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Is low birth weight in the causal pathway of the association between maternal smoking in pregnancy and higher BMI in the offspring?

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Abstract

Introduction: A number of cross-sectional and prospective studies suggested a priming effect of maternal smoking in pregnancy on offspring's obesity. It has been hypothesized that this association might be explained by low birth weight and subsequent catch-up growth in the causal pathway. We therefore examined the role of birth weight in children exposed vs. not exposed to cigarette smoking *in utero* on later body mass index (BMI).

Methods: Using data of 12,383 children and adolescents (3-17 years of age) recorded in a German population-based survey (KiGGS), we assessed mean body mass index standard deviation scores (BMI-SDS) in different birth weight SDS categories, stratified for children with smoking and non-smoking mothers. We calculated spline regression models with BMI-SDS as outcome variable, cubic splines of birth weight SDS, and potential confounding factors.

Results: Children whose mothers had been smoking during pregnancy had lower birth weight SDS and higher BMI-SDS at interview compared to children of non-smoking mothers. However, we observed a linear association between birth weight SDS and BMI-SDS in crude analyses for both groups. Similarly, almost linear effects were observed in adjusted spline regression analyses, except for children with very low birth weight. The respective 95% confidence bands did not preclude a linear effect for the whole birth weight SDS distribution.

Discussion: Our findings suggest that low birth weight is unlikely to be the main cause for the association between intrauterine nicotine exposure and higher BMI in later life. Alternative mechanisms, such as alterations in the noradrenergic system or increased food efficiency, have to be considered.

Introduction

A number of cross-sectional and prospective studies have suggested a priming effect of maternal smoking in pregnancy on offspring's overweight (1-12). Although the epidemiological evidence for this association is consistent, the underlying mechanisms remain largely unknown.

Low birth weight is another well-established adverse effect of maternal smoking in pregnancy (13-15)**.** Infants with low birth weight are known to catch up their weight and to a smaller extent their height deficit within the first two years of life (16, 17). Catch-up growth has also been established and confirmed in meta-analyses as an important risk factor for overweight and the metabolic syndrome later in life (18).

Therefore, it appears possible that low birth weight and subsequent catch-up growth might explain the association between intrauterine nicotine exposure and childhood overweight. However, in most studies birth weight was considered as a linear confounding variable (1, 3, 5-7, 9-12) despite an assumed J-shaped relationship between birth weight and later overweight (19).

In order to examine the role of birth weight for the association of maternal smoking in pregnancy and offspring's overweight explicitly, we used spline regression methods to assess potential non-linear effects of birth weight on later body composition, analysing data from a large German population-based survey on children and adolescents.

Methods

Subjects and data

The data were collected from May 2003 to May 2006 in the German Health Interview and Examination Survey for Children and Adolescents (KiGGS), a representative nation-wide survey on children and adolescents selected within 167 communities (primary sample points). In a second step, addresses of families were drawn randomly from local registries to invite the children to participate in the survey. The study was approved by the Institutional Review Board of the Virchow-Klinikum of the Humboldt-University Berlin. A detailed description of the survey has been published elsewhere (20, 21). Overall, n = 17,641 children aged 0 to 17 years were enrolled.

Information on covariates and life style factors was obtained from self-administered questionnaires from parents and also from the children themselves (in children aged 11 years and older). For non-German families with poor command of the German language, questionnaires in their native languages were provided. Maternal smoking in pregnancy was documented in three categories (never, occasionally or regularly) and dichotomised to never or any. Maternal body mass index (BMI) was calculated from self-reported height and weight at interview. Maternal age was recorded in years. Children were classified as having a migration background either if they were immigrated from another country and at least one of their parents was not born in Germany, or if both parents were immigrants or were of non-German nationality (22). Socioeconomic status (SES) was classified based on the parents' professional status, income and educational achievements and assigned to low, middle or high according to the parent with the higher status, with about ¼ of the children and adolescents falling into the lowest category (23, 24). Breastfeeding (yes/no) refers to any breastfeeding of the index child as reported by the mothers. The child's TV viewing time per day was recorded separately for working days and weekends in the following categories (ordinal value in brackets): none (1), 0.5 hours (2), 1-2 hours (3), 3-4 hours (4), >4 hours (5). We summed the values of working days and weekend TV viewing time up and defined high TV viewing time as a summary score of ≥ 7. For questions related to their pregnancy, e. g. concerning birth weight or gestational age at birth, parents were encouraged to consult their "maternity pass". In Germany, every pregnant woman receives this booklet for complete documentation of antenatal care visits and is advised to keep it for possible subsequent pregnancies for likewise documentation.

