American Journal of Epidemiology Advance Access published June 14, 2006

American Journal of Epidemiology

DOI: 10.1093/aje/kwj209

Original Contribution

Does Maternal Smoking during Pregnancy Have a Direct Effect on Future Offspring Obesity? Evidence from a Prospective Birth Cohort Study

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Received for publication October 26, 2005; accepted for publication February 17, 2006.

The authors used a population-based birth cohort of 3,253 children (52% males) born in Brisbane, Australia, between 1981 and 1984 to prospectively examine whether maternal smoking during pregnancy was associated with offspring overweight and obesity. The authors compared mean body mass indexes (weight (kg)/height $(m)^2$) and levels of overweight and obesity at age 14 years among offspring by patterns of maternal smoking (never smoked, smoked before and/or after pregnancy but not during pregnancy, or smoked during pregnancy). Adolescent body mass index and prevalences of overweight and obesity were greater in offspring whose mothers had smoked during pregnancy than in those whose mothers had never smoked. Body mass index and levels of overweight and obesity among adolescent offspring whose mothers stopped smoking during pregnancy but smoked at other times in the child's life were similar to those among offspring whose mothers had never smoked. These results were independent of a range of potentially confounding factors and suggest a direct effect of maternal smoking during pregnancy on adolescent overweight and obesity. They provide yet another incentive for pregnant women to be persuaded not to smoke and for young women to be encouraged to never take up smoking.

body mass index; obesity; overweight; pregnancy; smoking

Abbreviation: BMI, body mass index.

The population prevalence of childhood overweight and obesity has increased approximately threefold in most industrialized countries, including Australia (1), over the past two or three decades (2). These trends are likely to have major public health consequences. Obesity tracks from childhood to adulthood, and there is emerging evidence that the precursors of diabetes and cardiovascular disease, some of which will be irreversible, already exist in obese children (1–7). In addition to the influence of dietary factors and physical activity on overweight and obesity, it is increasingly being recognized that prenatal factors influence childhood and adulthood body mass index (BMI; weight (kg)/height $(m)^2$) and obesity levels (2, 8–14).

A number of studies have implicated maternal smoking in pregnancy as an important determinant of childhood and adult obesity (15–19). However, the mechanisms underlying this association are unclear. In particular, it is unclear whether the association between maternal smoking during pregnancy and offspring obesity is an indirect effect of socioeconomic position and/or dietary factors. Female smokers are more likely to be from poorer socioeconomic backgrounds and are less likely to breastfeed their babies. Lower

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socioeconomic status and lack of breastfeeding have been found to increase a child's likelihood of becoming obese. In the general population, smokers are also more likely to have a diet that is higher in total and saturated fat (20). If mothers who smoke also follow this dietary pattern and feed their children similar high-fat foods, this could be a further indirect pathway linking maternal smoking to childhood obesity. In one small study that found a positive association between maternal smoking at 17 weeks' gestation and being obese at age 5 years, the odds ratio was reduced from 3.0 to 2.5 upon adjustment for percentage of fat intake by the mother at 33 weeks' gestation; however, a positive association remained (18). Using the same study population, Vik et al. (19) found that, in addition to elevated BMI, children of smokers also had a higher ponderal index and a greater skinfold thickness than children of nonsmokers at 5 years of age. However, no adjustment was made for childhood diet in that study. Of the further seven studies (15–19, 21–23) that evaluated the association between maternal smoking during pregnancy and later BMI, overweight, or obesity—all of which found positive associations—only two adjusted for dietary factors in the offspring; both found that associations persisted even after these adjustments (15, 16).

One way to try to disentangle whether maternal smoking during pregnancy has a direct or indirect effect on future offspring obesity is to compare the BMIs of persons whose mothers smoked during their pregnancy with both the BMIs of persons whose mothers smoked at other times (before or after pregnancy) but not during the offspring's pregnancy and the BMIs of persons whose mothers never smoked. If there is a specific direct effect of smoking during pregnancy on later development of obesity in the offspring, one would anticipate levels of obesity among persons whose mothers stopped smoking during pregnancy but smoked at other times in the child's life to be similar to levels among persons whose mothers never smoked. If the effect of maternal smoking during pregnancy were exerted primarily via indirect pathways related to socioeconomic position, diet, and the mother's general lifestyle, one might anticipate that even if a mother gave up smoking during pregnancy but was otherwise a smoker, the BMI of her offspring would be similar to that of the offspring of women who continued to smoke throughout pregnancy.

Our aim in this study was to understand the mechanisms linking maternal smoking during pregnancy to offspring overweight and obesity by comparing mean BMIs and levels of overweight and obesity at age 14 years among the offspring of mothers categorized by different patterns of smoking, using prospectively collected data.

