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Does Low Birth Weight Share Common Genetic or Environmental Risk with Childhood Disruptive Disorders?

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Abstract

Although advances in neonatal care over the past century have resulted in increased rates of survival among at-risk births, including infants with low birth weight, we have much to learn about the psychological outcomes in this population. In particular, although it appears that there is growing evidence that low birth weight may be associated with an increased risk for Attention-Deficit/Hyperactive Disorder (ADHD) symptoms in childhood, few studies have examined birth weight as a risk factor for disruptive disorders that commonly co-occur with ADHD [e.g. Oppositional Defiant Disorder (ODD) or Conduct Disorder (CD)]. In addition, the etiology of the relation between birth weight and these disorders is unknown. The current investigation aimed to better understand the putative role of birth weight in disruptive behavior disorders in the context of potentially confounding genetic and environmental influences by examining phenotypic associations between birth weight and disruptive disorder symptoms across families (using generalized linear models with generalized estimating equations) as well as within families (using linear regression) in two independent twin samples (Sample 1: N = 1676 individuals; Sample 2: N = 4038 individuals). We found negative associations between birth weight and several childhood disruptive disorder symptom dimensions, including inattentive, hyperactive-impulsive, and broad externalizing symptoms in both samples. Nonetheless, the overall magnitude of these associations was very small, contributing to less than 1% of the variance in these symptom dimensions. Within-family associations between birth weight and disruptive disorder symptoms did not differ for monozygotic and dizygotic twin pairs, suggesting that nonshared environmental influences rather than common genetic influences are responsible for these associations. These consistent albeit weak associations between birth weight and disruptive disorder symptoms suggest that, at least in the general population, low birth weight does not represent a major risk factor in the development of these symptoms.

Keywords

Birth weight; disruptive behavior disorders; conduct disorder; ADHD; twins

Low Birth Weight as a Risk Factor for Negative Outcomes in Childhood

Since the introduction of modern neonatal intensive care in the 1960’s and 1970’s, the infant mortality rate in the United States has decreased significantly from 26 deaths per 1000 live births in 1960 to just under 7 deaths per 1000 live births (CDC, 2009; Hack, 2006). As a
consequence, infants with heightened perinatal risk, including those with low birth weight, are now more likely to survive. Because individuals of low birth weight reach childhood, adolescence, and adulthood in greater numbers as a result of these healthcare improvements, it is important to understand the challenges that these individuals may face. Low birth weight is typically defined in human infants as fewer than 2500 grams, or 5.5 pounds (WHO, 2009). Even more extreme categories of low birth weight include very low birth weight (VLBW; fewer than 1500 grams) and extremely low birth weight (ELBW; fewer than 1000 grams). Between the years 2000 and 2007, 7% of all infants born in the United States weighed fewer than 2500 grams (UNICEF, 2007). Although this traditional system of classifying birth weight as low, VLBW, or ELBW may serve as a clinically useful tool, it is important to note that these cutoffs are fairly arbitrary, and birth weight is in fact a continuous construct. As such, the current investigation operationalized birth weight continuously in order to prevent the loss of statistical power associated with the analysis of categorical variables.

Birth weight has been associated with numerous heritable and environmental factors, including gender, race, maternal height, maternal pre-pregnancy weight, paternal height, parity, intrauterine growth and gestational duration during previous pregnancies, prior spontaneous abortion, and maternal nutrition, among others (Kramer, 1987). Recently, birth weight has been examined as an early predictor of child and adolescent neurological and psychological health. Low birth weight has been associated with increased risk for a variety of negative outcomes, including higher rates of neurosensory impairment (e.g. cerebral palsy, blindness, deafness) (Hack, 2006), autism and Asperger’s Syndrome (Hack et al., 2009), smaller head circumference (Allin et al., 2006), poorer social skills and peer problems (Grunau, Whitfield, & Fay, 2004), lower academic achievement (Asbury, Dunn, Pike, & Plomin, 2003), decreased cognitive skills (Bhutta, Cleves, Casey, Cradock, & Anand, 2002) and IQ (Rickards, Kelly, Doyle, & Callanan, 2001), attention problems (Bhutta, Cleves, Casey, Cradock, & Anand, 2002), lower self-esteem (Rickards, Kelly, Doyle, & Callanan, 2001), and even clumsiness (Saigal, Pinelli, Hoult, Kim, & Boyle, 2003). The mechanisms underlying associations between birth weight and these mental health outcomes are not yet fully understood, but birth weight appears to share common etiological pathways with a variety of developmental influences that contribute to cognitive and emotional functioning later in life.

