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Low and High Birth Weight and the Risk of Child Attention Problems

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Objective To study the prospective association between birth weight and attention problems and to explore the role of maternal body mass index (BMI) in this association.

Study design In 6015 children of a population-based cohort (Rotterdam, The Netherlands, 2001-2005), information on birth weight was collected and gestational age-adjusted SDS were calculated. At age 6 years, parents assessed attention problems with the Child Behavior Checklist. We used linear regression to study the association of birth weight with attention problem score and examined the modification of this association by maternal early pregnancy BMI.

Results The observed association between birth weight and attention problem score was curvilinear (adjusted β per birth weight SDS^2: 0.02, 95% CI 0.00; 0.03, $P = .008$); the turning point equals 3.6 kg at term. In analyses of the extreme tails of the birth weight distribution, the associations with attention problem score disappeared after adjustment for socioeconomic confounders. Maternal early pregnancy BMI moderated the association of child birth weight with attention problem score (P interaction = .007, with curvilinear term in model).

Conclusions Higher birth weight was related to less attention problems but from a birth weight of about 3.6 kg or more, a higher birth weight did not reduce the risk of attention problems any further. However, in children of obese mothers (BMI >30 kg/m^2), high birth weight may increase the risk of attention problems. *(J Pediatr 2015;166:862-9)*.

Low birth weight has been linked to depression, anxiety,[1] and schizophrenia,[2,3] and in particular to childhood attention deficit hyperactivity disorder (ADHD).[4] Children with low birth weight are at a greater risk of symptoms of inattention and to a lesser extend at risk of hyperactivity/impulsivity.[5,6]

A full understanding of the association between birth weight and ADHD symptoms has been hampered by several limitations. First, with a few exceptions, previous studies have focused on the lower end of the birth weight distribution. Children with a very low birth weight (<1.5 kg) or moderately low birth weight (<2.5 kg) were repeatedly reported to have an increased risk of ADHD symptoms.[4] Some studies have suggested nonlinear associations between birth weight and cognitive and behavioral functioning,[7,8] but a relation between the entire range of birth weight and ADHD symptoms is not well established. Studies that modeled birth weight as a continuous exposure include investigations of Linnet et al, Schlotz et al, Hultman et al, and Kelly et al.[9-12] Whereas these studies observed an inverse relationship between birth weight and risk of ADHD symptoms or ADHD diagnosis, Lahti et al[13] did not observe an association.

Second, since these studies were conducted, the population distribution of birth weight has changed. Over the last decades, a rise in median birth weight was observed.[14] It has been suggested that the increase in birth weight is explained by, among other factors, higher maternal body mass index (BMI) and altered smoking patterns.[15] However, studies have not investigated the association between the continuum of child birth weight and ADHD symptoms in children born in the last 2 decades.

We postulated that because of time trends in mother's weight the relationship between child birth weight and attention problems may have changed. In a large population-based cohort, we addressed the following aims. First, we investigated the linear association between birth weight and Child Behavior Checklist (CBCL/1.5-5) attention problem score at age 6 years and also determined if the association between birth weight and attention problem score at age 6 years is curvilinear. In addition to this aim, we studied the associations between low and high birth weight with attention problem score. We also examined the role of maternal early pregnancy BMI in these associations. We tested whether maternal early pregnancy BMI precedes high child birth weight and accounts for its association with ADHD using a mediation analyses. In addition, we tested whether the association between child birth weight and attention

ADHD	Attention deficit hyperactivity disorder
BMI	Body mass index
CBCL	Child Behavior Checklist

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problems is moderated by maternal early pregnancy BMI by using an interaction model. We hypothesized that low and very high birth weights confer a higher risk of attention problems than average birth weight. No hypothesis for the effect of maternal early pregnancy BMI on this association was formulated.

Methods

This analysis was embedded in the Generation R Study, an ongoing population-based birth cohort from fetal life onward.[16] All pregnant women were enrolled between 2001 and 2005 in Rotterdam, The Netherlands. Assessments during pregnancy and childhood comprised physical examinations, ultrasonography, biological sampling, and parental questionnaires. The study was approved by the Medical Ethical Committee of the Erasmus Medical Center in Rotterdam. Written consent was obtained from all participating women.

In total, 8301 mother-child pairs participated in the postnatal phase of the Generation R study. As depicted in the flow chart of the study population (**Figure 1**; available at www.jpeds.com) of 8009 mothers who gave birth to singleton live-born children, information on child weight and gestational age at birth was available. Twin pregnancies (n = 200) were excluded because growth potentials for individual fetuses in multiple pregnancies are not comparable with singleton pregnancies. Parents of 6015 children (75%) provided behavioral data of the child at age 6 years by completing the CBCL/1.5-5. In 5448 mother-child pairs, information on birth weight, maternal early pregnancy BMI, and attention problem score was available.

