



## Early Intrauterine Exposure to Tobacco-inhaled Products and Obesity

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An association between maternal smoking during pregnancy and offspring obesity has been reported. This study assessed the impact of maternal smoking during the first trimester. Data on 4,974 German children aged 5–6 years were obtained at school entry health examinations in 2001–2002 in Bavaria. Obesity was defined by body mass index using International Obesity Task Force cutpoints. Prevalence of obesity was 1.9% (95% confidence interval (CI): 1.5, 2.4) in offspring of never smokers, 4.5% (95% CI: 2.9, 6.7) for maternal smoking during the first trimester only, and 5.9% (95% CI: 3.8, 8.7) for maternal smoking throughout pregnancy. Unadjusted odds ratios were higher for maternal smoking throughout pregnancy (odds ratio = 3.23, 95% CI: 2.00, 5.21) compared with the first trimester only (odds ratio = 2.41, 95% CI: 1.49, 3.91). Adjusted odds ratios were similar: 1.70 (95% CI: 1.02, 2.87) for maternal smoking throughout pregnancy and 2.22 (95% CI: 1.33, 3.69) for maternal smoking in the first trimester only. When modeled together, no statistically significant difference in obesity risk was found between maternal smoking in the first trimester compared with throughout pregnancy. The effect of intrauterine tobacco exposure on childhood obesity may depend largely on cigarette smoking during the first trimester, whereas the additional impact of smoking throughout pregnancy might be due to confounding by sociodemographics. Women should be encouraged to quit smoking prior to conception.

body weight; growth; metabolism; nutrition disorders; obesity; pregnancy

Among children, the prevalence of overweight and obesity is increasing worldwide (1, 2). Although several intervention programs are available, long-lasting success has rarely been observed (3). Therefore, effective prevention remains a major challenge, and underlying mechanisms still have to be identified. Several recent studies have reported an association between maternal smoking during pregnancy and offspring obesity (4–7). Surprisingly, in one of these studies, a similar effect was observed in the offspring of mothers who smoked before but not throughout pregnancy (6). We hypothesized that many of these mothers smoked in the early course of pregnancy but stopped thereafter.

Therefore, we designed a cross-sectional study enrolling 4,974 German children in Bavaria to investigate whether maternal smoking during only the first trimester of pregnancy is associated with obesity among offspring. We also explored whether smoking in pregnancy beyond the first trimester further increases the risk of an offspring's obesity.

## MATERIALS AND METHODS

### Study population and data sources

In six Bavarian communities of Germany, 8,741 parents were invited to participate in a self-completion questionnaire study associated with their child's obligatory school entry examination from September 2001 to August 2002. Parents received questionnaires and were invited to participate in the study when they were notified about the health examination. Some 7,026 (80 percent) completed questionnaires were returned at the health examinations. Information was obtained on maternal smoking in different time periods and on a wide range of potential obesity-related confounding factors. Data were linked with children's anthropometric measures collected during the examination. Stature and weight were measured in light clothing without shoes.

The analysis was confined to German children (477 exclusions) aged at least 5 years but less than 7 years (234 exclusions) and for whom there was full information on maternal smoking (212 exclusions), potential confounding factors

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(breastfeeding: 212 exclusions, parental education: 296 exclusions, parental obesity: 361 exclusions, watching television: 90 exclusions, playing electronic games: 70 exclusions, physical activity: 193 exclusions, and infant weight gain: 609 exclusions), and anthropometric measures (355 exclusions; multiple reasons for exclusion were possible). After exclusions, data for 2,360 girls and 2,614 boys (total  $n = 4,974$ ) were available for analysis.

## Measures

Overweight and obesity were defined according to sex- and age-specific cutpoints for body mass index (weight in kilograms divided by height in meters squared) proposed by the International Obesity Task Force (8) that are equivalent to the widely used cutpoints of 25 and 30 for adult overweight and obesity, respectively.