Children's height was measured, without wearing shoes, by trained staff with an accuracy of 0.1 cm, using a portable Harpenden stadiometer (Holtain Ltd., Crymych, UK). Body weight was measured with an accuracy of 0.1 kg, wearing underwear, with a calibrated electronic scale (SECA, Birmingham, UK). These measures were used to calculate children's BMI. To adjust children's BMI for sex and age, we transformed the observed BMI values to sex- and age-specific standard deviation scores (SDS) established by the World Health Organisation (WHO) (25, 26) using the LMS method (27).

Likewise, we calculated sex- and gestational age-specific SDS values for birth weight (recorded in grams) based on German reference percentiles (28, 29). Preterm birth was defined by gestational age < 37 weeks if gestational age was reported or if parents reported premature birth otherwise.

We excluded 2,805 children aged 0 to 2 years, since BMI measurements do not allow for an appropriate definition of overweight in this age group. Further 355 children not living with their biological mother were excluded as were 705 children with missing values on BMI-SDS or birth weight and 145 children for whom information about maternal smoking during pregnancy was missing. Since children of smoking mothers are more likely to be born prematurely, and premature birth and the associated illnesses during the first few weeks of life might influence the relationship between birth weight and BMI in childhood, we further excluded preterm children from our analyses. Restriction to term born children (1,248 further exclusions) yielded a final dataset of n=12,383 observations. If gestational age at birth was unknown but term birth was reported (n=1,505; 12.2 %), a gestational age of 39 weeks was assumed corresponding to the mean gestational age in German term births (30).

Statistical analysis

Unadjusted mean values of BMI-SDS were estimated for different birth weight SDS categories (< -2, -1.5 to -1, -1 to -0.5, -0.5 to 0, 0 to 0.5, 0.5 to 1, 1 to 1.5, 1.5 to 2 and >2) and stratified by pregnancy smoking status of their mothers. To examine potentially differential effects by child's age (and by potential differences in maternal recall of smoking habits during pregnancy after time), a further stratification by four age groups (3-6 years, 7-10 years, 11-13 years and 14-17 years) was carried out in a supplementary analysis.

To adjust for potential confounders, we calculated spline regression models (31, 32) on the whole dataset. We considered BMI-SDS as outcome variable, birth weight SDS as continuous explanatory variable, maternal smoking during pregnancy as a binary explanatory variable, and maternal BMI, maternal age at birth of the index child (both continuous), high TV viewing time (as a proxy for low physical activity), migration background, exclusive formula-feeding and low parental SES (all dichotomous) as potential confounding factors. To assess potential non-linear effects, birth weight SDS was modelled by cubic splines with three degrees of freedom (df), since the respective regression model showed a slightly superior fit to models with one or two df, as determined by the Akaike Information Criterion (33). Again, we stratified for maternal smoking in pregnancy (thus without this variable as predictor in the respective models). This approach allowed us to quantify and visualize potentially different effects in children whose mothers smoked or did not smoke during pregnancy. Additionally, we stratified for offspring's sex in order to address potential sex-specific effect modifications.

In a sensitivity analysis, we further adjusted for child's age (modelled by cubic splines with three df). The rationale for these supplementary analyses was to preclude potential age-specific confounding effects which might arise if the BMI-SDS values derived from external reference values would not be in accordance with the BMI development in German children. In a further sensitivity analysis, we used regular (instead of any) smoking during pregnancy as explanatory and stratifying variable, respectively.

All calculations were carried out with R 2.9.0 (http://cran.r-project.org). All analyses were done with weighted estimates based on weights accounting for the two-staged sample design. We included only observations with full information about all covariates into the regression analyses (complete case analysis). Cluster effects within the sample points were considered negligible and were not incorporated in the analysis.