To estimate gestational age, crown-rump length (until a gestational age of 12 weeks and 5 days), or biparietal diameter (from 12 weeks and 5 days onward), measured by fetal ultrasound examination, as previously described,[17] were used. Inter- and intraobserver intraclass correlation coefficients were all >0.98.[17] Information on birth weight of the child was obtained from community midwifery and hospital registries. Birth weight was established directly postpartum and expressed in kilograms (kg).

To disentangle the effects of birth weight from gestational age, we express birth weight in units adjusted for gestational age and sex (ie, birth weight SDS). The birth weight SDS were constructed based on distributions in the Generation R cohort.[18]

We measured attention problem score of the child at 6 (range 4.9-8.0) years of age by using the attention problems subscale of the CBCL/1.5-5. The CBCL is a parent-report questionnaire that contains 99 problem items rated on a 3-point scale: 0 (not true), 1 (somewhat or sometimes true), and 2 (very true or often true). By summing the raw scores, seven syndrome scales, including the continuous attention problems scale, consisting of 5 items, can be computed (Cronbach alpha 0.70). Higher scores represent higher severity of problems. For the CBCL good reliability and validity have been reported.[19]

Maternal Anthropometrics

In early pregnancy (median gestational age 14.4 weeks, IQR 12.5-17.8), maternal height and weight were measured without shoes and heavy clothing. BMI (kg/m^2) was calculated using weight (kg) and height (cm) in 5448 women. Throughout the article, we refer to this variable as 'early pregnancy BMI'. The correlation between early pregnancy BMI and prepregnancy BMI (n = 4619) obtained by questionnaire in early pregnancy was very good (Pearson correlation 0.95 [$P < .001$]).

Covariates

Possible confounders of the association between birth weight and attention problem score were derived from the literature.[20,21] Child sex, Apgar score, mode of delivery, presence of gestational diabetes, and pre-eclampsia were derived from medical records completed by midwives and gynecologists. At enrollment (median gestational age 14.7 weeks, SD 3.6) we obtained information on maternal age, national origin, educational level, parity, prenatal smoking, alcohol use, and folic acid supplementation by questionnaire. National origin of the mother was based on the country of birth of the parents. Educational level of the pregnant woman was assessed by the highest completed education and categorized as primary school only, secondary school, or higher education. Maternal prenatal smoking and alcohol use were classified as 'no use,' 'use until pregnancy was confirmed,' and 'continued use during pregnancy.' Folic acid supplementation was classified as 'no use,' 'use started during the first 10 weeks of pregnancy,' or 'use started preconceptional.' At 20 weeks pregnancy, we measured maternal psychological symptoms using the Brief Symptom Inventory.[22] In this study, the total sum scale of maternal psychological symptoms was tested as a confounder, as maternal psychopathology may affect both fetal growth and may independently be related to child behavioral problems. Moreover, as this study is based on parent report information on attention problems, maternal psychological symptoms may influence the report. All analyses were also adjusted for age at attention problem assessment.

Statistical Analyses

Attention problems were studied as a continuous outcome using linear regression models. To approximate a normal distribution, the CBCL attention problem scale is square-root transformed. In the first step of our analyses, we studied whether birth weight of the child was linearly related to attention problem score at age 6 years in our population. Second, we explored a curvilinear association with attention problem score by adding a squared term of birth weight to the model. Third, we investigated low birth weight (as defined by <10th and <20th percentile SDS) and high birth weight (as defined by >90th and >80th percentile SDS) in relation to attention problems. We report the results of the 10% and 20% extremes on both ends of the birth weight distribution to test whether results depended on any choice of cut-off. We defined low and high birth weight based on population-specific percentiles rather than using predefined cut-off points derived from other settings with different birth weight distributions.

Next, we examined whether the association between maternal early pregnancy BMI and child attention problem score was mediated by child birth weight. Toward this aim, we tested whether maternal early pregnancy BMI was associated with child birth weight as previously reported among 6959 mothers and their children, in the current study population. Subsequently, we studied the association between maternal early pregnancy BMI and attention problem score. The Preacher and Hayes bootstrapping procedure[23] was followed to assess formally whether an indirect or mediation effect of child birth weight was present. This procedure involves taking 5000 random samples from the obtained data, sampling with replacement, and calculating the indirect effect for each sample by multiplying the coefficient for the a-path (determinant to potential mediator association) by the coefficient of the b-path (potential mediator to outcome association). CIs were obtained using the SPSS macro developed by Preacher and Hayes. In the current analysis, child attention problem score was entered as the dependent variable, maternal early pregnancy BMI was entered as the independent variable, and child birth weight (SDS^2) as the mediator. Emerging perspectives pose that assessing mediation does not require the presence of a direct or total association between determinant and outcome.[24]

Finally, we tested whether maternal early pregnancy BMI moderated the association between child birth weight and attention problem score by adding an interaction term of birth weight and maternal early pregnancy BMI (both linear terms) to the model. We followed the approach by Ganzach[25] and kept the linear and curvilinear term of birth weight in the model. This approach ensures that the model correctly indicates whether an interactive relationship is present and describes the correctly modeled relation between the independent variables (eg, offsetting or synergistic).