The questionnaire was self-administered. Questions on maternal smoking in categories of none, 1–9, 10–20, and >20 cigarettes daily differentiated between 1) smoking 3 months before pregnancy; 2) smoking until pregnancy diagnosis; 3) smoking until, but not beyond, the 12th gestational week (after the last menstrual period); 4) persistent smoking from the 12th gestational week until birth; 5) smoking during the child's first year of life; and 6) smoking at the time of the child's school entry health examination.

Mothers indicating nonsmoking during every interval were categorized as never smoking and were considered the reference group. Smoking during the first trimester but not later in the pregnancy was defined by smoking at time 1 and 2 and/or 3 but not at time 4. Smoking throughout pregnancy was defined by smoking at times 1–4, whereas smoking only after pregnancy was considered nonsmoking at times 1–4 but smoking at time 5 or 6.

The following variables were considered potential confounding factors for the association between maternal smoking during pregnancy and childhood overweight/obesity:

- Parental education: highest level attained by either parent, ordinal number, five levels (self-reported by parents) (9)
- Parental obesity: metric self-reporting, height in centimeters and weight in 0.1-kg increments (10, 11)
- Single parenthood: dichotomous (yes/no) (self-reported by parents) (12)
- Population density at region of residence: taken from the statistical yearbook according to region of the respective public health office (9)
- Birth weight (9): continuous measure (grams) from well-baby checkup book measurements; the well-baby checkup includes nine recommended examinations by a pediatrician from birth until 5 years of age (free of charge) and always contains measured length and weight, which are documented in the well-baby-checkup booklets
- High infant weight gain: difference between birth weight and weight at well-baby checkup at 1 year (13, 14)
- Watching television or playing video games: daily number of hours at school entry (self-reported by parents) (15, 16)

- Physical activity at school entry: reported by parents according to the Child Behavior Checklist (CBCL), four categories (17)
- Breastfeeding: categories of none,  $\leq 1$  month, and  $> 1$  month (18)

## Statistical analysis

The prevalence of overweight and obesity associated with maternal smoking was calculated. Crude and adjusted odds ratios and their respective 95 percent confidence limits for maternal smoking and overweight/obesity were calculated by using logistic regression analysis. All covariates associated ( $p < 0.2$  (19)) with both maternal smoking and overweight/obesity were considered as potential confounders. Confounding was defined by at least a 10 percent change in the odds ratio for overweight/obesity associated with maternal smoking after adding the potential confounding factor to the model. Multicollinearity between maternal smoking and covariates or among covariates was assumed if the absolute value of the respective coefficients exceeded 0.4 (Pearson's correlation coefficient, Spearman correlation coefficient, or Pearson's contingency coefficient, as appropriate). A number of possible interactions (parental education, child's sex, parental obesity, breastfeeding) with maternal smoking and their influence on offspring obesity were considered ( $p < 0.2$ ). In multiple logistic regression analysis, all potential confounding and independent risk factors ( $p < 0.05$ ) were included, and they were modeled in their ordinal or continuous forms or were coded by using binary dummy variables (breastfeeding) to reduce residual confounding (20). Forward selection was used to create the final regression model.

All calculations were carried out with the software package SAS, version 8.2 (SAS Institute, Inc., Cary, North Carolina).

## RESULTS

Some 3,564 mothers reported never smoking and 1,028 smoked prior to pregnancy, of whom 406 smoked throughout pregnancy. Of those mothers who smoked before pregnancy, 109 had already stopped, when pregnancy was diagnosed (mean, 7.5 weeks since the last menstrual period; 74 mothers restarted smoking during any period). There were 513 mothers who had smoked during the first trimester (at least until pregnancy was diagnosed or at maximum until the 12th week). A total of 223 mothers had not smoked before or during pregnancy but started smoking afterward.

The focus of our study was to assess the impact on obesity in offspring of smoking during the first trimester only, smoking throughout pregnancy, and starting to smoke after pregnancy. Other patterns of smoking would have been interesting, such as starting to smoke in the first trimester ( $n = 55$ ), starting to smoke in the second and/or third trimester ( $n = 3$ ), and smoking before pregnancy only ( $n = 35$ ). However, these subgroups contained too few observations for meaningful analysis.

