Evidence for a Causal Association of Low Birth Weight and Attention Problems

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Objective: Low birth weight (LBW) is associated with attention problems (AP) and attention-deficit/hyperactivity disorder (ADHD). The etiology of this association is unclear. We investigate whether there is a causal influence of birth weight (BW) on AP and whether the BW effect is mediated by catch-up growth (CUG) in low-BW children. **Method:** Longitudinal data from >29,000 twins registered with the Netherlands Twin Register with BW ≥1,500 g and gestational age (GA) ≥32 weeks were analyzed with the cotwin control method. Hyperactivity and AP were assessed at ages 3, 7, 10, and 12 years; weight was assessed at birth and age 2 years. **Results:** Children in the lowest BW category of 1,500 to 2,000 g scored 0.18 to 0.37 standard deviations (SD) higher on AP than children in the reference category of 3,000 to 3,500 g. This effect was present in term-born and preterm-born children. Importantly, in BW discordant monozygotic (MZ), dizygotic (DZ), and unrelated (UR) pairs, the child with the lower BW scored higher on hyperactivity and AP than the child with the higher BW and within-pair differences were similar for MZ, DZ, and UR pairs. This pattern is consistent with a causal effect of BW on AP. MZ and DZ twin pairs concordant for LBW but discordant for CUG showed similar AP scores, thus ruling out any effect of CUG on AP. **Conclusions:** These results strongly indicate that the association of birth weight and AP represents a causal relationship. The effects of BW are not explained by CUG in LBW children. J. Am. Acad. Child Adolesc. Psychiatry, 2011;50(12):1247–1254. **Key Words:** attention problems, birth weight, catch-up growth, twins, causality

With a prevalence of 3% to 10%, attention-deficit/hyperactivity disorder (ADHD) presents a major burden for society and causes considerable impairment in the lives of children and adults.[1,2] Twin studies have estimated the heritability of ADHD in children to be at least 60%.[1,3] This implies that up to 40% of the variance of ADHD can be explained by other factors. Specific risk factors that have consistently been associated with attention problems (AP) and ADHD are male sex, perinatal trauma, maternal smoking during pregnancy, and low birth weight (LBW) (<2,500 g).[4]

This paper focuses on the relationship between birth weight (BW) and AP. A recent meta-analysis reported children who were born very preterm (gestational age [GA] <32 weeks) and/or with a very low birth weight (VLBW; <1,500 g) to score respectively 0.43 and 0.59 SD higher on parent and teacher ratings of AP compared to controls.[5] Less attention has been devoted to the influence of less extreme forms of prematurity and LBW on symptoms of AP. However, studies that included the complete BW distribution in their analysis found the effect to extend over all BW categories below the average.[6,7]

The question arises how the association between BW and AP originates. Does LBW increase the risk for AP? Or do other factors, such as GA, socioeconomic status, maternal stress, an unfavorable lifestyle during pregnancy, or genetic factors increase the risk for both LBW and AP? Twin studies provide a unique opportunity to investigate which mechanisms underlie an observed association. Monozygotic (MZ) twins share almost all of their genes, whereas dizygotic (DZ) twins share on average 50% of their segregating genes. Both types of twins share many environmental factors, including SES, GA, and

Supplemental material cited in this article is available online.

exposure to smoking during pregnancy. The cotwin control design provides the possibility to test for an association while controlling for genetic and environmental factors.[8,9]

Two twin studies have previously investigated the association between BW and AP. A study in 1,480 twin pairs from the Swedish Twin Registry and a study in 2,007 MZ twin pairs from the Twin Early Development Study showed that the association between BW and AP was not due to common genetic or environmental factors but rather to a causal effect of BW on AP.[10,11] For the present study a much larger dataset was available consisting of 14,789 twin pairs who have been followed longitudinally from birth on.

Uniquely in this sample, it was possible to address the question whether the effect of LBW on AP is mediated by the effects of later catch-up growth (CUG). CUG describes the gain in weight SD score over time in the fist years after birth. LBW children frequently receive special nutritional programs to reach CUG. Although CUG has many positive effects, recent studies have reported negative effects of rapid CUG on diabetes, hypertension and, more recently, IQ.[12-14] We hypothesize that the BW effect on AP might be explained by CUG. To our knowledge, this is the first study to test the effect of CUG on AP.

