the associations we observe in later childhood for BMI are due to confounding rather than a causal effect of maternal smoking in pregnancy.

The main strengths of our analyses are the large sample size, the use of repeat measures of height and adiposity, the multiple approaches to control for

both measured and unmeasured confounding factors and the use of dose information and data on post-natal smoking. One limitation of our study is that we have used self-reported data on smoking during pregnancy, although a meta-analysis of studies comparing self-reported smoking with biochemical measures provides reassurance for using self-reported smoking behaviour, since it was found to have good sensitivity and specificity.[33] This meta-analysis did not, however, include studies during pregnancy, when the bias may be greater due to the stigma attached to pregnancy smoking. However, the fact that we do not see a reduction in birth length for the offspring of women who report not having smoked during pregnancy, but (re-)started within 8 weeks of delivery, provides support for the validity of the self-reported smoking data. We have reported results separately for boys and girls because the growth trajectories were modelled separately by gender; thus we cannot formally test for interactions by gender. Any gender differences may be due to chance, and differences observed between girls and boys should be interpreted with caution.

Thus, overall, these analyses are consistent with an intrauterine effect of maternal smoking on birth length and possibly also on adiposity at birth and on height and adiposity changes in infancy. We do not find any strong evidence of an intrauterine effect on changes in height or adiposity after infancy. Apart from the associations with birth length, most other coefficient sizes were small with large standard errors, and therefore these associations require replication in other studies and utilization of other methodologies such as Mendelian randomization.[34]

Supplementary Data

Supplementary Data are available at *IJE* online.

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KEY MESSAGES

- Maternal smoking during pregnancy is a known causal risk factor for smaller birth size, but associations with post-natal growth are less clear.
- Although smoking during pregnancy has been postulated as a risk factor for offspring obesity, causality has not been established.
- Using longitudinal analysis of growth trajectories and several approaches to control for known and unknown confounders, we show that although height deficits for offspring of women who smoke during pregnancy persist into childhood, these are largely due to the lower birth length rather than differences in post-natal growth rates.
- We observe that children of women who smoke during pregnancy have higher BMI, but comparisons with partner smoking during pregnancy indicate that this association may be confounded by unmeasured familial factors.
- Taken together, our different methods for assessing causality suggest that maternal smoking during pregnancy has an intrauterine effect on birth length, and possibly on adiposity at birth and changes in height and adiposity in infancy, but does not affect the change in height or adiposity after the age of 2 years.

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