We found that the prevalence of overweight and obesity in offspring was significantly increased if the mother smoked

**TABLE 1. Prevalences of overweight, obesity, and several potential confounders with respect to time period of fetal tobacco exposure, Bavaria, Germany, 2001–2002†**

	Time period of maternal smoking‡							
	Never (n = 3,564)		Early pregnancy (n = 513)		Throughout pregnancy (n = 406)		After pregnancy (n = 223)	
	% with covariate present	95% CI§	% with covariate present	95% CI	% with covariate present	95% CI	% with covariate present	95% CI
<i>Outcome</i>								
Overweight in offspring	9.2	8.3, 10.2	14.4***	11.5, 17.8	15.8***	12.4, 19.7	11.2	7.4, 16.1
Obesity in offspring	1.9	1.5, 2.4	4.5***	2.9, 6.7	5.9***	3.8, 8.7	4.5*	2.2, 8.1
<i>Covariate</i>								
Birth weight ≤10th percentile at the respective week of gestation (46)	7.0	6.2, 7.9	9.0	6.6, 11.8	15.0***	11.7, 18.9	10.3	6.7, 15.1
Prematurity (<37th week of gestation)	4.7	4.1, 5.5	5.1	3.3, 7.3	8.9***	6.3, 12.1	6.7	3.8, 10.9
Breastfeeding for ≤1 month	16.5	15.3, 17.8	14.8	11.9, 18.2	21.7**	17.8, 26.0	17.0	12.3, 22.6
Breastfeeding for >1 month	63.6	62.0, 65.2	54.8***	50.4, 59.1	27.1***	22.8, 31.7	51.1*	44.4, 57.9
Watching television ≥1 hour daily	32.9	31.4, 34.5	43.9***	39.5, 48.3	58.4***	53.4, 63.2	44.4***	37.8, 51.2
Playing electronic games occasionally	38.4	36.8, 40.0	40.2	35.9, 44.5	46.3***	41.4, 51.3	42.6**	36.0, 49.4
High educational level (≥10 years)	75.2	73.8, 76.6	70.0*	65.8, 73.9	48.3***	43.3, 53.3	64.1***	57.5, 70.4
Body mass index of ≥30 kg/m <sup>2</sup> in either parent	13.1	12.0, 14.2	13.5	10.6, 16.7	18.5**	14.8, 22.6	20.2***	15.1, 26.1
Single parenthood¶	5.8	5.0, 6.6	13.8***	11.0, 17.1	22.7***	18.7, 27.0	19.3***	14.3, 25.1
Infant weight gain of >7.5 kg in the first year of life	12.0	11.0, 13.1	12.9	10.1, 16.9	18.0***	14.4, 22.1	15.7	11.2, 21.1
Physical activity (never or sometimes lethargic vs. often lethargic)	21.5	20.2, 22.8	20.7	17.2, 24.4	26.6*	22.4, 31.2	21.1	15.9, 27.0
Population density of >500 inhabitants/km <sup>2</sup>	13.8	12.7, 15.0	14.4	11.5, 17.8	16.7	13.2, 20.7	12.6	8.5, 17.6

\*  $p < 0.05$ ; \*\*  $p < 0.01$ ; \*\*\*  $p < 0.001$ .

† In crude analysis, covariates were dichotomized to improve understanding.

‡ Reference group: offspring of never-smoking mothers.

§ CI, confidence interval.

¶ For 2.1% of the children in the study population, information on living in intact families or with a single parent was missing.

during the first trimester only or throughout pregnancy (table 1) compared with offspring of never-smoking mothers. Maternal smoking throughout pregnancy was associated with a low educational level, a lower prevalence of breastfeeding, and an increased prevalence of parental obesity, low birth weight, prematurity, single parenthood, high infant weight gain, and watching television/playing electronic games (table 1). On the other hand, smoking during the first trimester only was only associated with a lower educational level, less breastfeeding, and single parenthood (table 1).