The aim of the current study was to investigate the association of BW and AP along the entire distribution of BWs, to apply the cotwin control method to examine the mechanism underlying the BW–AP relationship and to addresses the question whether CUG in the first 2 years of life is causally related to later AP and possibly explains the BW–AP association.

METHOD

Subjects

Children included in this study are registered with the Netherlands Twin Register (NTR), established at the VU University Amsterdam in 1987. At birth, parents of multiples are invited to participate in longitudinal survey studies. A first survey is sent out after registration and later surveys are collected when the twins are 2, 3, 5, 7, 10, and 12 years old. A more detailed description of the cohort and the data collection has been published by Bartels et al.[15]

The twins included in this study were born between 1986 and 2003. Data on BW and AP were available for 16,398 twin pairs. Twin pairs were excluded if one of the children had a severe handicap that interfered with daily functioning (n = 415 pairs) or if there were no data on GA (n = 74 pairs). As the focus of the study was on the less extreme values of BW and GA, 1,120 twin pairs with a GA <32 weeks or a BW <1,500 g were excluded from the main analysis.[16] The final sample thus consisted of 14,789 twin pairs including 13,371 pairs with data available at age 3 years, 8,084 at age 7 years, 5,367 at age 10 years, and 4,578 at age 12 years. The number of twin pairs with available data decreases with increasing age because of nonresponse and the fact that not all children have reached the particular ages under study. Response rates of the questionnaires were 84% at age 1 year, 70% at age 3, 58% at age 7, 56% at age 10, and 50% at age 12 years.

Zygosity

For 14% of same-sex twins, zygosity was based on the results of DNA or blood group typing.[17,18] For the remaining pairs, zygosity was determined by a set of questions on twin similarity, that was included in longitudinal surveys. Of the 14,789 twin pairs included, there were 2,269 monozygotic male (MZM) pairs, 2,600 dizygotic male (DZM) pairs, 2,562 monozygotic female (MZF) pairs, 2,363 dizygotic female (DZF) pairs, and 4,995 dizygotic opposite-sex (DOS) pairs. Based on DNA assigned "true" zygosity, we looked at the percentage of twins correctly classified by questionnaire items as a function of their true zygosity and their concordant/discordant status. Across surveys, the percentage of correctly classified twin pairs was 97.3% for MZ concordant twins and 93.7% for DZ concordant twins. For MZ discordant pairs, 96.2% was correctly classified, and 94.5% of DZ discordant pairs was correctly classified. These differences were not significant, and discordance status clearly is not associated with misclassification.

Birth Weight and Gestational Age

In the first survey that is sent out after registration, mothers are asked to fill out the BWs of their twins as assessed in the hospital and the duration of the twin pregnancy. Gestational age was rounded at half weeks. Twin pairs were classified as BW discordant if the BW of the smallest twin was at least 15% lower than the BW of the heaviest twin or if there was a BW difference of at least 400 g.[11,19] To exclude the most extreme cases who may have transfusion syndrome, 300 twin pairs with a BW difference of >40% or >1,000 g were excluded from the analysis of BW-discordant pairs.

Catch-up Growth

In the surveys, when subjects are age 2 and 3, mothers are asked to fill out the weights of their twins as assessed by the Dutch National Health Services at regular intervals. For weight at age 2 years, we selected the measurement between 18 and 30 months that was closest to 24 months. Twin pairs were classified as concordant for LBW if both twins had a BW of <2,500 g and if the BW of the smallest twin was <10% lower than the BW of the heaviest twin. Discordance for CUG was defined as a gain in weight SD score over the first 2 years of >0.67 SD in one twin and ≤0.50 SD in the other twin.[20] Weight data at age 2 years were standardized with the sex- and age-specific Dutch growth charts for the general population from 1997 using the software package Growth Analyser 3.[21,22] Weight at birth was standardized using the reference data of Niklasson et al. with correction for gestational age.[23]

Attention Problems

An age-appropriate Dutch version of the Achenbach System of Empirically Based Assessment (ASEBA) is included in the NTR surveys at ages 3, 7, 10, and 12 years.[24,25] The Overactive scale at age 3 years contains five items, and the Attention Problems scale at age 7, 10, and 12 contains 11 items describing both hyperactive and inattentive behaviors. As the number of items differs over the CBCL scales, T scores were calculated to facilitate interpretation. A T score of 50 represents the mean and a deviation of 10 points from the mean represents a deviation of 1 SD. A T score >65 indicates clinically significant problem behavior. T scores were calculated separately for boys and girls. We report on maternal AP ratings; results were similar when analyzing ratings from fathers (see Table S1, available online).