Results

The mean BMI-SDS of the subjects analysed was 0.32, indicating that these children and adolescents had slightly higher BMI values compared to the population on which the WHO z-scores had been calculated. Children whose mothers had been smoking during pregnancy had lower birth weight SDS values, but higher BMI-SDS values at interview compared to children of non-smoking mothers (table 1). Due to the sample design, children's age was rather equally distributed, with a mean age of 10.8 years in the children analysed. Maternal smoking during pregnancy was positively associated with low parental SES, high TV viewing time, exclusive formula-feeding, a lower maternal age at birth of the index child and a slightly increased maternal BMI. Each binary-coded potential risk factor for overweight except migration background had a prevalence of <25 % in children of non-smoking mothers and of <50 % in children of smoking mothers.

For both groups an unadjusted linear association between birth weight SDS and BMI-SDS was observed (figure 1). However, the mean BMI-SDS values of children whose mothers had smoked during pregnancy were above the upper limits of the 95% BMI-SDS confidence intervals of non-smoking mothers in any birth weight SDS interval. Similar patterns were observed in all age groups considered (data not shown).

In adjusted regression analyses, maternal smoking during pregnancy was associated with a mean increase of 0.31 [95% CI: 0.25, 0.36] in BMI-SDS independent of effects of the considered confounders, including non-linear effects of birth weight SDS (table 2). Figure 2 shows predicted BMI-SDS values by birth weight SDS (conditional for the effects of the confounding factors), indicating an almost monotonous association between these two variables in the adjusted analyses except for a slight inverse effect in birth weight SDS values below -

2. However, the implemented boxplot indicated that the proportion of observations with very low birth weight was small (< 5 %), with predicted BMI-SDS values of <0 for this subgroup. The respective 95% confidence bands did not exclude a linear effect for the whole birth weight SDS distribution. Similar findings were observed in the subgroups of children of both smoking and non-smoking mothers (figure 2). Further analyses did not yield evidence for effect modification by offspring's sex (supplementary figure).

The results of the spline regression models were almost identical if child's age was added as a potential confounder in sensitivity analyses, and if regular smoking was used as explanatory or stratifying variable (data not shown).

Discussion

While confirming the well known association between maternal smoking in pregnancy and body composition in childhood / adolescence, we did not detect evidence for low birth weight being in its causal pathway: Maternal smoking in pregnancy was strongly associated with higher offspring's BMI independent of potential non-linear effects of birth weight in our data. We observed an almost monotonous association between birth weight and later BMI in children of both smoking and non-smoking mothers, excluding a decisive role of low birth weight in determining obesity in children of smoking mothers.

Our crude analyses suggest a rather linear association between birth weight and BMI-SDS in children of both smoking and non-smoking mothers. This association may be somewhat stronger in children of smoking mothers, but the confidence limits in the smoking group – especially at higher birth weight values – were too wide to draw final conclusions on that. However, the primary finding from these analyses was that we consistently observed a higher BMI-SDS in children of smoking mothers compared to children of non-smoking mothers, irrespective of their birth weight. If low birth weight was the main cause for obesity in children of smoking mothers, one would rather expect to find higher BMI-SDS values in children with low birth weight, irrespective of the smoking status of their mother (but a higher proportion of children of smoking mothers falling into the low birth weight category).

This interpretation is in keeping with our findings from adjusted analyses: Only for children with birth weight SDS values below -2, an inverse relation between birth weight and later BMI appeared possible from our data. An SDS value of -2 represents the 3rd percentile of the reference distribution, corresponding with birth weights of 2690 g or less in males and 2570 g or less in females born in the 39th week of gestation (28). It is unlikely, though, that the association between maternal smoking in pregnancy and offspring obesity can mainly be explained by a small effect which affects less than 5 % of a population. Furthermore, the respective predicted BMI-SDS values were <0, therefore not indicating an increased risk for overweight in this subgroup compared to the mean population.

These findings are in accordance with results from a recent study from our study group, which had suggested that overweight in children exposed to tobacco smoking in utero was apparently not mediated through foetal growth retardation (34). However, this study was limited by the fact that it was based on data from 1986-88 with a relatively small sample size (n=561). We are aware of only one further study examining the type of relationship between birth weight and overweight in childhood in the context of pregnancy smoking. In this study, four categories of birth weight were analysed alongside pregnancy smoking and other factors as potential predictors of overweight at 4.5 years (35). The authors concluded that low birth weight was not in the causal pathway of maternal smoking in pregnancy and offspring's overweight. Interestingly, crude analyses for all children (irrespective of maternal smoking status) showed that, compared to the reference category (3000-4000 g), a lower risk for overweight occurred in the second-lowest (2500-2999 g), but not in the lowest birth weight category (<2500 g), which is in accordance with our findings.