MATERIALS AND METHODS

Participants

The Mater-University Study of Pregnancy and Its Outcomes is a prospective study of 7,223 women and their offspring. The women received antenatal care at a major public hospital in Brisbane, Australia, between 1981 and 1984 and delivered a live singleton child who was not adopted before leaving the hospital (24). Participants gave signed informed consent for their participation and that of their children. Full details on the study participants and measurements have been previously reported (24, 25). In this paper, analyses were restricted to the 3,253 mothers for whom we had prospective data on self-reported smoking status from prepregnancy to 14 years postdelivery and those offspring (52 percent males) who had attended a follow-up examination at age 14 years during which their height and weight were measured.

Outcome measurements

The main outcome in all analyses was the adolescent's BMI at the 14-year follow-up examination. In all assessments, the average of two measurements of the adolescent's weight, taken with a scale accurate to 0.2 kg while the child was lightly clothed, was used. A portable stadiometer was used to measure height. Overweight and obesity were defined according to standard definitions derived from international surveys by Cole et al. (26). For 14-year-olds, these BMI cutoffs for overweight and obesity are equivalent to the 85th and 95th percentiles of the US Centers for Disease Control and Prevention's year 2000 growth charts (27).

Measurements of exposure

Smoking status was assessed at the first clinical visit when the duration of gestation was 18 weeks, on average, and then again 3–5 days after delivery and at 6 months, 5 years, and 14 years of follow-up. On each occasion, mothers were asked to record on a questionnaire whether they smoked (yes or no). If the mothers indicated in any of the follow-ups that they smoked, they were further asked to report their frequency and quantity of tobacco use during the previous week. In addition, at the first clinical visit, women were asked about whether and how much they had smoked before they became pregnant. At 3–5 days postdelivery, mothers were asked to recall their level of smoking during the last trimester of the pregnancy.

For in utero smoking, we combined the two smoking variables from early pregnancy and the retrospective report on smoking in late pregnancy to form a binary variable: ''never smoked during pregnancy'' (response was ''no'' to the questions about smoking at the first clinical visit and smoking in the third trimester) or ''smoked during pregnancy'' (response was ''yes'' to either the question on smoking at the first clinical visit or the question on smoking in the third trimester). Initially, we grouped maternal smoking status over the 14-year follow-up period into six mutually exclusive categories: 1) never smoked; 2) smoked only before pregnancy; 3) smoked before and during pregnancy but quit sometime between the child's birth and age 14 years; 4) smoked only after pregnancy, not during or before pregnancy; 5) smoked before pregnancy and after pregnancy but not during pregnancy; and 6) smoked before, during, and after pregnancy. However, for categories 2–5, numbers were too low for meaningful analysis (table 1); therefore, in the main analysis, we grouped maternal smoking status into three mutually exclusive categories: 1) never smoked (responded ''no'' at all stages of the study); 2) smoked

TABLE 1. Prevalence of maternal smoking* over 14 years of follow-up and mean body mass index in the offspring at age 14 years, Mater-University Study of Pregnancy and Its Outcomes, Brisbane, Australia, 1981–1984

Maternal smoking status over 14 years of follow-up	No. of subjects ($n = 3,253$)	Prevalence (%)	Mean body mass index†	Standard deviation
Six categories				
Never smoked	1,676	51.5	20.4	3.7
Smoked only before pregnancy and not at any other time during follow-up	106	3.3	20.4	3.9
Smoked before and during pregnancy but stopped smoking after pregnancy	50	1.5	20.8	3.6
Smoked only after pregnancy and not before or during pregnancy	118	3.6	20.8	3.9
Smoked before pregnancy and after pregnancy but not during pregnancy	161	5.0	20.7	3.8
Smoked before, during, and after pregnancy	1,142	35.1	21.0	3.9
Three categories				
Never smoked	1,676	51.5	20.4	3.7
Smoked before and/or after pregnancy but not during pregnancy	385	11.8	20.6	3.9
Smoked during pregnancy‡	1,192	36.6	21.0	3.9

* In the mutually exclusive categories used in this study.
† Weight (kg)/height $(m)^2$.
‡ Fifty women who smoked before and during pregnancy but stopped smoking after the birth are included.

throughout pregnancy (responded ''yes'' to the question on smoking at the first clinical visit and/or ''yes'' to the question on smoking in the third trimester); and 3) smoked before and/or after pregnancy but not during pregnancy (responded ''no'' to the questions on smoking at the first clinical visit and during the third trimester but ''yes'' to questions on smoking before pregnancy and/or at any stage of follow-up).