Children born to mothers with diabetes have an elevated risk for adverse development, owing to hyperglycemia and other associated intrauterine factors.[26] Moreover, high maternal weight is associated with a substantially higher risk of gestational diabetes.[27] Therefore, we further explored the role of maternal gestational diabetes on child attention problem score.

In all these analyses, we carefully evaluated socioeconomic factors and pregnancy characteristics. Model 1 is adjusted for child sex and age at attention problem assessment. In model 2, we adjust for child sex, age at assessment of attention problems, Apgar score 1 minute after birth, mode of delivery, maternal age, educational level, parity, psychological symptoms, smoking, alcohol use, and folic acid supplementation, gestational diabetes, and pre-eclampsia. Model 3 is comparable with model 2 but includes additional controls for child birth weight (SDS). Model 4 is comparable with model 2 but does not include gestational diabetes as an additional covariate. As the CBCL attention problem scale remained skewed after transformation, we also present the results of analyses of the association between birth weight and attention problems using a dichotomous outcome. We chose a median split to minimize the loss of statistical power in this dichotomous analysis.

Analyses were performed using SPSS software, v 21.0 (IBM-SPSS Inc, Chicago, Illinois).

Results

Characteristics of the children and their mothers in the study are presented in Table I. The children were on average born after 39.9 (SD 1.7) weeks of pregnancy. Median birth weight was 3.5 kg (IQR 3.1-3.8 kg).

First, we investigated the linear association between birth weight and attention problem score at age 6 years. As shown in Table II, the association between birth weight studied continuously and attention problem score showed a negative relationship if adjusted only for child age and sex (unadjusted β per birth weight SDS −0.05, 95% CI −0.07; −0.03, P < .001). This association was substantially attenuated after adjustment for possible confounders.

Next, we explored the possibility of a curvilinear association between birth weight and attention problem score. We found a curvilinear association of birth weight with attention problem score (β per birth weight SDS^2 0.02, 95% CI 0.01; 0.03, P = .002). That did not materially change after adjustment for potential confounders (β per birth weight SDS^2 0.02, 95% CI 0.00; 0.03, P = .008) (Table II and Figure 2). The turning point of this curvilinear association was calculated at a SDS birth weight of 0.3 (calculated as 0.01/

Table I. Characteristics of mothers and their children (n = 6015)

Child characteristics	
Sex, % boys	50.3
Birth weight, kg	3.4 (0.6)
Median (IQR)	3.5 (3.1-3.8)
Gestational age at birth, wk	39.9 (1.7)
Apgar score 1 min after birth	8.6 (1.2)
Maternal and pregnancy characteristics	
Age, y	31.0 (4.9)
National origin, %	
Dutch	60.3
Western other	12.2
Non Western	27.5
BMI, kg/m^2	24.6 (4.3)
Smoking during pregnancy, %	
Never	76.1
Until pregnancy was known	8.7
Continued	15.2
Educational level, %	
Primary	18.8
Secondary	52.7
Higher	26.9
Nulliparous, %	57.3
Mode of delivery, %	
Spontaneous vaginal	72.1
Instrumental vaginal	15.0
Cesarean	12.9
Gestational diabetes (% yes)	1.1

Values represent means SD unless otherwise indicated.

Table II. Associations between birth weight and ADHD symptoms at age 6 years (n = 6015)

Birth weight, SDS	Attention problems, model 1: age- and sex-adjusted* β (95% CI)	*P* value	Attention problems, model 2: fully adjusted analyses*,† β (95% CI)	*P* value
Continuous	−0.05 (−0.07; −0.03)	**<.001**	−0.01 (−0.03; 0.01)	.37
Curvilinear, continuous	−0.05 (−0.07; −0.03)	**<.001**	−0.01 (−0.03; 0.01)	.40
Squared	0.02 (0.01; 0.03)	**.002**	0.02 (0.00; 0.03)	**.008**
Dichotomous: low birth weight				
<10th percentile	0.13 (0.06; 0.20)	**<.001**	0.04 (−0.03; 0.11)	.26
<20th percentile	0.11 (0.06; 0.16)	**<.001**	0.04 (−0.01; 0.10)	.11
Dichotomous: high birth weight				
>90th percentile	−0.02 (−0.09; 0.05)	.62	0.05 (−0.02; 0.12)	.17
>80th percentile	−0.08 (−0.13; −0.03)	**.002**	−0.01 (−0.07; 0.04)	.61

CBCL attention problem scale is square-root transformed to approximate normal distribution.
Data in bold are statistically significant.
*Analyses were adjusted for child age at ADHD assessment and sex (model 1).
†Analyses were adjusted for Apgar score 1 minute after birth, mode of delivery, maternal age, national origin, educational level, parity, BMI, psychologic symptoms, smoking, alcohol use, folic acid supplementation use, gestational diabetes, and pre-eclampsia (model 2).