BW and AP

Mean T scores on the AP scale at age 3, 7, 10, and 12 years were obtained for each BW category. Data from two individuals within a twin pair are not independent. Therefore, mean AP scores for all BW categories are given for the following four groups: first-born males, second-born males, first-born females, and second-born females. A linear regression was performed to test whether BW significantly predicted AP scores. Effect sizes were calculated in terms of Cohen's *d*: the difference between two means divided by the pooled SD for those means.[26]

Cotwin Control Method

The cotwin control method addresses issues of causality.[8,9] In this design, the association between BW and AP is tested in three groups: MZ twin pairs, DZ twin pairs, and a sample of UR pairs discordant for BW. Monozygotic (MZ) twins share almost all their DNA, whereas dizygotic (DZ) twins share on average 50% of their segregating genes. Both types of twins share many environmental factors including SES, GA, and exposure to smoking during pregnancy, whereas the UR pairs share genetic and environmental factors at a random level. The upper part of Figure 1 depicts an example of the expected mean AP scores in BW discordant pairs from the MZ, DZ, and UR group under the three models that possibly explain the association between BW and AP. In the case of a causal model, all within-pair differences in BW will result in within-pair differences in AP. Hence, the individuals with the higher BW in a pair will show similarly lower AP scores in the MZ, DZ, and UR pairs. If the association between BW and AP is due to an environmental factor that is shared between twins, only UR pairs will differ in their AP scores, with the individuals with the higher BW showing lower AP scores than the individuals with the lower BW. Because twins have equal exposure to the environmental factor causing both LBW and AP, the twins with the higher BW in a pair will show the same mean AP scores as the cotwins with the lower BW. Finally, if the association is due to shared genetic factors, the difference in BW will again be present in the UR pairs. However, MZ twins discordant for BW will share the causal genetic factors for AP and hence, the MZ twins with the higher BW in a pair are expected to show the same mean AP score as the cotwins with the lower birth weight, whereas the DZ group will show an intermediate pattern.