Measurement of confounders

The following characteristics of mothers during pregnancy, reported at the first clinical visit, were considered potentially confounding factors on the basis of their potential association with maternal smoking during pregnancy and offspring obesity: maternal age, annual (gross) family income (in Australian dollars: low, ≤A$15,599; medium, A$15,600–$31,148; high, ≥A$31,149), maternal education (did not complete secondary school, completed secondary school, completed further/higher education), and marital status. The child's characteristics that were considered as potential confounders were breastfeeding (categorized into three groups: never, <4 months, ≥4 months; recorded at the 6-month follow-up), exact age (in days) at which BMI was assessed, sex, childhood intelligence, and behavior patterns. Finally, we considered the effect of childhood diet and physical activity patterns as possibly explaining any association (as discussed above). Childhood diet and physical activity data were obtained from maternal report at the 14-year follow-up. Mothers were asked to report the frequency of their child's consumption of fast food, salad, soft drinks, and red meat (all with response options of ''rarely or never,'' ''at least two or three times a week,'' and ''most days'') and to report the amount of time their child spent watching television (<1 hour/day, 1–<3 hours/day, 3–<5 hours/day, or ≥5 hours/day) and the amount of time their child spent engaging in sports or exercise (4–7 days/week or 0–3 days/week).

Statistical analyses

We examined the association between maternal smoking categorized into different mutually exclusive groups and offspring BMI (assessed as a continuous outcome and as three categories (26): normal weight, overweight, and obese). We first categorized the different patterns of maternal smoking into six mutually exclusive exposure groups and then into three mutually exclusive exposure groups (table 1). The outcomes in these exposure groups were compared by one-way analysis of variance, using an F test when the outcome was based on continuous BMI and a chi-squared test when the outcome was based on BMI categories (tables 1 and 2). Statistical evidence for a difference in effect between males and females was assessed by means of a likelihood ratio test of the interaction with sex. Since we found no statistical evidence that the effect differed between the sexes, results are presented for males and females combined.

A series of multiple linear regression models (see footnotes to table 3) was used to determine the mean difference in BMI by maternal smoking status in the three mutually exclusive categories, taking into account potentially confounding factors. Similarly, a series of multinomial regression models was used to assess the association between maternal smoking status in the same three mutually exclusive

TABLE 2. Characteristics (%*) of mothers and their adolescent offspring according to maternal smoking† during pregnancy, Mater-University Study of Pregnancy and Its Outcomes, Brisbane, Australia, 1981–1984

	No. of subjects	Maternal smoking status			*p* value‡
		Never smoked	Smoked before and/or after pregnancy but not during pregnancy	Smoked during pregnancy	
Maternal characteristics					
Mean maternal age (years) at pregnancy	3,253	26.9	24.4	24.6	<0.001
Annual (gross) family income during pregnancy§					<0.001
Low	204	4.5	7.5	8.4	
Medium	2,588	81.8	77.7	77.0	
High	164	5.9	4.4	4.1	
Missing data	297	7.9	10.4	10.5	
Mother's education					<0.001
Did not complete secondary school	514	13.1	15.9	19.7	
Completed secondary school	2,072	63.1	65.1	64.8	
Completed further/higher education	655	23.8	19.0	15.5	
Marital status during pregnancy					<0.001
Not married	591	9.1	23.1	29.3	
Married	2,660	90.9	76.9	70.7	
Breastfeeding					<0.001
Never breastfed	582	14.6	15.9	23.5	
Breastfed for <4 months	1,198	31.2	39.8	44.3	
Breastfed for ≥4 months	1,454	54.2	44.3	32.2	
Offspring characteristics (at age 14 years)					
Body mass index¶					0.005
Normal	2,423	76.9	74.8	71.1	
Overweight	628	17.5	20.5	21.4	
Obese	202	5.6	4.7	7.5	
Frequency of consumption					0.342
Fast food					
Never or rarely	802	75.6	76.4	73.5	
Most days/2 or 3 days per week	2,396	24.4	23.5	26.5	
Salad					0.001
Never or rarely	278	7.1	8.9	10.7	
2 or 3 times per week	1,401	42.3	43.1	45.6	
Daily or more often/most days	1,534	50.6	48.0	43.7	
Soft drinks					<0.001
Never or rarely	1,131	37.7	34.3	31.9	
2 or 3 days per week	1,098	35.3	36.7	31.8	
Most days	987	27.0	29.0	36.3	
Red meat					0.066
Never or rarely	213	7.5	6.7	5.4	
2 or 3 days per week	1,385	44.3	41.9	42.0	
Most days	1,614	48.2	51.4	52.7	
Engaging in sports or exercise (days/week)					0.58
0–3	1,572	49.4	46.7	48.0	
4–7	1,665	50.6	53.3	52.0	
Television watching (hours/day)					0.018
<1	269	10.0	8.6	6.0	
1–<3	859	26.3	24.9	27.7	
3–<5	893	27.7	27.0	28.1	
≥5	1,200	36.0	39.5	38.2	

* All data shown are numbers and percentages, except for mean maternal age at pregnancy.

