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Maternal smoking during pregnancy and appetite control in offspring

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1 Introduction

Prevalences of obesity are increasing and obese individuals have a higher risk of experiencing obesity related morbidity [1, 2, 12]. The causes of obesity, however, are sparsely understood or unknown.

Recently an effect of maternal smoking in pregnancy on adult obesity among offspring has been observed in a birth cohort study [10, 14]. Another study confirming this association among children suggested early intrauterine exposure to tobacco smoke products might modify neurobehavioral appetite control among offspring [15].

To assess whether smoking in pregnancy is associated with appetite control in offspring, we used data from the British 1958 longitudinal birth cohort: the National Child Development Study (NCDS).

2 Methods

2.1 Study population and data sources

The National Child Development Study (NCDS) began as a Perinatal Mortality Survey to examine the social and obstetric factors associated with stillbirth and infant mortality among the 17,000+ babies born in Great Britain from 3–9 March 1958 [3]. Details on birth were available for 17,414 (98 %) participants including medical records and interviews of mothers by midwives. Follow-up information of survivors was obtained at ages 7, 11, 16, 23, 33 and 42 years. Biases associated with sample attrition have tended to be small, although in the direction of under representing more deprived social groups over time [4]. Details of the study are reported elsewhere [4]. Some 10,557 cohort members had complete information on their mother's smoking in pregnancy and on their own appetite at age 42 years.

2.2 Measures

As part of the birth data collection sweep, midwives recorded details of the mother's cigarette smoking after the 4th month of her pregnancy. Maternal smoking during pregnancy was divided into medium (1–9 cigarettes/day), heavy (>10 cigarettes/day) and variable smokers (a balance between medium and heavy). At age 42 years computer assisted personal interviews (CAPI) were performed and cohort members were asked: 'Is your appetite poor?' Answered yes or no. This question is one item of the Malaise Inventory.

We considered the following as potential confounding factors of the association between maternal smoking during pregnancy and reported poor appetite of offspring:

- Currently smoking at age 42 years: reported in 4 categories; dichotomized (never-/exsmoker and occasional/regular smoker).
- Social class during childhood (Sweep III) based on parental occupation and coded using the Registrar General's classification; dichotomized into non-manual and manual.

- Self-reported indigestion, answered yes or no. This is another item from the Malaise Inventory at age 42 years.
- Depression: estimated from the Malaise Inventory, a 24 item scale usually dichotomized (eight positive answers or more) to identify those with the greatest tendency to depression [5]. As we used two of the items and because here tendency to depression is a potential confounding factor, the Malaise Inventory score was categorized into a series of dummy variables to provide finer-grain adjustment [11]. The score was categorized into 1–6, 7–11, 12–16 and 17–22 positive answers (the two questions on appetite and indigestion were excluded).
- BMI at age 42 years: dichotomized at 25 kg/m^2.

2.3 Statistical analysis

Crude and adjusted odds ratios and their respective confidence interval for maternal smoking with poor appetite were calculated using logistic regression analysis. All covariates significantly associated ($p < 0.05$) both with maternal smoking and having a poor appetite were considered as potential confounding factors. To avoid potential selection bias, missing values for covariates were replaced by the respective means as basic imputation procedure [16]. All potential confounding factors and independently significant ($p < 0.05$) risk factors were included in the adjusted models. All calculations were carried out with the software package SAS version 6.12.

3 Results

There were n = 5,383 (51.0 %) women and n = 5,174 (49.0 %) men with information on self reported appetite at age 42 years and maternal smoking during pregnancy. Some 3,476 (32.9 %) of their mothers said that they had been smoking during pregnancy after the 4th month.

The associations between maternal smoking during pregnancy and a number of potential risk factors for a poor appetite are shown in table I. Most of these were associated with maternal smoking during pregnancy.

Prevalences of having a poor appetite in relation to maternal smoking during pregnancy increase in the order of: non-smoking 4.5 % (4.0 %–5.0 %), medium smoking 5.6 % (4.5 %–6.8 %), variable smoking 6.8 % (4.9 %–9.1 %) and heavy smoking 7.7 % (6.3 %–9.4 %) (table II). There is a dose response with respect to the numbers of cigarettes smoked ($p < 0.001$, Cochrane-Armitage trend test). The unadjusted odds ratio for maternal smoking during pregnancy (ever/never) and having a poor appetite is 1.49 (1.25–1.77) (table III).