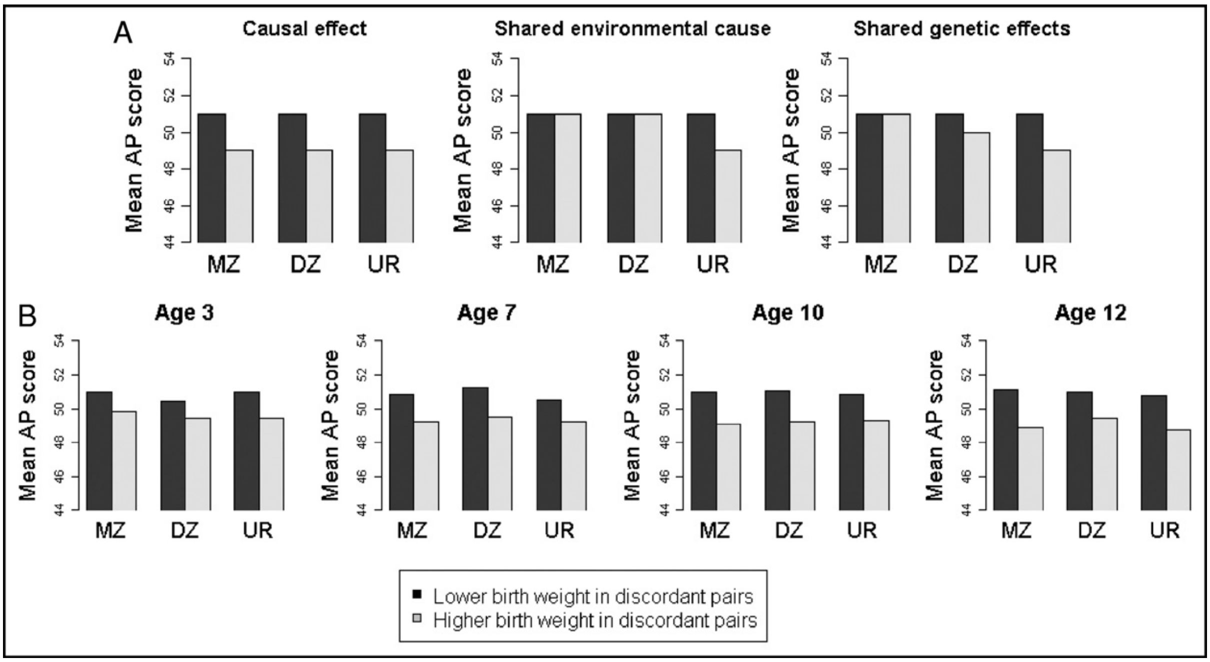
Because sex is an important determinant of both BW and AP, only same-sex pairs were included in the DZ BW discordant group. A group of UR pairs discordant for BW was created as follows. Pairs of unrelated individuals were drawn from the group of twins that were not discordant for BW and matched to the BW discordant MZ and DZ pairs based on sex, GA (rounded at 1 week) and BW category (categories of 100 g were used). Thus, the group of UR pairs has the same characteristics with regard to BW discordance and GA as the MZ and DZ BW discordant groups.

To test for mean differences within BW discordant twin pairs, a paired t test was performed in MZ and DZ twin pairs and an unpaired t test was performed in UR pairs. To test for the different explanatory models, a linear regression was performed in which it was tested whether MZ, DZ and UR group membership (coded as 0, −1, and −2) significantly predicted AP scores in the group of individuals with the higher birth weight in a pair and in the group of individuals with the lower birth weight in a pair. As an additional test, it was tested whether group membership (MZ, DZ, or UR) modified the effect of within-pair BW differences on AP, by including the interaction term in the linear regression.

Catch-up Growth

LBW and CUG are highly correlated. To disentangle the effects of LBW and CUG on AP, 190 same-sex twin pairs concordant for LBW yet discordant for CUG were selected. To test for the effect of CUG on AP, mean differences in AP scores at age 3, 7, 10, and 12

FIGURE 1 Expected and observed patterns of Attention Problems (AP) scores in monozygotic (MZ) and dizygotic (DZ) twin pairs and unrelated (UR) pairs discordant for birth weight (BW). Note: (A) Expected patterns under three theoretical models: association between BW and AP due to a causal effect of BW on AP; association between BW and AP due to an environmental factor that influences both BW and AP and is shared between twins; and association between BW and AP due to genetic factors that influence both BW and AP. (B) Observed mean T scores at the AP scale in MZ and DZ twin pairs and UR pairs discordant for BW at ages 3, 7, 10, and 12 years.



between the twin with the higher CUG and the cotwin with the lower CUG were tested with a paired t test.

RESULTS

BW and APs

The mean AP scores at age 3, 7, 10, and 12 years for each BW category are shown in Table 1. As the results were roughly the same for first- and second-born twins, only the results for first-born males and females are shown. Clearly, AP scores decrease with increasing BW up to BWs of 3,500 g in all age groups. The association between BW and AP was tested in a linear regression; BW significantly predicted AP scores at all ages ($p < .05$). Taking the BW category of 3,000 to 3,500 g as the reference category, children with a BW of 1,500 to 2,000 g scored 0.18 to 0.37 SD higher on the AP scale. In line with this, the percentage of children scoring above the clinical cutoff decreases with increasing BW (Table 1). In a subsample of children who were term-born (GA ≥37 weeks) the same pattern was found with somewhat larger differences of 0.27 to 0.70 SD (see Table S2, available online).