† In the mutually exclusive categories used in this study.

‡ Three smoking categories were compared by one-way analysis of variance, using an *F* test when the outcome was a continuous assessment of body mass index and a chi-squared test when the outcome was based on body mass index categories.

§ In Australian dollars: low, ≤A$15,599; medium, A$15,600–$31,148; high, ≥A$31,149.

¶ Weight (kg)/height $(m)^2$.

TABLE 3. Difference in mean body mass index* between the adolescent (age 14 years) offspring of mothers who smoked throughout pregnancy or before or after pregnancy but not during pregnancy and the adolescent offspring of mothers who never smoked (reference category; $n = 1{,}590$), Mater-University Study of Pregnancy and Its Outcomes, Brisbane, Australia, 1981–1984

Model no.	Maternal smoking status			
	Smoked before or after pregnancy but not during pregnancy ($n = 372$)		Smoked during pregnancy ($n = 1{,}138$)	
	Mean difference	95% CI†	Mean difference	95% CI
1‡	0.22	–0.20, 0.65	0.57	0.28, 0.86
2§	0.17	–0.26, 0.60	0.56	0.27, 0.85
3¶	0.22	–0.22, 0.65	0.59	0.29, 0.89
4#	0.21	–0.22, 0.64	0.57	0.26, 0.87
5**	0.18	–0.24, 0.61	0.51	0.22, 0.80
6††	0.23	–0.20, 0.66	0.54	0.24, 0.85

* Weight (kg)/height (m)^2.
† CI, confidence interval.
‡ Unadjusted.
§ Adjusted for age and sex.
¶ Adjusted for age, sex, and socioeconomic position (income, education, maternal age, and marital status) at birth.
# Adjusted for age, sex, socioeconomic position, and breastfeeding.
** Adjusted for age, sex, maternal report of the child's consumption of fast food, salad, soft drinks, and red meat, and maternal report of the child's amount of television watching and participation in sports and exercise.
†† Adjusted for all of the potentially confounding factors mentioned above.

categories and obesity and overweight in the offspring at age 14 years.

Dealing with loss to follow-up

Participants who were lost to follow-up (did not attend the 14-year follow-up examination) were more likely to have weighed 2.5 kg or less at birth, to be male, and to have an Asian or Aboriginal/Torres Strait Islander background (all p's < 0.001). Their mothers were more likely to have been teenagers at their birth, to be less educated, to be single or cohabiting, to have three or more children, to have used tobacco and alcohol during pregnancy, and to have been anxious and depressed at their first antenatal visit (all p's < 0.001). To determine whether this affected the validity of our findings, we undertook a weighted analysis using inverse probability (of having missing outcome data) weights (28). We computed the probability weights using a logistic regression model, with the outcome being complete data versus no complete data. We assessed the influence of all other covariates used in the primary analyses on our having complete data in combination in a logistic regression model. We then used the regression coefficients from this model to determine probability weights for the covariates in the main analyses. For example, using the predictive model, if we found that the probability of nonresponse was 0.65 for a mother who did not complete secondary school, for her the inverse probability weight was 1.54.

All analyses were undertaken using Stata, version 8.0 (Stata, Inc., College Station, Texas).

RESULTS

Table 1 presents prevalences of maternal smoking over 14 years of follow-up and mean BMIs by category of smoking status. Of the 3,253 women, 36.6 percent reported smoking at some stage of pregnancy, 11.8 percent reported smoking before and/or after pregnancy but not during pregnancy, and the rest (51.5 percent) reported never smoking. There was no woman who reported smoking during pregnancy but not at any other time.

Table 2 presents maternal and child characteristics throughout the 14 years of follow-up by maternal smoking status. Mothers who smoked during pregnancy were younger, were less likely to have completed a secondary education, had a lower annual family income, and were more likely to be unmarried during pregnancy than mothers who either never smoked or smoked before and/or after pregnancy but not during pregnancy. Offspring of mothers who smoked during pregnancy, as compared with offspring of mothers who did not, were less likely to have been breastfed (for at least 4 months), consumed less salad in childhood but more soft drinks and red meat, and spent more time watching television.