In addition, other studies on overweight in children and adults showed that the association of maternal smoking in pregnancy and offspring's overweight in adulthood was robust to adjustment for offspring's birth weight (1, 5, 6, 9). Also, results from the Dutch famine study suggested that persons whose mothers had been exposed to famine during their pregnancy were more likely to be overweight in later life, irrespective of their birth weight (36).

Other recent studies, however, have suggested a role of (low) birth weight in the pathway of the association of intrauterine nicotine exposure and later overweight (4, 7, 8, 37). Based on our data, a potential role of low birth weight for offspring's later overweight is not confined to children of smoking mothers: Although birth weight was slightly shifted towards lower values in children of smoking mothers, the mostly linear association between birth weight and later BMI was maintained.

A study on Sprague-Dawley rats suggested differential effects of intrauterine nicotine exposure by sex (38). There is, however, only scarce epidemiological evidence for this assumption. While two studies suggested that

potential effects might be stronger in male children (39, 40), others showed similar odds ratios for overweight and obesity in male and female offspring (5, 41). The results from the latter studies are well in accordance with those from our previous study (34) and the present one, in neither of which we found indications of sex-specific effect modifications.

Interestingly, our main results remained virtually unchanged when we examined the effects of regular smoking during pregnancy. However, these findings should not be overinterpreted, since the mothers in our study did not get a reference point for what would be considered as "occasional" or "regular" smoking (e. g. in terms of cigarettes per day) when they filled out their questionnaires. It is also possible that regularly smoking mothers might have been inclined to underreport their smoking as occasional, thus blurring the difference between "regular" and "occasional".

The validity of most of the variables considered in this study is likely to be high. Children's BMI was calculated from weight and height measured by trained staff. Parents were encouraged to consult their "maternity passes" when answering the questions on gestational age and weight at birth. Recall of smoking habits has been reported to yield valid results in general (42), but the validity of self-reported smoking in pregnancy – which was also the standard method of smoking assessment in other studies (1, 3-15) - is doubtful, since the number of smoking mothers might be underestimated (43). However, we do not feel that this limitation should have caused substantial bias to the main results of our study: If a number of mothers who smoked during pregnancy were misclassified as non-smokers, the effect size of smoking on BMI-SDS might even have been underestimated in the overall analyses. In stratified analyses, a small overestimation of the potential effect of very low birth weight might have occurred in children of non-smoking mothers. However, the findings in smoking mothers are unlikely to have been biased, since it appears unrealistic that any non-smoking mother was classified as a smoking mother. It may appear debatable whether our findings (and, consequently, those of most previous epidemiological studies on this topic) may have been biased by mothers who did not smoke during their pregnancy but lived together with a smoking partner, thus exposing the fetus to nicotine in a supposedly unexposed pregnancy. Unfortunately, we were not able to examine this potential limitation, because there was no information available on paternal smoking during pregnancy in our data. However, we showed recently that the effect of maternal smoking during pregnancy could only partially be explained by paternal smoking (44).

It may be argued that we examined effects on mean BMI-SDS and generalized them with respect to overweight or obesity. Since the effects of a number of risk factors for obesity appear to be stronger on the upper parts of the BMI distribution as recently shown (45), use of the mean BMI is a conservative approach in assessing the effects of maternal smoking on offspring's overweight.

It might further be argued that our findings might at least partly be due to psychosocial characteristics associated with smoking in pregnancy. For example, we observed that maternal smoking during pregnancy was positively associated with all other risk factors for childhood overweight in the data analysed. However, our adjusted regression analyses revealed that the effect of smoking on offspring's body composition was independent of these risk factors, and a recent review concluded that confounding is less likely to be a major issue (4). Furthermore, a comprehensive analysis of risk factors for obesity in the KiGGS study, including physical activity and diet, indicated that smoking during pregnancy is indeed an independent risk factor (2). Biological explanations should therefore also be taken into account.