(0.02 × 2)); this equals a birth weight of 3.6 kg at 40 weeks of gestation. These analyses were adjusted for child sex, age at assessment of attention problems, Apgar score 1 minute after birth, mode of delivery, maternal age, educational level, parity, psychological symptoms, smoking, alcohol use, and folic acid supplementation, gestational diabetes, and pre-eclampsia.

Low birth weight (SDS <10th percentile; <20th percentile) was associated with higher attention problem score in child age and sex adjustment models (model 1; **Table II**) but was considerably attenuated in the fully adjusted model (model 2). Further, the association between high birth weight (SDS >80th and 90th percentile) and the level of attention problem score was tested. We found that high birth weight children (SDS >90th percentile) had no increased risk of attention problems, and the association between birth weight above the 80th percentile disappeared after adjustment for confounders in model 2 (**Table II**).

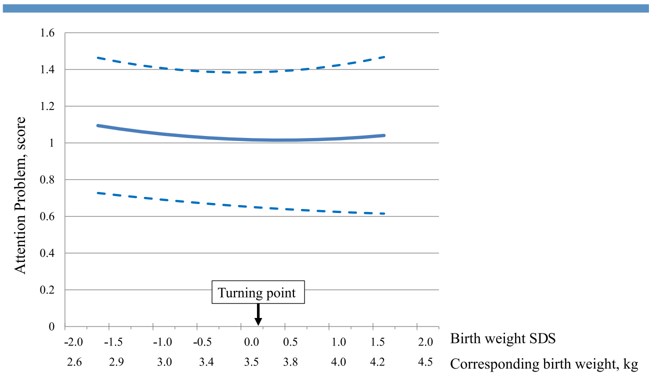

Figure 2. The association between child birth weight and attention problems at age 6 years (N = 6015). Estimated effects with 95% CIs of gestational age-adjusted birth weight SDS (90% range) on attention problems (score, square-root transformed). Estimates of effect size were obtained from an adjusted multiple regression. A birth weight SDS of 0 at 40 weeks of gestational age equals a birth weight of 3.5 kg.

Confounders with a relatively large effect on the association between birth weight and attention problem score were maternal educational level, maternal psychological symptoms, parity, maternal early pregnancy BMI, and child sex (**Table III**; available at www.jpeds.com).

We tested whether child birth weight mediated the association between maternal early pregnancy BMI and child attention problem score. As reported previously in the current cohort,[28] higher maternal early pregnancy BMI predicted higher child birth weight in the current sample (n = 5448) (adjusted β per 10 kg/m^2 0.42, 95% CI 0.35; 0.48, $P < .001$) and was positively related to the squared term of child birth weight (β per 10 kg/m^2 0.18, 95% CI 0.07; 0.28, $P = .001$). The association between maternal early pregnancy BMI and attention problem score of the child at age 6 years attenuated after adjustment for confounders (early pregnancy BMI: model 1 adjusted for child sex and age at ADHD assessment β per 10 kg/m^2 0.09, 95% CI 0.04; 0.14, $P = .001$, model 3 fully adjusted β per 10 kg/m^2 0.04, 95% CI −0.01; 0.10, $P = .12$).

Results from the mediation analyses are presented in a graphical representation (**Figure 3**; available at www.jpeds.com). Results indicated a mediation effect of child birth weight (SDS^2) for attention problem score (β 0.003, 95% CI 0.001; 0.010).

Moreover, maternal early pregnancy BMI and child birth weight interacted (*P* interaction of maternal early pregnancy BMI and child birth weight = .007, model 3 adjusted with linear and quadratic terms of birth weight in the model) (**Table IV**; available at www.jpeds.com). To illustrate this interaction of continuous variables, we categorized maternal early pregnancy BMI in 3 groups: normal weight (BMI 18.5-24.9 kg/m^2; n = 3354); overweight women (BMI 25-29.9 kg/m^2; n = 1415); and obese women (BMI ≥30 kg/m^2; n = 577). Underweight women (BMI <18.5 kg/m^2) were not depicted because of the small number of women at risk (n = 102). **Figure 4** shows the association between child birth weight and attention problem score in strata of maternal early pregnancy BMI. In particular, when we restricted the analyses to obese women, we found a strong association between high birth weight and higher attention