Table 3 shows the mean difference in BMI at age 14 years between offspring in each smoking group and offspring in the reference group (never smoking), with adjustment for potential confounders in a series of multiple regression models. Results are presented for the 3,100 adolescents with complete data on all variables included in any of the multivariable models. In the age- and sex-adjusted model (model 2),

TABLE 4. Adjusted odds ratio for overweight and obesity at age 14 years* among offspring of mothers who smoked throughout pregnancy or smoked before or after pregnancy but not during pregnancy as compared with the offspring of mothers who never smoked (reference category; $n = 1,590$), Mater-University Study of Pregnancy and Its Outcomes, Brisbane, Australia, 1981–1984

Model no. and offspring weight status	Maternal smoking status			
	Smoked before or after pregnancy but not during pregnancy ($n = 372$)		Smoked during pregnancy ($n = 1,138$)	
	Odds ratio	95% CI†	Odds ratio	95% CI
1‡				
Overweight	1.12	0.84, 1.49	1.30	1.07, 1.58
Obese	0.84	0.50, 1.41	1.41	1.04, 1.91
2§				
Overweight	1.12	0.84, 1.49	1.31	1.08, 1.59
Obese	0.84	0.50, 1.42	1.42	1.05, 1.93
3¶				
Overweight	1.12	0.83, 1.50	1.33	1.08, 1.62
Obese	0.89	0.53, 1.52	1.46	1.06, 2.02
4#				
Overweight	1.11	0.83, 1.49	1.31	1.06, 1.60
Obese	0.89	0.52, 1.51	1.41	1.02, 1.96
5**				
Overweight	1.14	0.85, 1.52	1.29	1.06, 1.57
Obese	0.84	0.50, 1.42	1.36	1.00, 1.86
6††				
Overweight	1.14	0.85, 1.53	1.30	1.05, 1.60
Obese	0.90	0.53, 1.53	1.40	1.01, 1.94

* Body mass index (weight (kg)/height $(m)^2$) cutoffs for overweight and obesity at age 14 years were equivalent to the 85th and 95th percentiles of the Centers for Disease Control and Prevention's year 2000 growth charts (27).

† CI, confidence interval.

‡ Unadjusted.

§ Adjusted for age and sex.

¶ Adjusted for age, sex, and socioeconomic position (income, education, maternal age, and marital status) at birth.

Adjusted for age, sex, socioeconomic position, and breastfeeding.

** Adjusted for age, sex, maternal report of the child's consumption of fast food, salad, soft drinks, and red meat, and maternal report of the child's amount of television watching and participation in sports and exercise.

†† Adjusted for all of the potentially confounding factors mentioned above.

we found that the offspring of mothers who smoked during pregnancy had a BMI that was higher by 0.56 kg/m^2 (95 percent confidence interval: 0.27, 0.85), on average, than that of offspring of mothers who never smoked, whereas the BMI of offspring whose mothers smoked at any other time but not during pregnancy was the same as that of offspring of mothers who never smoked. Adjustment for covariates did not substantively alter these associations.

In the age- and sex-adjusted model, the offspring of women who smoked throughout pregnancy had increased odds of overweight (odds ratio = 1.31, 95 percent confidence interval: 1.08, 1.59) and obesity (odds ratio = 1.42, 95 percent confidence interval: 1.05, 1.93) at age 14 years (table 4, model 2). As with BMI examined as a continuous variable, adjustment for a range of potentially confounding factors, including child intelligence and behavior patterns (results not shown), did not substantially alter these associations.

When we repeated the analyses after removing the 106 women who reported smoking before the birth of their child but at no other time, the results did not differ from those presented here. Similarly, when we repeated the analyses after removing the 50 women who reported smoking during their child's pregnancy but then quitting afterward, the results were not altered. When we repeated the analyses using weights for factors that predicted nonresponse, the results did not differ from those presented here.

DISCUSSION

In this prospective follow-up study of mothers and their offspring, adolescent BMI and the prevalences of overweight and obesity were greater among offspring whose mothers had smoked during pregnancy than among offspring whose mothers had never smoked. These associations were robust after adjustment for a variety of potentially confounding factors, including childhood dietary patterns, television watching, and participation in sports and exercise. Mean BMI and the prevalences of overweight and obesity among adolescents whose mothers smoked before and/or after pregnancy but not during pregnancy were similar to these outcomes in persons whose mothers had never smoked. These findings provide some evidence for a direct effect of maternal smoking in utero on the later development of obesity in offspring.