In the unadjusted analyses (table III) risk factors for poor appetite at age 42 years were: depression,

Table I. Associations between maternal smoking in pregnancy and potential confounding factors

Covariate	Prevalence (%) of maternal smoking in pregnancy		p-value (chi-square)
	covariate present	covariate absent	
Currently smoking (n=3.173)	37.3	31.1	<0.001 (38.4)
High social class (Registrar General's class ≤ III) (n=2.648)	23.6	36.9	<0.001 (134.5)
Male sex (n=5.174)	33.6	32.2	0.140 (2.2)
High mother's age at birth (≥30 years) (n=3.507)	34.7	32.0	<0.010 (7.4)
BMI μ25 kg/m^2 (n=5.359)	64.7	35.3	<0.001 (27.9)
Ever breastfed (n=6.521)	30.4	37.1	<0.001 (40.2)
No depression (1–6 positive answers) (n=8.903)	33.6	32.2	<0.001 (25.4)
Mild depression (7–11 positive answers) (n=1.310)	38.3	31.9	<0.010 (10.5)
Medium depression (12–16 positive answers) (n=290)	36.9	32.4	<0.001 (17.0)
Severe depression (17–22 positive answers) (n=54)	44.1	32.6	0.220 (1.5)
Low birthweight (<-1SD gestational age for sex) (n=1.303)	42.8	31.0	<0.001 (71.0)
Currently suffering from indigestion (n=1.898)	36.8	32.1	<0.001 (15.5)

Table II. Prevalence and odds ratios (95 % CI in brackets) of having a self-reported poor appetite at the age of 42 years in British adults born in 1958 (NCDS-cohort)

Mother's smoking in pregnancy	Prevalence (%) of poor appetite (95 %CI)	Odds ratios (95 %CI)
No (n=7.081)	4.5 (4.0–5.0)	1
Yes (n=3.476)	6.6 (5.8–7.4)	1.49 (1.25–1.77)
medium smoker (1–9 cigarettes/day) (n=1.631)	5.6 (4.5–6.8)	1.10 (0.87–1.38)
variable smoker (balance between med. and heavy) (n=605)	6.8 (4.9–9.1)	1.36 (0.98–1.89)
heavy smoker (>10 cigarettes/day) (n=1.240)	7.7 (6.3–9.4)	1.65 (1.31–2.07)

Table III. Crude and adjusted odds ratios for having a poor appetite

Variables	OR having a poor appetite (95 %CI)	
	crude	adjusted[c]
Maternal smoking during pregnancy	1.49 (1.25, 1.77)	1.22 (1.01, 1.48)
Currently smoking (y/n)	3.93 (3.29, 4.69)	2.90 (2.40, 3.50)
High social class	0.49 (0.38, 0.62)	0.65 (0.50, 0.85)
BMI μ25 kg/m^2	0.54 (0.45, 0.65)	0.47 (0.38, 0.57)
mild depression (7–11 positive answers)[a]	5.86 (4.78, 7.19)	4.77 (3.85, 5.90)
medium depression (12–16 positive answers)[a]	20.10 (15.29, 26.43)	14.63 (10.89, 19.64)
severe depression (17–22 positive answers)[a]	53.89 (30.84, 94.16)	33.28 (18.28, 60.59)
Currently suffering from indigestion	3.10 (2.59, 3.71)	1.82 (1.48, 2.24)
Ever breastfed[b]	0.84 (0.69, 1.02)	
Mother's age at birth (μ 30 years)[b]	0.95 (0.79, 1.14)	
Low birthweight (<-1SD gestational age for sex)[b]	1.14 (0.88, 1.48)	
Male sex[b]	1.43 (1.20, 1.71)	

[a] confounder, reference: having no depression
[b] failed to enter final logistic regression model
[c] adjusted for currently smoking, social class, BMI, depression and indigestion

currently smoking, suffering from indigestion and maternal smoking during pregnancy. Protective factors were: non-manual social class and higher BMI at the age of 42 years.

The impact of adjustment for potential confounding and independent risk factors on the association of maternal smoking during pregnancy with poor appetite is shown in table III. The most marked reduction of the odds ratio for maternal smoking with poor appetite in offspring (more than 10 % change) was observed after introduction of dummy variables for depression using the Malaise Inventory. The magnitude of the covariate effect on poor appetite was highest for the Malaise Inventory score, followed by currently smoking, BMI at the age of 42 years, suffering from indigestion and non-manual social class. Although these factors reduced the crude odds ratios considerably from 1.49 (1.25–1.77) to 1.22 (1.01–1.48) for maternal smoking during pregnancy and poor appetite, the effect remained statistically significant in the final logistic regression model and was however the weakest predictor of a poor appetite. Similar results were observed for poor appetite at the age of 23 and 33 years (data not shown). After stratification by sex and after considering only either cohort members with a score of zero for the Malaise Inventory (excluding the items for appetite and indigestion) or partici-

pants without indigestion or non smokers, the odds ratios remained in the same range (data not shown).

4 Discussion

In offspring of mothers who smoked during pregnancy a higher prevalence of having a poor appetite at the age of 42 years was observed and could not be explained by the potential confounding factors that we investigated. This finding contradicts our hypothesis that smoking in pregnancy might result in a lower prevalence of poor appetite among offspring. However, our results do suggest direct or indirect mechanisms linking maternal smoking during pregnancy and appetite in offspring.

Smoking cessation is known to be related to hunger and weight gain [7]. Since transdermal nicotine replacement after tobacco withdrawal showed a reduction of hunger and weight gain in 211 participants of a randomized trial, nicotine is supposed to be instrumental in this effect [7]. Fetal nicotine treatment has been associated with a long lasting alteration in the dopamine and serotonin neurotransmitter systems in animal models [17]. Long term mental effects of nicotine exposure in utero were observed in animal and human studies [8, 9, 13, 18]. Fetal nicotine exposure and subsequent withdrawal therefore might account for a long term lack of impulse control resulting in lower prevalences of poor appetite. This mechanism would provide a plausible mechanism for the higher prevalence of obesity among offspring of mothers who smoked in pregnancy [15].