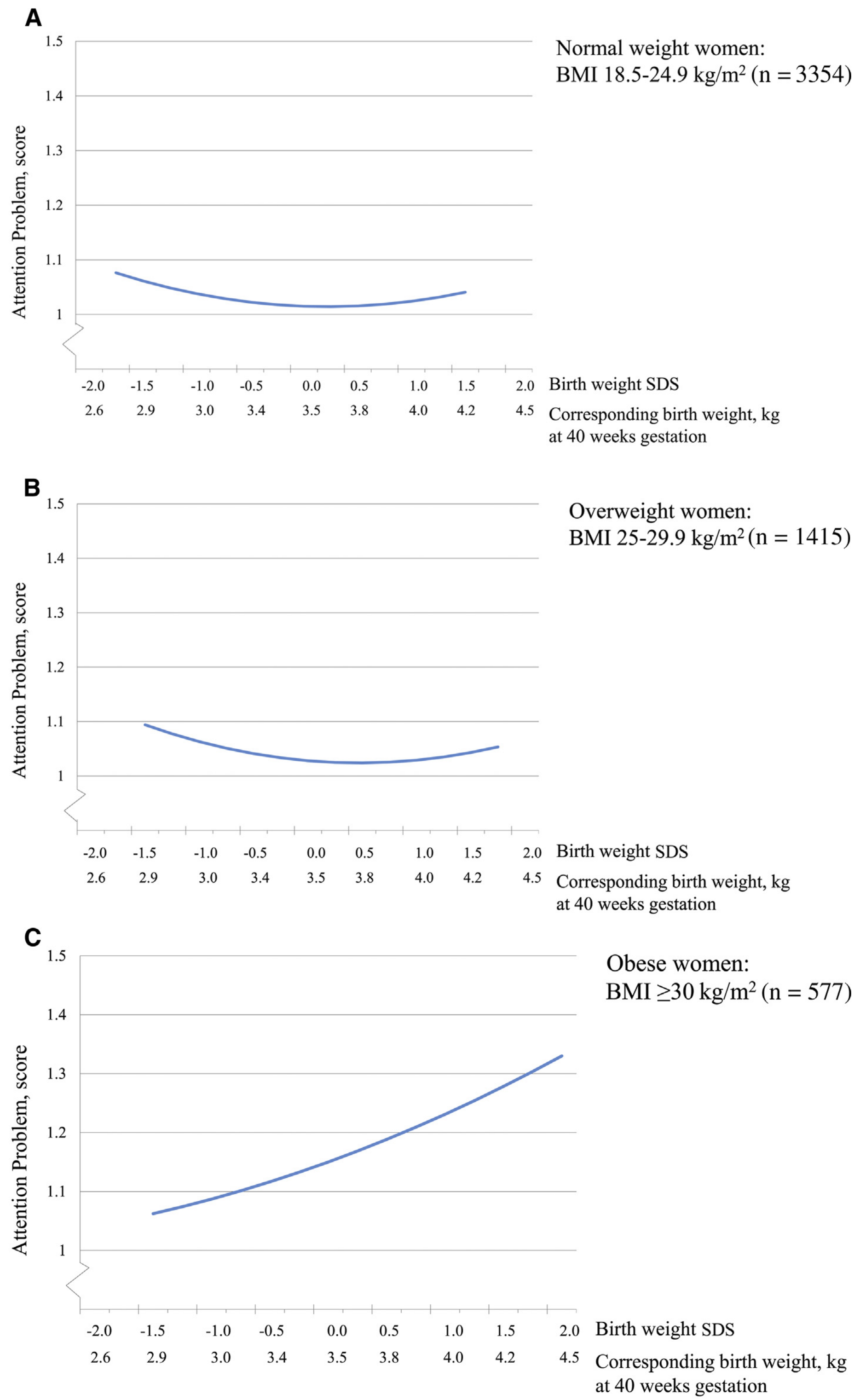

Figure 4. The association between child birth weight and attention problems at age 6 years in children from **A**, normal weight, **B**, overweight, and **C**, obese mothers, Rotterdam, The Netherlands, 2001-2005. Estimated effects of gestational age-adjusted birth weight SDS (stratum specific 90% range) on attention problems (score, square-root transformed) in 3 strata of maternal early pregnancy BMI. Estimates of effect size were obtained from an adjusted multiple regression model.

problem score (model 2 adjusted β per birth weight SDS 0.07, 95% CI 0.00; 0.14, P = .04 and β per birth weight SDS^2 0.01, −0.03; 0.05, P = .64 [results not shown]).

We did not observe an association between maternal gestational diabetes and attention problem score (model 4 adjusted β 0.09, 95% CI −0.10; 0.29, P = .36) in the total study population. We performed an additional sensitivity analyses post hoc restricting the sample to those born with a birth weight in the range in which we observed a positive association between birth weight and attention problems. Thus, we restricted analyses to children born with a birth weight SDS >0.03 (the turning point of the curvilinear association between child birth weight and attention problem score). In these children, the presence of gestational diabetes predicted more child attention problem score at age 6 years (model 4 adjusted β 0.50, 95% CI 0.32; 0.68, $P < .001$). However, results from this post hoc analyses should be interpreted with caution.