Parental obesity was most strongly associated with offspring obesity, followed by high infant weight gain, little physical activity, and watching television. Breastfeeding and high educational level were most strongly associated with protection against obesity (table 2). None of the interaction terms (parental education, child's sex, parental obesity, or breastfeeding with maternal smoking) was significantly associated with overweight/obesity. Birth weight was not considered for adjustment because of potential multicollinearity with high infant weight gain (Pearson's correlation coefficient, >0.4) as well as eating snacks while watching television (Pearson's contingency coefficient, >0.4 with watching television).

Maternal smoking throughout pregnancy accounted for higher unadjusted odds ratios for offspring obesity compared

with maternal smoking during the first trimester only. However, after adjustment for breastfeeding and educational level, the odds ratios for obesity associated with smoking during the first trimester only and in later pregnancy were almost identical (table 3). The final regression model adjusted for breastfeeding, educational level, parental obesity, watching television, playing electronic games, physical activity, and high infant weight gain.

Stratification by offspring sex did not change the results (data not shown). Adjustment for the same confounders used in the final model (table 3) resulted in an odds ratio of 1.03 (95 percent confidence interval: 0.65, 1.61) for maternal smoking only *after* pregnancy and overweight among offspring. The association of maternal smoking only after pregnancy with offspring obesity is not reported here because there were too few observations ( $n = 10$  obese children of mothers who started smoking after pregnancy).

To further examine differences in the associations of maternal smoking during the first trimester only and throughout pregnancy with risk of obesity and overweight, we compared both exposures in the same logistic regression model in which smoking throughout pregnancy was considered the reference. The adjusted odds ratio for offspring overweight associated with mothers who smoked only during the first trimester compared with mothers who

**TABLE 2. Unadjusted odds ratios for the association between possible confounders and overweight/obesity in offspring, Bavaria, Germany, 2001–2002\***

Variable	% overweight	95% CI†	% obesity	95% CI
Birth weight ≤10th percentile at the respective week of gestation (46)	0.74	0.44, 1.25	0.69	0.25, 1.88
Prematurity (<37th week of gestation)	0.91	0.61, 1.39	1.19	0.60, 2.37
Breastfeeding for ≤1 month	1.09	0.86, 1.38	1.02	0.66, 1.59
Breastfeeding for >1 month	0.65	0.54, 0.77	0.47	0.34, 0.66
Watching television ≥1 hour daily	1.94	1.63, 2.33	3.11	2.21, 4.39
Playing electronic games occasionally	1.13	0.95, 1.36	0.97	0.69, 1.35
High educational level (≥10 years)	0.67	0.55, 0.80	0.52	0.37, 0.72
Body mass index of ≥30 kg/m <sup>2</sup> in either parent	2.85	2.30, 3.50	5.20	3.71, 7.29
Single parenthood	1.41	1.06, 1.86	1.22	0.72, 2.08
Infant weight gain of >7.5 kg in the first year of life	3.17	2.57, 3.92	3.92	2.76, 5.56
Physical activity (never or sometimes lethargic vs. often lethargic)	2.16	1.78, 2.62	3.59	2.58, 5.01
Population density of >500 inhabitants/km <sup>2</sup>	1.07	0.83, 1.38	0.91	0.51, 1.48

\* In crude analysis, covariates were dichotomized to improve understanding.  
 † CI, confidence interval.

smoked throughout pregnancy was 1.10 (95 percent confidence interval: 0.75, 1.59). The adjusted odds ratio for offspring obesity associated with maternal smoking during the first trimester compared with throughout pregnancy was 1.03 (95 percent confidence interval: 0.56, 1.91). This analysis revealed no statistically significant difference in the associations with overweight and obesity for maternal smoking only during the first trimester of pregnancy compared with smoking throughout pregnancy, although the odds ratios were slightly (nonstatistically significantly) greater for smoking during the first trimester only.

