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


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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