Study limitations

The participants who did not attend the 14-year follow-up examination were more likely to be from poorer backgrounds, and their mothers were more likely to have a low level of education and to be non-White. Our results would be biased if the associations we assessed were nonexistent or pointed in the opposite direction in nonparticipants—that is, if, among nonresponders, those whose mothers smoked during pregnancy were less likely to be overweight and obese. However, since most studies find that children of mothers who smoked during pregnancy exhibit a range of poorer physical and mental health outcomes (29–31), this is unlikely. To further assess whether loss to follow-up produced bias in our results, we attached inverse probability weighting to subjects included in the analyses to restore the representation of persons lost to follow-up. We followed the method suggested by Hogan et al. (28) and used robust standard error estimates in this model. We found no difference between the weighted results and the unweighted results, which suggests that attrition is unlikely to have substantively biased our findings. We compared our estimates of overweight or obesity at age 14 years with estimates from the 1995 Australian National Nutrition Survey for a similar age category, and the results were comparable. At age 14 years, the prevalence of overweight or obesity was 25 percent in the Mater-University Study of Pregnancy and Its Outcomes and 23 percent in the National Nutrition Survey (32). The small differences are likely to be explained by regional variations, and this comparison did not suggest a major problem with selection due to loss to follow-up.

An important limitation of our study and others in this area is the use of maternal self-reports of smoking status. Since smoking throughout pregnancy has been discouraged and socially frowned upon for several decades, the most likely form of measurement error would be for some mothers who actually smoked during pregnancy to deny this and to be categorized in our study as mothers who smoked at other times but not during pregnancy. The effect of this measurement error on our results would have been to attenuate them. Thus, it is possible that the effect of smoking during pregnancy on later offspring obesity is actually greater than we have estimated here.

Because of the nature of the questions asked at the first clinic visit for women who reported smoking before pregnancy but at no other time, we had no information on when these women had stopped smoking. This group is likely to have been very heterogeneous, including women who stopped smoking years before conceiving and those who stopped at the time that they first realized they might be pregnant. There were only 106 women (3.3 percent) who fell into this category, and when we conducted a sensitivity analysis in which these women were removed, our results did not differ from those presented here. We have interpreted our results as demonstrating a specific intrauterine effect. However, because of small numbers in some categories when we tried to grade maternal smoking more finely (see table 1), we were unable to distinguish between women who smoked only before pregnancy, those who smoked both before and during pregnancy, and those who smoked before and after pregnancy but not during pregnancy. As can be seen in table 1, mean BMIs for these groups are similar, whereas a specific intrauterine effect would be supported by a mean BMI's being lower in persons whose mothers smoked only before pregnancy and also in those whose mothers smoked before and after pregnancy but not during pregnancy. When we tried to explore this further in multivariable models, the confidence intervals were very wide and the effect estimates were difficult to interpret. Much larger prospective studies with detailed data on maternal smoking across the life course would be necessary to further explore whether the intrauterine period was truly critical or sensitive for the effects of maternal smoking on later offspring obesity. What should be noted in our study is that the two largest categories were mothers who never smoked and mothers who smoked before, during, and after pregnancy, with very little evidence of women giving up smoking during pregnancy in great numbers. Given the known adverse effects of smoking on mothers' health and that of their developing offspring, these findings point towards the need for greater efforts to stop young women from taking up smoking.

Finally, while we made every effort to adjust for the child's diet and levels of physical activity in order to determine whether the effect of maternal smoking during pregnancy is direct or related to these general lifestyle factors, there is likely to have been some measurement error in the maternal reporting of these characteristics. Therefore, we cannot be certain that these factors were taken fully into account.

Comparisons with other studies and implications

This study, based on prospective follow-up of a mother-and-child cohort, extends the existing evidence on the relation between maternal smoking in pregnancy and later obesity in childhood (15–19, 21–23) to a persistence of the effect into adolescence. We added to the findings of earlier studies by being able to adjust for a greater range of potentially explanatory factors, including the child's diet and

physical activity levels, and by being able to compare the offspring of mothers who smoked during pregnancy with the offspring of both never smokers and persons who smoked at other times before or after pregnancy but not during pregnancy. Our findings provide stronger evidence than was obtained from previous studies that there is a direct effect of in-utero exposure to tobacco on future obesity risk. However, it is impossible to prove causality from observational studies, and other explanations for our findings are possible. For example, it is plausible that women who stop smoking during pregnancy but then start to smoke again later in life are more health-conscious (particularly with respect to their child's health) than women who continue to smoke both throughout pregnancy and afterwards. This somewhat greater level of health consciousness may then be reflected in the food these women feed to their children and other lifestyle factors that would affect their children's BMIs. In our study, adjustment for maternal reporting of children's diet and physical activity did not substantively alter the association, but we cannot rule out residual confounding. While it would not be possible to randomize pregnant mothers to smoke or not smoke in order to determine whether there was a true causal effect, one could carry out follow-up studies of the many randomized trials that have evaluated smoking cessation counseling provided during pregnancy. Long-term follow-up of the offspring of mothers who participated in trials that found an effective means of reducing smoking during pregnancy would provide valuable evidence in this area.