Attention Problems in Birth Weight–Discordant Pairs

A total of 1,258 MZ twin pairs were discordant for BW. AP data were available for 1,133 of these twin pairs at age 3 years, 723 at age 7 years, 500 at age 10 years, and 441 at age 12 years. There were 1,587 same-sex DZ twin pairs discordant for BW. AP data were available for 1,425 of these twin pairs at age 3 years, 846 at age 7 years, 528 at age 10 years, and 444 at age 12 years. The average BW differences were similar in the MZ, DZ, and UR pairs, with mean BW differences of respectively 21%, 20%, and 20% and mean absolute differences of 562, 581, and 560 g. The average AP scores in the BW discordant MZ, DZ, and UR pairs are depicted in the lower figure of Figure 1. At all ages, the average AP score of the individuals with the lower BW in a pair was higher than the average score of the individuals with the higher BW in a pair, with differences between 0.10 to 0.24 SD. These differences were significant in all pairs at all ages of measurement ($p < .01$). A linear regression was performed to test for the different explanatory models. At all

TABLE 1 Mean and Standard Deviation (SD) of T scores of Maternal Ratings of the Attention Problems (AP) Scale and the Percentage of Children With a T Score >65 at Age 3, 7, 10, and 12 Years for Each Birth Weight (BW) Category in First-Born Males (M) and Females (F) With Gestational Age ≥32 Weeks

Sex	BW	N	AP 3	n	AP 7	n	AP 10	n	AP 12
M	1,500–1,999	598	51.3 (10.2) 8.7%	348	51.8 (10.9) 14.7%	209	50.6 (10.3) 9.6%	173	51.4 (10.0) 9.8%
	2,000–2,499	1,817	50.6 (9.9) 7.4%	1,126	50.6 (10.1) 9.1%	723	50.6 (10.3) 7.9%	629	51.0 (11.0) 11.4%
	2,500–2,999	2,627	50.0 (9.8) 6.6%	1,540	49.8 (9.7) 9.0%	1,029	50.1 (9.9) 6.5%	876	49.8 (9.7) 8.1%
	3,000–3,499	1,384	49.4 (9.7) 6.4%	870	49.0 (9.5) 8.3%	562	48.4 (9.5) 5.9%	497	49.0 (10.0) 7.6%
	≥3,500	235	48.4 (9.7) 5.1%	131	49.1 (9.7) 6.9%	87	50.2 (9.6) 4.1%	74	49.4 (8.2) 4.0%
F	1,500–1,999	740	51.5 (9.9) 11.4%	457	51.9 (10.5) 9.6%	308	51.7 (10·9) 9.4%	265	51.5 (9.6) 12.1%
	2,000–2,499	2,131	50.7 (10.1) 11.4%	1,271	51.2 (10.8) 9.9%	885	50.8 (10.7) 9.0%	731	51.0 (10.7) 12.9%
	2,500–2,999	2,637	49.6 (9.9) 9.0%	1,646	49.6 (9.8) 7.7%	1,099	49.7 (9.6) 6.4%	939	49.4 (9.7) 8.4%
	3,000–3,499	990	48.9 (9.7) 8.6%	605	49.3 (9.8) 7.8%	398	49.0 (9.3) 6.0%	347	49.1 (9.5) 7.8%
	≥3,500	133	48.6 (9.0) 6.0%	78	49.6 (11.3) 12.8%	56	47.5 (9.0) 3.6%	44	46.1 (8.3) 6.8%

ages of measurement, group membership (MZ, DZ, or UR) did not predict AP scores in both the higher birth weight individuals and the lower birth weight individuals in a pair. In line with this, group membership (MZ, DZ, or UR) did not significantly interact with the effect of within-pair BW differences on AP scores at all ages ($p > .05$).