Surprisingly, the prevalence of poor appetite was increased instead of decreased among offspring of smoking mothers participating in the National Child Development Study (NCDS).

Several possible mechanisms to account for this unexpected finding were considered. It is possible that offspring of smoking mothers compensate a lack of impulse control by substitution of nicotine via smoking and therefore report poor appetite. The data give no support for this mechanism since a higher prevalence of poor appetite among non smoking offspring of smoking mothers could be observed (data not shown).

It is possible that offspring's poor appetite might be a symptom or a surrogate for depression because the malaise inventory contains a poor appetite as depression item. Although observational studies cannot rule out residual confounding because of non randomized exposure, maternal smoking as a proxy for depression seems to be unlikely since similar results were observed in offspring of smoking mothers who did not have other positive items on the Malaise Inventory.

Another striking finding is the constancy of the effect of intrauterine tobacco exposure and a poor appetite by age. At the age of 23 and 33 years a similar prevalence of poor appetite among offspring of smoking mothers could be observed suggesting that the reporting of a poor appetite is not due to temporal circumstances. It is possible that appetite control in childhood was different from that reported in adult life and a differential influence on childhood appetite may be important in determining obesity risk.

Although the statement on poor appetite is not validated for calorific intake, its association with lower food intake of specific foods (e.g. chips; data not shown) is consistent with objective reporting of poor appetite. Additionally, a lower prevalence of a poor appetite was observed in persons with higher BMI-values assuming no misclassification due to socially accepted answers.

Adjustment after dichotomization of BMI might be an insufficient control for confounding. However, we observed similar odds ratios for adjustment by a dichotomized BMI compared to adjustment by BMI as a series of dummies (data not shown). For better intelligibility we therefore provided a dichotomized BMI in the tables. However, in the stratum of individuals with BMI values above the 3rd quartile ($\geq$ 28.2 kg/m^2) in whom the most striking effect of maternal smoking on overweight among the offspring was observed (data not shown) maternal smoking in pregnancy accounted for an adjusted odds ratio of 1.66 (1.10–2.51) for poor appetite at the age of 42 years [10]. This gives further evidence that a lack of impulse control and a possible higher appetite seems to be unlikely the mechanism producing a higher prevalence of obesity among offspring of smoking mothers.

The question on appetite was limited to a *poor* appetite, however. It is possible that some off-

spring of smoking mothers have an increased appetite. We had no ability to control for a higher appetite, although a U-shaped distribution of appetite would be surprising. Therefore other mechanisms accounting for the association between maternal smoking in pregnancy and obesity in offspring should be addressed in future studies. Associations between intrauterine tobacco products exposure, conditions in utero and glucose intolerance, diabetes have been observed suggesting a neuroendocrine metabolic dysregulation that might be accounting for the increased prevalence of obesity after intrauterine tobacco exposure [6, 10]. Maternal smoking during pregnancy may mimic fetal malnutrition, resulting in an alteration in insulin signaling that favors storage of a higher proportion of the dietary products in offspring.

A higher prevalence of poor appetite has been observed among offspring of smoking mothers and could not be explained by a number of potential confounding factors, but the data give no indication that a lower prevalence of poor appetite in those offspring could be instrumental in the observed higher prevalence of obesity. These findings are consistent with one or more effects of maternal smoking in pregnancy on neuroendocrine or metabolic dysregulation in offspring and should be investigated in future studies.

Abstract

Aims: Intrauterine exposure to tobacco smoke products has been associated with long-term neurobehavioral effects. Modified appetite control might explain the recently observed association between maternal smoking during pregnancy and obesity in offspring.
Methods: Some 10,557 British adults aged 42 years born between 3–9 March 1958 were followed up in a birth cohort study (NCDS). The main outcome measure was self-reported poor appetite at age 42 years and main exposure was maternal smoking during pregnancy.
Results: The proportion of offspring with poor appetite increased with maternal smoking during pregnancy: non-smoking 4.5 %; (4.0 %–5.0 %), medium smoking 5.6 %; (4.5 %–6.8 %), variable smoking 6.8 %; (4.9 %–9.1 %) and heavy smoking 7.7 %; (6.3 %–9.4 %). The unadjusted odds ratios for maternal smoking during pregnancy (ever/never) and poor appetite is 1.49 (1.25–1.77) and after adjustment for BMI at 42 years and other potential confounding factors it is 1.22 (1.01–1.48).
Conclusions: Offspring of mothers who smoked during pregnancy were more likely to report a poor appetite independent of a number of potential confounding factors. Although not in the expected direction, the results suggest maternal smoking during pregnancy may influence appetite perception through a developmental influence or through confounding by social factors.

Keywords: Epidemiology, logistic models, perinatal risks, pregnancy, primary prevention, smoking.

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