Since there are as many as 4,000 chemicals in cigarette smoke (33, 34), it is difficult to determine the precise mechanism through which maternal smoking may result in increased offspring obesity. A recent study of rats found that fetal and early neonatal exposure to nicotine resulted in accelerated postnatal weight gain and increased visceral adiposity, as well as increased adiposity around the rat's vasculature (35). The authors concluded that nicotine may be the main chemical driver of the association between maternal smoking during pregnancy and offspring obesity seen in human studies, though they did not assess the effects of other chemicals found in cigarettes. Other work has also implicated nicotine, which may affect levels of neurotransmitters and, via this effect on the in-utero development of hypothalamic function, exert an impact on appetite control throughout the life course (36–38). Studies using well-designed animal models would be useful to further examine the likelihood that this is a causal relation and to explore the impact of other chemicals in cigarettes and other possible mechanisms. Understanding these mechanisms might provide insights into appetite control and the development of obesity.

In conclusion, using longitudinal analysis of a mother-and-offspring cohort, we found that the adolescent offspring of mothers who reported having smoked during pregnancy were more likely to be overweight and obese than those whose mothers did not smoke during pregnancy. Our findings suggest a direct effect of maternal smoking in pregnancy on adolescent overweight and obesity. They provide yet another incentive for pregnant women to be persuaded not to smoke and for young women to be encouraged to never take up smoking.

ACKNOWLEDGMENTS

This work was funded by the National Health and Medical Research Council (NHMRC) of Australia (grant 252834) and was carried out at the University of Queensland and the Mater Hospital (Brisbane, Australia). The core study was funded by the NHMRC and the Telstra Foundation. Dr. Debbie A. Lawlor was supported by a (United Kingdom) Department of Health Career Scientist Award.

The authors thank Greg Shuttlewood of the University of Queensland for help with data management.

The views expressed in this paper are those of the authors and not necessarily those of any funding body.

Conflict of interest: none declared.

REFERENCES

1. Lazarus R, Wake M, Hesketh K, et al. Change in body mass index in Australian primary school children, 1985–1997. Int J Obes Relat Metab Disord 2000;24:679–84.
2. Ebbeling CB, Pawlak DB, Ludwig DS. Childhood obesity: public-health crisis, common sense cure. Lancet 2002;360: 473–82.
3. Ferguson MA, Gutin B, Owens S, et al. Fat distribution and hemostatic measures in obese children. Am J Clin Nutr 1998; 67:1136–40.
4. Ford ES, Galuska DA, Gillespie C, et al. C-reactive protein and body mass index in children: findings from the Third National Health and Nutrition Examination Survey, 1988–1994. J Pediatr 2001;138:486–92.
5. Freedman DS, Dietz WH, Srinivasan SR, et al. The relation of overweight to cardiovascular risk factors among children and adolescents: The Bogalusa Heart Study. Pediatrics 1999; 103:1175–82.
6. Tounian P, Aggoun Y, Dubern B, et al. Presence of increased stiffness of the common carotid artery and endothelial dysfunction in severely obese children: a prospective study. Lancet 2001;358:1400–4.
7. Srinivasan SR, Myers L, Berenson GS. Predictability of childhood adiposity and insulin for developing insulin resistance syndrome (syndrome X) in young adulthood: The Bogalusa Heart Study. Diabetes 2002;51:204–9.
8. Lobstein T, Baur L, Uauy R. Obesity in children and young people: a crisis in public health. Obes Rev 2004;5(suppl 1): 4–85.
9. Daniels SR, Arnell DK, Eckel RH, et al. Overweight in children and adolescents: pathophysiology, consequences, prevention, and treatment. Circulation 2005;111:1999–2012.
10. Oken E, Gillman MW. Fetal origins of obesity. Obes Res 2003;11:496–506.
11. Levin BE, Govek E. Gestational obesity accentuates obesity in obesity-prone progeny. Am J Physiol 1998;275: R1374–9.
12. Levin BE. The obesity epidemic: metabolic imprinting on genetically susceptible neural circuits. Obes Res 2000;8: 342–7.
13. Freinkel N. Of pregnancy and progeny. Diabetes 1980;29: 1023–35.
14. Whitaker R, Dietz WH. Role of the prenatal environment in the development of obesity. J Pediatr 1998;132:768–76.
15. Power C, Jefferis BJ. Fetal environment and subsequent obesity: a study of maternal smoking. Int J Epidemiol 2002;31: 420–1.