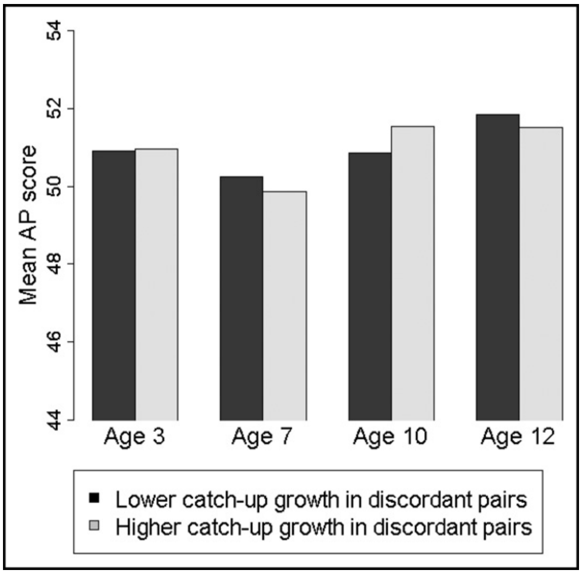
Catch-up Growth and Attention Problems

A total of 52 MZ and 138 same-sex DZ twin pairs were concordant for LBW and discordant for CUG. The AP scores of the twins with the higher CUG in a pair did not differ from the AP scores of the twins with the lower CUG in a pair, at all ages of measurement ($p > .05$) (Figure 2).

DISCUSSION

In this large twin study (n = 14,789 twin pairs), there was a clear negative relationship between BW and AP. Children with a BW of 1,500 to 2,000 g scored 0.18 to 0.37 SD higher on the AP scale than children in the reference category of 3,000 to 3,500 g. This effect was present in term-born (GA ≥37 weeks) and preterm-born children (GA 32–37 weeks). Within MZ, DZ, and UR BW discordant pairs, individuals with the lower BW in a pair scored 0.10 to 0.24 SD higher on the AP scale than the individuals with the higher BW in a pair. The effect of BW on AP was similar over the MZ, DZ, and UR groups, in line with a causal effect of BW on AP. We were able to identify a group of twin pairs who were concordant for LBW yet discordant for CUG. In this group no

FIGURE 2 Mean T scores at the Attention Problems (AP) scale at age 3, 7, 10, and 12 years in twin pairs concordant for low birth weight yet discordant for catch-up growth.



differences in longitudinally assessed AP scores was found.

The strength of the present study lies in the prospective data collection, the large sample size and the possibility to control for prematurity, genetic factors, maternal factors, and CUG within the cotwin control design.

Many studies have focused on the effects of VLBW and extreme prematurity on AP. In line with previous studies, the influence of BW on AP was present over the full range of BWs in our cohort.[6,7] The clinical importance of this finding is considerable, as the number of children with moderately LBW (1,500–2,500 g) is much larger than the number of children with VLBW.

The effect sizes observed in our study are slightly smaller than the effect sizes described previously.[5] These differences can be explained by the fact that children with BW <1,500 g were excluded. When all children with available BW and AP scores were included, differences in AP scores of 0.21 to 0.53 SD were found between children with a BW <1,500 g and children in the reference category of 3,000 to 3,500 g.

Previous reviews have criticized the existent studies on the influence of LBW on AP, as many of these studies did not control for the effect of prematurity, socioeconomic status, maternal tobacco and alcohol consumption, and genetic factors.[4] The fact that we found the effect of BW on AP in preterm- and term-born children and, more importantly, that the effect was the same in MZ, DZ, and UR BW discordant pairs, makes clear that BW is a risk factor for AP independent from the above-listed factors.

This raises the question how LBW might cause AP, i.e., is this a direct effect or is LBW a proxy for another risk factor causing AP? Animal studies and human postmortem studies suggest that growth restriction in utero, as reflected in LBW, contributes to later AP. These studies consistently showed an influence of intrauterine growth restriction (IUGR) on brain volume and development (reviewed by de Bie et al. and Schlotz et al.[27,28]). Some of the animal studies are of particular importance for AP as they found an effect of IUGR on the striatum, a brain structure that is thought to play a key role in the pathogenesis of ADHD.[29,30] Interestingly, one MRI study in MZ twins discordant for ADHD found smaller caudate volumes in affected twins, pointing to a deficit in frontal-striatal processing.[31] In another MRI study in MZ twins discordant for AP, the high-scoring twins showed a volume reduction of the inferior dorsolateral prefrontal cortex and decreased activation in the left and right temporal lobe areas during the color-word Stroop task compared to the low-scoring twins.[32,33] The high-scoring twins were previously found to have a lower average BW than the AP low-scoring twins.[34] Together, these findings support the idea that BW differences in MZ twins reflect differential nourishment in utero, leading to impaired neurodevelopment. This is in line with the Developmental Origins of Health and Disease model (Barker's hypothesis), an influential hypothesis that states that an adverse environment during critical periods of fetal life increases the risk of a wide range of diseases later in life, including diabetes, cardiovascular disease, cancer, and neuropsychiatric disorders.[28,35] A recent study[36] in newborn MZ twins obtained evidence for the hypothesis that epigenetic factors accumulated in utero can contribute to low birth weight and predisposition to complex diseases later in life. The number of twins in this study were small, and more studies are needed to confirm that MZ twins can be discordant at birth for epigenetics and gene expression.[37]