To test the stability of the association between birth weight and attention problems, we repeated the analyses with a dichotomous categorization of attention problems using a median split. The effects were consistent with the analyses using a continuous variable of attention problems (**Table V**; available at www.jpeds.com).

Discussion

In this large, prospective, population-based cohort we observed a reverse J-shaped association of birth weight with attention problems. Higher birth weight was related to less attention problems but from a birth weight of about 3.6 kg or more, a higher birth weight did not reduce the risk of attention problems any further. In the model adjusted for the quadratic term of birth weight, maternal early pregnancy BMI moderated the effect of birth weight on attention problems. In children of obese mothers (BMI >30 kg/m^2), a high birth weight increased the risk of attention problems. Yet, if modeled dichotomously, low birth weight was not associated with attention problem score after adjusting for confounders such as maternal age, educational level, early pregnancy, psychologic symptoms, and smoking during pregnancy.

We are not aware of any previous study showing that higher risks of attention problems can be found on both ends of the birth weight distribution. This curvilinear association may reflect that Generation R is a relatively young cohort; all children were born in the 21st century when the Western countries have experienced the obesity epidemic and lifestyle changes related to higher birth weights. Although birth cohorts traditionally have tested mostly linear associations between birth weight and health outcomes, nonlinear associations between birth weight and various other neurodevelopmental outcomes have been reported. Analyses after 4503 singletons born between 1976 and 1990 with cerebral palsy revealed a reversed J-shaped rate variation.[29] Gunnell et al[30] reported in a 1973-1980 cohort of 246 655 male conscripts a reverse J-shaped association between gestation-adjusted birth weight and schizophrenia. Leonard et al described that both children with lower and very high birth weight have an increased risk of intellectual disability.[31] More recently, in the Avon Longitudinal Study of Parents and Children cohort (born between 1991 and 1992), Wiles et al[8] reported some evidence for nonlinear associations of birth weight and infant prosocial behavior (inverted J-shape) and emotional problems (J-shape). In the current cohort, our group previously reported an inverted J-shape association of measures of fetal size in both mid- and late pregnancy and infant alertness at 3 months of age.[32]

The mechanism underlying the association between child birth weight and ADHD symptoms is not well understood. A few studies have attempted to investigate the causality of the effect of low birth weight on ADHD symptoms. Recently, a study in twins discordant for birth weight suggested a causal effect for birth weight on attention problems. The authors hypothesized that deficient nourishment in utero leads to impaired neurodevelopment and affects fetal brain development, which is reflected in ADHD symptoms.[33] Some studies reported that the disturbance of the fetal maturation by intrauterine growth restriction leads to cerebral immaturity at birth and increased risk for cerebral palsy that represents a risk for neurodevelopment of low birth weight children.[34,35]

Most likely, different processes underlie the association of birth weight and ADHD symptoms in low birth weight and high birth weight children. A heterogeneity of pathogenesis underlying an association between birth weight and a disease has been suggested among for type 2 diabetes. Namely, those born with low birth weight were more likely to be insulin resistant, whereas those born with a high birth weight were more likely to have metabolic syndrome.[36] Another explanation that has increasingly been proposed is that the effect of low birth weight on later health risks might rather result from rapid early postnatal weight gain.[37,38]

The association between birth weight and attention problems is complex and likely to be subject to confounding. Previous studies adjusted for several confounders such as socio economic factors and maternal psychological symptoms but the control for pregnancy characteristics was typically less complete.[39] Here, we also tried to account for intrauterine exposures by adjusting for maternal smoking, psychological symptoms, folic acid supplementation, and pregnancy complications. Moreover, the use of a gestational age-adjusted birth weight variable prevents that the observed associations are driven by duration of gestation.

We found that maternal early pregnancy BMI moderated the association between child birth weight and attention problem score. Children born large for gestational age were at higher risk of attention problems if born to obese mothers. In general, a high birth weight reflects fetal and maternal health. Social deprivation, maternal disease, and unhealthy life styles are all correlated negatively with birth weight.[40] However, this might be different if a high birth weight results from high maternal weight. Maternal overnutrition and obesity may lead to metabolic alterations including elevated leptin and estrogen levels and insulin resistance. Insulin and insulin-like growth factors are known to affect neuronal differentiation, and survival, as well as neurite formation.[41] In addition, studies have demonstrated that obesity in pregnancy is associated with a wide spectrum of peripartum complications including prolonged labor, increased cesarean delivery rates, and asphyxia of the child.[42] However, we controlled for mode of delivery, gestational diabetes, preeclampsia, and child Apgar score to reduce the effects of confounding peripartum factors associated with maternal early pregnancy BMI.