Animal studies helping to disentangle the biological mechanism of intrauterine tobacco exposure and later obesity are based on nicotine exposure (46). Studies in rodents with a follow-up for at least 10 postnatal weeks reported emergence of higher body weight exposed to nicotine *in utero* compared to controls (38, 47, 48). In two of these studies (38, 47), mean birth weights were not different between offspring exposed and not exposed. Although some differences do exist between the pregnancies of rodents and humans, these findings suggest that low birth weight does not appear to be a necessary precursor for higher weights in offspring exposed to nicotine *in utero*.

Growth in late pregnancy is likely to affect mainly birth weight while early pregnancy was supposed to be instrumental in the association of fetal tobacco exposure and later obesity (10). Since offspring with intrauterine tobacco exposure were reported to have deficits in impulse control or control of food consumption, we have previously postulated that the mechanism underlying might purely affect appetite behaviour due to alterations of the cholinergic and catecholaminergic neurotransmitter systems (49) that have been linked to learning deficits or the brain's reward system (50). We therefore had postulated that fetal nicotine exposure may result in persistent deficits in impulse control and possible decreased control of food consumption (9, 11).

Surprisingly a poor rather than an increased appetite was observed after fetal nicotine exposure in rats and in 42 year old adults in the 1970 British Cohort Study (51, 52). Other mechanisms seem to be likely involved such as a higher food efficiency or lower physical activity. Indeed, in rodents disruptions in the mesoaccumbens dopaminergic pathway, a decreased thermogenesis or a decreased sympathetic responsiveness resulting in

hypoactivity of the noradrenergic system was observed after fetal nicotine exposure or prenatal nicotinic overload (53-55).

A higher food efficiency after intrauterine nicotine exposure might be another possible mechanism since fetal nicotine exposure was associated with increased epididymal, mesenteric and perirenal fat pad weights in rodents at 26 weeks (47), hypertriglyceraemia in 7 weeks old Wistar rats (48), enhanced PPAR-γ gene expression (also in vitro) (56) or an increased adipocyte differentiation in Sprague-Dawley (51).

In summary, it appears unlikely from our findings that the consistently observed increased risk for low birth weight – via subsequent catch-up growth – is the main cause of the higher overweight prevalence in offspring of mothers smoking during their pregnancy.

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Conflict of interest

The authors had no conflicts of interest.

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Table 1. Study characteristics of the data analyzed (n=12,383). Two-sided p-values for comparison of non-smoking and smoking mothers (during pregnancy) are based on two-sample t-tests or Fisher's exact test as appropriate.

		Non-smoking mothers (n=10,335)	**Smoking mothers (n=2,048)**	**p-value**
		Mean (SD)	**Mean (SD)**	
Birth weight [g]		3,467 (472)	3,318 (500)	<0.01
Birth weight SDS		-0.07 (1.08)	-0.41 (1.16)	<0.01
Child's BMI at interview [kg/m²]		18.7 (3.8)	19.5 (4.5)	<0.01
Child's BMI-SDS		0.28 (1.11)	0.59 (1.22)	<0.01
Maternal BMI [kg/m²]*		24.5 (4.7)	24.8 (4.8)	<0.05
Maternal age at birth of the index child [years]*		28.6 (4.8)	27.2 (5.3)	<0.01
		n (%)	**n (%)**	
Male children		5,251 (50.8 %)	1,016 (49.6 %)	0.33
Low parental social status*		2,231 (21.6 %)	953 (46.5 %)	<0.01
Exclusive formula-feeding*		1,731 (16.7 %)	765 (37.4 %)	<0.01
High TV viewing time*		2,429 (23.5 %)	772 (37.7 %)	<0.01
Migration background*		1,791 (16.5 %)	253 (17.1 %)	0.58
Child's age	3-6 years	2,724 (26.4 %)	580 (28.3 %)	---
	7-10 years	2,944 (28.5 %)	607 (29.6 %)	---
	11-13 years	2,148 (20.8 %)	415 (20.3 %)	---
	14-17 years	2,519 (24.4 %)	446 (21.8 %)	---

* Number (proportion) of missing values: maternal BMI: n=128 (1.0 %), maternal age: n=47 (0.4 %), parental social status: n=43 (0.3 %), formula-feeding: n=82 (0.7 %), TV viewing time: n=308 (2.5 %), migration background: n=34 (0.3 %)

Figure 1. Point estimates and 95% confidence limits of mean BMI-SDS by categories of birth weight SDS (< -2, -2 to -1.5, ...), stratified for children with mothers smoking or not smoking in pregnancy (age: 3-17 years).