16. von Kries R, Toschke AM, Koletzko B, et al. Maternal smoking during pregnancy and childhood obesity. Am J Epidemiol 2002;156:954–61.
17. Toschke AM, Montgomery SM, Pfeiffer U, et al. Early intrauterine exposure to tobacco-inhaled products and obesity. Am J Epidemiol 2003;158:1068–74.
18. Wideroe M, Vik T, Jacobsen G, et al. Does maternal smoking during pregnancy cause childhood overweight? Paediatr Perinat Epidemiol 2003;17:171–9.
19. Vik T, Jacobsen G, Vatten L, et al. Pre- and post-natal growth in children of women who smoked in pregnancy. Early Hum Dev 1996;45:245–55.
20. Dallongeville J, Marecaux N, Fruchart JC, et al. Cigarette smoking is associated with unhealthy patterns of nutrient intake: a meta-analysis. J Nutr 1998;128:1450–7.
21. Fried PA, Watkinson B, Gray R. Growth from birth to early adolescence in offspring prenatally exposed to cigarettes and marijuana. Neurotoxicol Teratol 1999;21:513–25.
22. Blake KV, Gurrin LC, Evand SF, et al. Maternal cigarette smoking during pregnancy, low birth weight and subsequent blood pressure in early childhood. Early Hum Dev 2000;57:137–47.
23. Williams S, Poulton R. Twins and maternal smoking: ordeals for the fetal origins hypothesis? A cohort study. BMJ 1999; 318:897–900.
24. Keeping JD, Najman JM, Morrison J, et al. A prospective longitudinal study of social, psychological and obstetric factors in pregnancy: response rates and demographic characteristics of the 8556 respondents. Br J Obstet Gynaecol 1989; 96:289–97.
25. Lawlor D, Najman JM, Sterne J, et al. Associations of parental, birth and early life characteristics with systolic blood pressure at age 5: findings from the Mater-University Study of Pregnancy and Its Outcomes. Circulation 2004;110:2417–23.
26. Cole TJ, Bellizzi MC, Flegal KM, et al. Establishing a standard definition for child overweight and obesity worldwide: international survey. BMJ 2000;320:1240–3.
27. Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, et al. CDC growth charts: United States. (Advance data from vital and health statistics, no. 314). Hyattsville, MD: National Center for Health Statistics, 2000.
28. Hogan JW, Roy J, Korkontzelou C. Handling drop-out in longitudinal studies. Stat Med 2004;23:1455–97.
29. Lawlor DA, Bor W, O'Callaghan MJ, et al. Intrauterine growth and intelligence within sibling pairs: findings from the Mater-University Study of Pregnancy and Its Outcomes. J Epidemiol Community Health 2005;59:279–82.
30. Stathis SL, O'Callaghan DM, Williams GM, et al. Maternal cigarette smoking during pregnancy is an independent predictor for symptoms of middle ear disease at five years' postdelivery. Pediatrics 1999;104:301–7.
31. Williams GM, O'Callaghan M, Najman JM, et al. Maternal cigarette smoking and child psychiatric morbidity: a longitudinal study. Pediatrics 1998;102:e11. (Electronic article).
32. McLennan W, Podger A. National Nutrition Survey: nutrient intakes and physical measurements, Australia, 1995. Canberra, Australia: Australian Bureau of Statistics, 1998. (Catalogue no. 4805.0).
33. Swauger JE, Steichen TJ, Murphy TA, et al. An analysis of the mainstream smoke chemistry of samples of the U.S. cigarette market acquired between 1995 and 2000. Regul Toxicol Pharmacol 2002;35:142–56.
34. Rustemeier K, Stabbert R, Haussmann HJ, et al. Evaluation of the potential effects of ingredients added to cigarettes. Part 2: chemical composition of mainstream smoke. Food Chem Toxicol 2002;40:93–104.
35. Gao YL, Holloway AC, Zeng Z, et al. Prenatal exposure to nicotine causes postnatal obesity and altered perivascular adipose tissue function. Obes Res 2005;13:687–92.
36. Kane JK, Parker SL, Matta SG, et al. Nicotine up-regulates expression of orexin and its receptors in rat brain. Endocrinology 2000;141:3623–9.
37. Li MD, Kane JK, Parker SL, et al. Nicotine administration enhances NPY expression in the rat hypothalamus. Brain Res 2000;867:157–64.
38. Slotkin TA. Fetal nicotine or cocaine exposure: which one is worse? J Pharmacol Exp Ther 1998;285:931–45.