A previous report of Rodriguez et al investigating the association with maternal prepregnancy adiposity and child ADHD symptoms in 3 large Scandinavian pregnancy cohorts,[43] described independent relationships with high maternal weight and child birth weight. Functional changes in the fetal brain of children exposed to excessive maternal weight, not related to high birth weight, may underlie these behavioral problems. Yet, this remains speculative, and no studies have described a very plausible pathway linking maternal obesity exposure and child health. Hence, the observed association may simply be the result of residual confounding because being overweight is known to correlate strongly with unfavorable socioeconomic and behavioral characteristics like impulsivity.[44,45]

The strengths of the present study include the ability to investigate the relationship between birth weight and attention problems in a large, population-based sample of children with a birth weight distribution typically seen in the general population. Prospective measures of exposure and outcome and data on several important confounding factors are other strengths.

Despite this, we cannot rule out that the observed association is the result of residual confounding from sociodemographic and lifestyle-related determinants. A second possible limitation of our study might be that child attention problems were assessed using the CBCL. Although behavior problem scales do not provide a clinical diagnosis, continuous traits have been shown to represent adequately behavioral problems on the population level and provide better statistical power. Some studies have shown evidence that the CBCL-attention problem scale predicts ADHD well[46,47] but is no measure of clinical ADHD symptoms. More importantly, many other studies have reported associations between reduced birth weight and increased attention problems instead of clinical diagnoses of ADHD. Our approach is, thus, in line with previous studies. Finally, because data were more complete in higher-educated mothers, we cannot rule out that selective nonresponse bias influenced our findings.

In conclusion, our results suggest that birth weight and attention problems are curvilinear related. Higher birth weight was related to less attention problems but from a birth weight of about 3.6 kg or more, a higher birth weight did not reduce the risk of attention problems any further. However, in children of obese mothers, a high birth weight may increase the risk of attention problems. Future research might focus not only on biological mechanisms and their effect of brain development in low birth weight children, but also high birth weight children. ■

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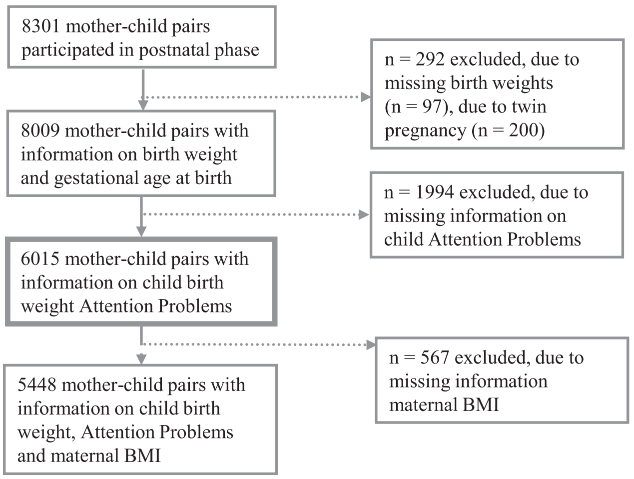

Figure 1. Flowchart of the study population.

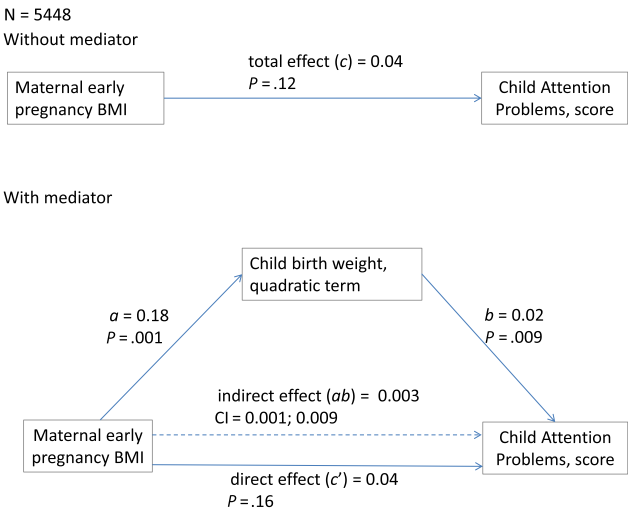

Figure 3. Model of maternal early pregnancy BMI as a predictor of child attention problems, mediated by child birth weight (SDS^2). Results are obtained from Preacher and Hayes bootstrapping procedure. Values represent unstandardized betas *P* values. The CI for the indirect effect is a bootstrapped CI based on 5000 samples. Analyses are adjusted for child sex, age at assessment of attention problems, Apgar score 1 minute after birth, child birth weight (SDS), mode of delivery, maternal age, educational level, parity, psychological symptoms, smoking, alcohol use, and folic acid supplementation, gestational diabetes, and pre-eclampsia.