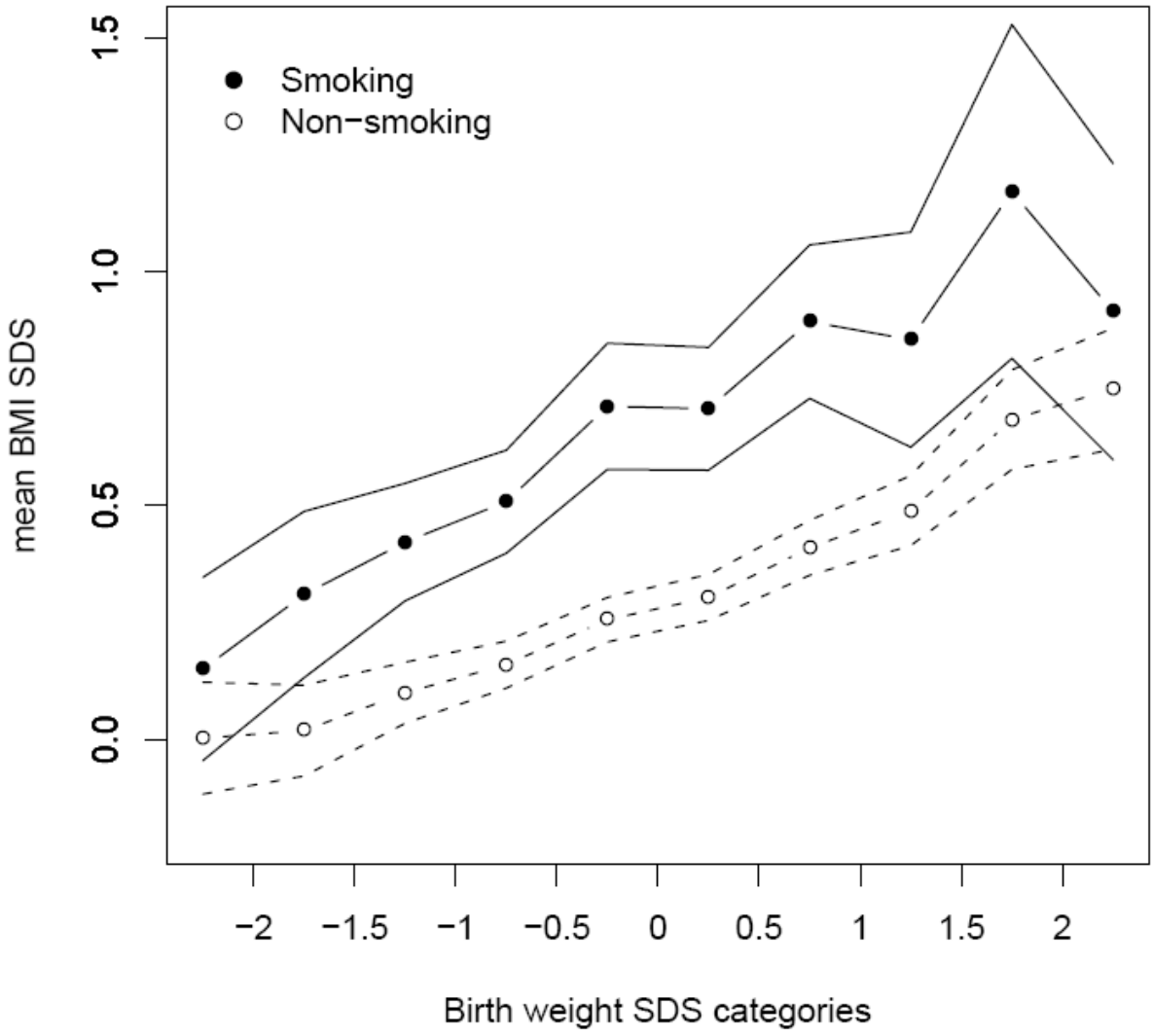


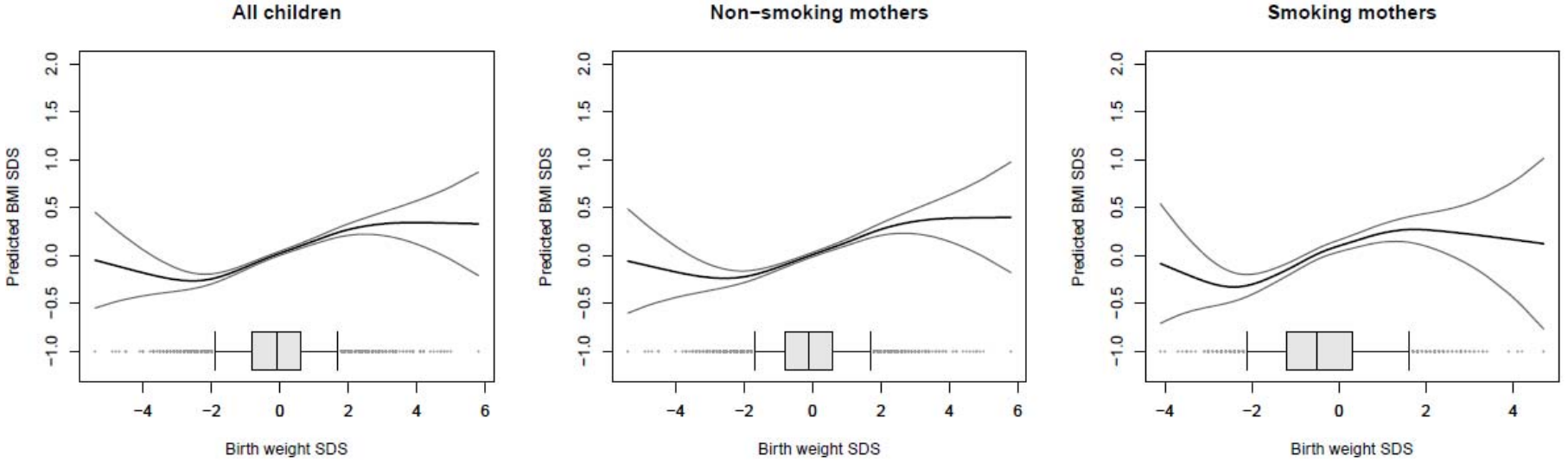
Table 2. Regression coefficients [95 % confidence intervals] of predictors for child's BMI-SDS (age: 3-17 years, n=11,788).

Predictor variable	**Effect estimate**
Maternal smoking in pregnancy	0.31 [0.25, 0.36]
Birth weight SDS (per additional unit)	0.12 [0.11, 0.14] *
High TV viewing time	0.15 [0.11, 0.20]
Exclusive formula-feeding	0.02 [-0.03, 0.07]
Low parental social status	0.09 [0.04, 0.14]
Migration background	0.09 [0.03, 0.15]
Maternal BMI (per additional kg/m²)	0.06 [0.05, 0.06]
Maternal age at birth of the index child (per year)	0.00 [0.00, 0.00]**

* modelled using cubic splines

** $p>0.05$

Figure 2. Conditional predicted values of BMI-SDS (at 3-17 years) plotted against birth weight SDS in regression models of all children, children of mothers who did not smoke and who smoked during pregnancy, respectively. Models were adjusted for high TV viewing time, breastfeeding, low parental socioeconomic status, migration background, maternal BMI, maternal age at birth of the index child and maternal smoking in pregnancy (if appropriate). The dark grey lines represent pointwise 95% confidence bands. Boxplots of birth weight SDS are depicted at the bottom of each plot (box = 25th to 75th percentile, whiskers = 5th to 95th percentile, points = outliers).



Supplementary figure. Conditional predicted values of BMI-SDS (at 3-17 years) plotted against birth weight SDS in regression models stratified by maternal smoking during pregnancy and offspring's sex. Models were adjusted for high TV viewing time, breastfeeding, low parental socioeconomic status, migration background, maternal BMI, maternal age at birth of the index child and maternal smoking in pregnancy (if appropriate). The dark grey lines represent pointwise 95% confidence bands. Boxplots of birth weight SDS are depicted at the bottom of each plot (box = 25th to 75th percentile, whiskers = 5th to 95th percentile, points = outliers).