**DISCUSSION**

These data suggest that intrauterine exposures associated with maternal-inhaled tobacco products increase the risk of

childhood overweight or obesity in offspring, which is consistent with earlier research. Maternal smoking during the first trimester of pregnancy was associated with an increased risk of obesity and overweight in offspring, which could not be explained by a wide range of potential confounding factors. Our analysis also suggests that, after adjustment for breastfeeding and other potential confounding factors, continuing to smoke beyond the first trimester may not independently further increase an offspring’s obesity risk.

The results of our study are in accordance with those from other studies regarding the direction and strength of observed effects for obesity risks. As in other studies, low educational level (9, 21), high weight gain (13, 14), high birth weight (9), parental obesity (10, 11), and watching television and playing electronic games (15, 16) were associated

**TABLE 3. Crude and adjusted odds ratios\* for maternal smoking early in pregnancy only vs. throughout pregnancy, Bavaria, Germany, 2001–2002†**

	Maternal smoking in early pregnancy				Maternal smoking throughout pregnancy			
	Overweight		Obesity		Overweight		Obesity	
	Odds ratio	95% CI‡	Odds ratio	95% CI	Odds ratio	95% CI	Odds ratio	95% CI
Maternal smoking in early pregnancy (unadjusted)	1.66	1.27, 2.18	2.41	1.49, 3.91	1.85	1.38, 2.47	3.23	2.00, 5.21
Adjusted for								
Breastfeeding§	1.59	1.21, 2.09	2.22	1.37, 3.61	1.62	1.20, 2.19	2.49	1.50, 4.11
+ educational level	1.56	1.19, 2.06	2.16	1.33, 3.52	1.50	1.10, 2.03	2.14	1.29, 3.55
+ parental obesity	1.58	1.20, 2.09	2.17	1.32, 3.56	1.47	1.08, 2.01	2.09	1.24, 3.51
+ watching television, playing electronic games occasionally, physical activity, high infant weight gain	1.52	1.14, 2.01	2.22	1.33, 3.69	1.23	0.89, 1.70	1.70	1.02, 2.87

\* All odds ratios are for the association of maternal smoking during pregnancy with overweight and obesity in offspring; they were successively adjusted for the cumulative influence of the variables listed.

† All potential confounding and independent risk factors were modeled in their ordinal or continuous forms.

‡ CI, confidence interval.

§ Maternal smoking throughout pregnancy: confounder (accounted for more than a 10% change in estimate).

with childhood obesity, whereas physical activity (17, 22) and breastfeeding (18, 23–25) were apparently protective.

The aim of this study was to assess the association of maternal smoking with childhood obesity and to differentiate the effects of smoking only during the first trimester from those of smoking throughout pregnancy. Under-reporting of smoking in pregnancy could be important. Results from other studies suggest that self-reported smoking is accurate in general (26), although number of cigarettes per day may be biased toward round numbers (particularly 20 cigarettes per day) (27). Since we compared smoking with nonsmoking, this factor was unlikely an issue here.

In our study, 20.7 percent of mothers said they had smoked at the beginning of pregnancy compared with 18.6 percent in Sweden in 1999 (28). Nondifferential denial of smoking during any period would result in classification of smokers as never smokers (reference group) and thus in bias toward unity. Since low educational level was associated with obesity (9), denial of any smoking during pregnancy by highly educated mothers could result in spurious increased odds ratios for maternal smoking, and stratification by parental education would result in different odds ratios by strata. This difference could not be observed (data not shown). If mothers who claimed to have stopped smoking during pregnancy continued to smoke throughout pregnancy, this difference should be reflected in lower birth weights; the risk of low birth weight and prematurity is determined mainly by smoking during the last trimester (29, 30). The observed rates of low birth weight among offspring of mothers who smoked only during the first trimester (9.0 percent) were almost identical to those for nonsmokers (7.0 percent) but were higher for those who smoked throughout pregnancy (15.0 percent). This finding indicated that the self-reported smoking data were broadly accurate.