Table III. Contribution of selected covariates on the association between child birth weight and attention problems at age 6 years (n = 6015)

Determinant	Child attention problems at age 6 y: Effect estimate (β) of child birth weight, unadjusted	Adjusted R^2
Child birth weight, continuous	−0.050	0.004
Covariates	**Effect estimate (β) of child birth weight after covariate inclusion**	**Adjusted R^2**
Maternal characteristics		
Educational level		
Low	−0.037	0.032
Mid		
High		
Psychological symptoms, score	−0.034	0.042
National origin	−0.027	0.046
Dutch		
Surinamese		
Turkish		
Moroccan		
Cape Verdean		
Dutch Antilles		
Other Western		
Other non-Western		
BMI, kg/m^2	−0.030	0.046
Parity	−0.014	0.056
Primiparous		
Multiparous		
Smoking during pregnancy	−0.010	0.060
Never		
Until pregnancy was known		
Continued		
Alcohol use	−0.007	0.062
Never		
Until pregnancy was known		
Continued		
Folic acid supplement use	−0.008	0.061
Started preconceptional		
Started postconceptional		
No use		
Gestational diabetes	−0.008	0.061
Gestational diabetes		
No gestational diabetes		
Pre-eclampsia	−0.007	0.061
Pre-eclampsia		
No pre-eclampsia		
Mode of delivery	−0.008	0.063
Spontaneous vaginal		
Instrumental vaginal		
Cesarean		
Child characteristics		
Sex	−0.008	0.085
Apgar score	−0.008	0.085
Age at assessment	−0.008	0.086

Covariates were introduced stepwise in the order given here.

Table IV. Interaction analyses of maternal BMI and child birth weight and attention problems at age 6 y (n = 5448)

Variables in the interaction-model	Attention problems, model 1: gestational age, child age- and sex-adjusted* β (95% CI)	P value	Attention problems, model 2: fully adjusted analyses*,† β (95% CI)	P value
Maternal BMI, kg/m^2	0.01 (0.01; 0.02)	**<.001**	0.00 (−0.00; 0.01)	.20
Birth weight, SDS, continuous	−0.25 (−0.37; −0.13)	**<.001**	−0.16 (−0.28; −0.04)	**.007**
Birth weight, SDS, squared	0.01 (0.00; 0.03)	**.06**	0.01 (0.00; 0.03)	**.04**
Interaction: Maternal BMI, kg/m^2 × birth weight, SDS, continuous	0.01 (0.00; 0.01)	**.001**	0.01 (0.00; 0.01)	**.007**

CBCL attention problem scale is square-root transformed to approximate normal distribution. Estimates of effect size were obtained from a multiple regression model with a interaction term of maternal BMI during pregnancy and child birth weight. This model included linear and quadratic terms of birth weight.
Data in bold are statistically significant.
*Analyses were adjusted for gestational age at measurement of BMI, child age at attention problem assessment and sex (model 1).
†Analyses were adjusted for Apgar score 1 minute after birth, mode of delivery, maternal age, national origin, educational level, parity, BMI, psychologic symptoms, smoking, alcohol use, folic acid supplementation use, gestational diabetes, and pre-eclampsia (model 2).

Table V. Associations between birth weight and dichotomous score of attention problems at age 6 years (n = 6015)

Birth weight, SDS	Attention problems, ≥50% score model 1: age- and sex-adjusted* OR (95% CI)	P value	Attention problems, ≥50% score model 2: fully adjusted analyses*,† OR (95% CI)	P value
Dichotomous: low birth weight				
<10th percentile	1.41 (1.19; 1.68)	**<.001**	1.17 (0.98; 1.40)	.08
<20th percentile	1.35 (1.19; 1.53)	**<.001**	1.17 (1.02; 1.34)	**.02**
Dichotomous: high birth weight				
>90th percentile	0.95 (0.80; 1.13)	.59	1.10 (0.91; 1.31)	.33
>80th percentile	0.80 (0.70; 0.91)	.001	0.92 (0.80; 1.05)	.22
Continuous	0.88 (0.84; 0.93)	**<.001**	0.95 (0.90; 1.01)	.09
Curvilinear, continuous	0.89 (0.84; 0.93)	<.001	0.96 (0.90; 1.01)	.11
Squared	1.04 (1.01; 1.08)	.01	1.03 (1.00; 1.07)	**.04**

Data in bold are statistically significant.
*Analyses were adjusted for child age at ADHD assessment and sex (model 1).
†Analyses were adjusted for Apgar score 1 minute after birth, mode of delivery, maternal age, national origin, educational level, parity, BMI, psychologic symptoms, smoking, alcohol use, folic acid supplementation use, gestational diabetes and pre-eclampsia (model 2).