It has been suggested that the number of children diagnosed with ADHD has increased over time, as expressed by a marked increase in medication use.[38] Interestingly, a recent study in more than 36 million term born children in the United States showed a decrease in BW over the period 1990 to 2005.[39] Based on our findings, an increase in ADHD might partly be explained by the decrease in BW.

Generalization from our study relies on the assumption that the liability to develop AP is influenced by similar factors in twins and singletons. Prematurity, LBW and IUGR occur more frequently in twins and, more importantly, the causes and effects of IUGR in twins might differ from those in singletons. However, one of the reasons to assume that the latter could be the case is the fact that studies linking LBW to various outcomes in twins have sometimes lacked to find an association that was present at the population level. As we do find a clear association between BW and AP in our large cohort and in the MZ and DZ BW discordant twin pairs, this argument does not hold for the relationship between BW and AP. Important to notice in this regard is that twins do not differ from singletons with regard to behavioral problems, and specifically AP.[40,41] This suggests that an unfavorable uterine environment leading to LBW is as much a risk factor for AP in the twin population as it is in singletons.

Another limitation of our study is that inattention and hyperactive behavior were assessed by means of a structured questionnaire instead of a clinical diagnosis of ADHD. Although the latter directly relates to clinical practice, a liability approach in which AP is considered a continuous trait instead of a dichotomy has been shown to adequately represent AP on the population level and provides better statistical power. More importantly, the CBCL–AP scale converges with the results of clinical interviews covering the *DSM-IV* criteria.[42]

As all data were collected by questionnaire surveys in a population based cohort, nonrandom participation and drop-out over time is a concern. A study by Gielen et al. compared the gestational ages and birth weights in the NTR with a reference data set of all Dutch live-born twins (NPR) and found that gestational age and birth weights of the NTR were higher then those of the NPR, although the differences were small: NPR: 35.9 (3.0) weeks and 2459 (615) g; NTR: 36.5 (2.4) weeks and 2498 (550) g.[16] Similarly, another study from the NTR found slightly higher overactive behavior scores at age 3 in children that did not participate in the surveys at age 7, 10 or 12.[43] These forms of selection bias might have led to an underestimation of the true effect sizes in the current study.

A final limitation is that the number of twin pairs concordant for LBW but discordant for CUG was still limited although the total sample size was large.

To conclude, this study provides evidence for the influence of LBW on AP over the full range of BWs. The analysis in BW discordant twins shows that this effect is not accounted for by prematurity, SES, or tobacco and alcohol consumption during pregnancy. We hypothesize that deficient nourishment in utero leads to impaired neurodevelopment and the occurrence of AP. Although recent studies have reported negative outcomes of rapid CUG, our analysis of the effects of CUG on AP indicate that CUG is neither beneficial nor harmful with regard to AP. The decision to treat children with LBW with nutritionally enriched diets should be based on a careful consideration of the positive and negative effects of CUG. Future research should aim to unravel the characteristics of healthy CUG. &

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TABLE S1 Mean and SD of T Scores of Paternal Ratings at the Attention Problems (AP) Scale and the Percentage of Children With a T score >65 at Age 3, 7, 10, and 12 for Each Birth Weight (BW) Category in First-Born Males (M) and Females (F) With Gestational Age ≥32 Weeks