Other potential sources of bias include confounding by parental obesity. We observed that obese mothers were more likely to smoke during pregnancy. It is also known that obese mothers often have obese partners (31), which could result in selection of genetic mechanisms that increase obesity risk for their children. Since adjustment for parental obesity could not explain the association between intrauterine tobacco exposure and obesity, a genetic explanation is unlikely. Selection bias by restriction to children for whom there was complete information on potential confounders seems unlikely since additional analysis in which multiple imputation was used resulted in similar adjusted odds ratios (data not shown).

Some biologic mechanisms might explain the observed association between smoking early in pregnancy and childhood obesity. Smoking during the first trimester could mimic fetal malnutrition because of reduced food intake by the mother or reduced blood supply because of vasoconstrictive effects on maternal and uteroplacental vasculature (32). Thus, smoking would be a surrogate for hunger in the first trimester, which accounted for higher proportions of obese offspring in the Dutch Famine Study (33, 34). Nutritional deprivation may affect differentiation of hypothalamic centers regulating food intake, growth, and number of filled adipocytes (35). Additionally, agents of inhaled tobacco

might have a potentiating effect on hypothalamic structures, resulting in impaired insulin signaling and metabolism. Some animal and human studies indicate an effect of intra-uterine nicotine exposure on neurobehavioral impulse control (36–40).

Breastfeeding was the most important confounding factor in our study and was responsible for the most marked reduction in risk estimates for maternal smoking throughout pregnancy and offspring obesity. This finding might be due to insufficient milk production by smokers (41–43), although other studies suggest psychological rather than physiologic reasons for lower breastfeeding rates among maternal smokers (44). Since the interaction of breastfeeding with maternal smoking was not significantly associated with offspring obesity ( $p > 0.6$  for both outcomes (overweight and obesity) and two different exposures (smoking during the first trimester only and smoking throughout pregnancy)), breastfeeding appears to be a confounder rather than an effect modifier. Therefore, some of the association of maternal smoking in *later* pregnancy might be due to a deficit in breastfeeding as well as to other associated characteristics.

We hypothesize that maternal smoking during the first trimester of pregnancy versus in later pregnancy has a more profound influence on the risk of obesity in offspring because of neuroendocrine or other metabolic dysregulation. We suggest that the apparently greater influence of smoking in later pregnancy is largely due to confounding, such that children of mothers who smoke throughout pregnancy are more likely to accumulate further risks for obesity not caused directly by maternal smoking during pregnancy. We demonstrated this possibility in our analysis described in table 3 and by comparing, in the same logistic regression model, smoking during the first trimester only with smoking throughout pregnancy regarding risk of overweight or obesity. The statistically significantly raised odds ratios for obesity and overweight in offspring associated with maternal smoking during the first trimester of pregnancy were only marginally affected by multiple adjustment for other risks associated with obesity. In contrast, the odds ratios associated with smoking throughout pregnancy were notably reduced by adjustment for the other obesity risks. This finding is consistent with the hypothesis that smoking during the first trimester of pregnancy has a direct metabolic effect on offspring, while smoking in later pregnancy is a marker of familial cultural and material circumstances that influence obesity risk through other mechanisms.

Smoking throughout pregnancy might even dilute the effect of smoking during the first trimester. Smoking-related fetal malnutrition may have an influence similar to nutritional deprivation during the last trimester of pregnancy observed in the Dutch Famine Study, which was associated with a *decreased* risk of obesity (45).

The effects of confounding (that may vary with time of exposure) and the potentially contradictory influences of smoking during early and late pregnancy are likely to result in inconsistent associations of smoking during pregnancy with offspring obesity. To disentangle these various influences, research into this subject should identify the period during pregnancy when the mother smoked and should quan-

tify the potential confounding influences of breastfeeding and other exposures that occur after birth.

The observed association of early fetal-tobacco-related exposure with subsequent obesity underlines the importance of advising women on smoking cessation in contexts such as gynecology and obstetric outpatient clinics. Similar to folic acid supplementation, smoking cessation is another challenge that, to encourage a successful outcome, must be addressed prior to conception. Women of reproductive age should be advised to stop smoking before attempting to become pregnant, because cessation after pregnancy diagnosis may be too late to protect their offspring from potential obesity and the associated risks.

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