Sex	BW	n	AP 3	n	AP 7	n	AP 10	n	AP 12
M	1,500–1,999	406	51.3 (10.2) 7.9%	260	51.7 (10.7) 9.2%	148	52.4 (12·0) 12.2%	135	51.3 (10.0) 8.9%
	2,000–2,499	1,179	50.4 (10.2) 7.8%	825	51.0 (10.3) 8.8%	513	50.1 (10.3) 9.6%	454	50.9 (10.8) 9.0%
	2,500–2,999	1,754	49.7 (9.8) 6.0%	1,155	49.7 (10.0) 6.8%	747	49.8 (9.9) 8.2%	641	49.6 (9.7) 7.6%
	3,000–3,499	923	49.8 (10.0) 6.2%	664	49.4 (9.5) 6.0%	425	49.3 (9.5) 5.2%	362	49.5 (9.6) 8.3%
	≥3,500	151	48.9 (9.1) 4.0%	96	47.9 (8.7) .2%	68	49.6 (8.1) 4.4%	60	48.8 (8.2) 10.0%
F	1,500–1,999	474	51.0 (10.0) 9.5%	327	51.0 (10.2) 9.5%	219	52.1 (12.8) 14.6%	188	51.3 (10.4) 10.1%
	2,000–2,499	1,395	50.6 (10.1) 9.8%	925	51.2 (10.9) 11.1%	628	50.8 (10.1) 10.5%	515	50.6 (10.2) 8.9%
	2,500–2,999	1,763	49.9 (9.9) 7.9%	1,196	49.5 (9.6) 7.6%	804	49.1 (9.4) 7.8%	702	49.7 (10.0) 8.4%
	3,000–3,499	652	49.0 (10.0) 7.7%	464	49.1 (9.8) 5.6%	286	49.3 (9.1) 7.0%	257	49.3 (9.4) 6.6%
	≥3,500	86	47.8 (8.6) 5.8%	58	50.7 (14.5) 13.8%	38	48.0 (8.8) 7.9%	35	46.8 (8.9) 8.6%

TABLE S2 Mean and Standard Deviation (SD) of T Scores of Maternal Ratings on the Attention Problems (AP) Scale and the Percentage of Children With a T Score >65 at Age 3, 7, 10, and 12 Years for Each Birth Weight (BW) Category in First-Born Males (M) and Females (F) With Gestational Age ≥37 Weeks

Sex	BW	n	AP 3	n	AP 7	n	AP 10	n	AP 12
M	1,500–1,999	72	52.3 (10.7) 12.5%	41	53.5 (10.6) 17.1%	28	53.1 (8.7) 14.3%	27	51.5 (7.6) 3.7%
	2,000–2,499	715	50.8 (9.8) 7.6%	458	50.8 (10.0) 9.2%	284	51.4 (10.2) 8.1%	242	52.6 (12.0) 14.5%
	2,500–2,999	2,040	49.9 (9.7) 6.4%	1,188	49.9 (9.8) 9.4%	799	50.1 (9·9) 6.3%	678	50.0 (9.7) 8.0%
	3,000–3,499	1,278	49.5 (9.7) 6.5%	809	49.0 (9.3) 7.9%	525	48.4 (9.3) 5.5%	466	48.9 (9.6) 7.3%
	≥3,500	226	48.6 (9.9) 5.3%	128	49.2 (9.8) 7.0%	85	50.4 (9.7) 5.9%	72	49.4 (8.2) 4.2%
F	1,500–1,999	98	52.4 (9.0) 12.2%	63	52.9 (12.0) 12.7%	39	52.6 (9.1) 7.7%	30	52.7 (10.5) 20.0%
	2,000–2,499	1,001	50.6 (10.1) 11.1%	597	51.1 (10.5) 8.9%	446	51.1 (10.8) 9.9%	351	51.5 (11.0) 12.8%
	2,500–2,999	2,188	49.7 (10.0) 9.2%	1,382	49.6 (9.8) 8·0%	913	49.7 (9.7) 6.4%	786	49.8 (9.9) 8.9%
	3,000–3,499	945	48.8 (9.7) 8.6%	584	49.0 (9.6) 7.2%	382	48.9 (9.2) 5.5%	335	49.0 (9.4) 7.5%
	≥3,500	131	48.6 (9.4) 6.1%	76	49.4 (11.0) 11.8%	54	47.4 (9.0) 3.7%	35	46.1 (8.3) 6.8%