Although utilizing birth weight as a proxy for undetermined prenatal genetic, nutritional, and obstetric influences may allow us to predict associated long-term health outcomes, it is important to note that birth weight is a product of both gestational age and fetal growth rate. Consequently, low birth weight may result from pre-term birth in which an infant’s weight is appropriate for his or her gestational age or from constitutional or pathological factors that predispose an infant to be small for his or her gestational age (WHO, 2003). Because birth weight is a heterogeneous construct that reflects natural and teratogen-induced variation in growth rate as well as stage of gestation, a deeper understanding of the etiology of associations between birth weight and long-term outcomes necessitates greater precision in measurement. Thus, in addition to utilizing a continuous form of measurement for birth weight, the current investigation included gestational age at birth as a covariate. By
controlling for the effects of gestational age, one may infer that variation in birth weight is due to individual differences in the rate of (as opposed to the length of) gestation.

**Childhood Disruptive Disorders as Potential Outcomes of Low Birth Weight**

Disruptive behavior disorders may represent psychological outcomes of particular relevance to birth weight because these disorders have also been associated with intellectual and socioeconomic functioning (Biederman et al., 2009; McKay & Halperin, 2001; Uekermann et al., 2010). Among these disorders, Attention-Deficit/Hyperactivity Disorder (ADHD) affects 3–7% of school-age children in the United States (APA, 2000; CDC, 2009). Symptoms of ADHD include inappropriate levels of hyperactivity, marked impulsivity, and difficulty attending to stimuli across settings. In childhood, these symptoms are associated with academic difficulties and peer rejection (Daley, 2006) and half or more of the children with ADHD will continue to exhibit symptoms into adulthood (Biederman & Faraone, 2005). These symptoms may lead to difficulty in relationships and employment, greater risk for personal injury, and higher rates of incarceration (Retz & Rosler, 2009). ADHD is highly heritable, with genetic influences accounting for 60–90% of the variance according to twin and adoption studies (I. D. Waldman & Gizer, 2006) and hyperactive-impulsive symptoms showing higher heritability than inattentive symptoms (Goodman & Stevenson, 1989; McLoughlin, Ronald, Kuntsi, Asherson, & Plomin, 2007).

Diagnoses of antisocial behavior in children and adolescents [i.e. Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD)] overlap considerably with ADHD diagnoses in childhood and adolescence. It has been estimated that as many as 50% of those diagnosed with ADHD may receive an ODD diagnosis, with 20–40% of those with ADHD also receiving the more severe CD diagnosis (NIMH, 2008). Behavior genetic studies have suggested that common genetic influences are primarily responsible for this overlap in both males and females (Dick, Viken, Kaprio, Pulkkinnen, & Rose, 2005; Kendler, Prescott, Myers, & Neale, 2003; Nadder, Rutter, Silberg, Maes, & Eaves, 2002; Thapar, van den Bree, Fowler, Langley, & Whittinger, 2006; I. D. Waldman, Rhee, S.H., Levy, F., & Hay, D.A., 2001). There is also evidence to suggest that the heritability of ADHD accompanied by antisocial symptoms is greater than the heritability of ADHD alone (Thapar et al., 2006).

ODD is described as a disposition toward anger, negativity, and disrespect for authority coinciding with aggressive behavior and interpersonal difficulties in individuals under 18 and is estimated to affect 2–16% of children in the United States (APA, 2000). It is more prevalent in males than females during childhood, with sex differences in prevalence no longer apparent by adolescence (APA, 2000). Although similar to ODD, diagnostic criteria distinguish CD as a separate disorder by including more serious aggression and rule-breaking, including physical fights, using a weapon in a fight, stealing, vandalism, abusing people or animals, running away, and truancy. Like ADHD, twin and adoption studies have found substantial genetic influences on ODD and CD (Dick et al., 2005; Karnik, McMullin, & Steiner, 2006; Raine, 2002; Simonoff, Pickles, Meyer, Silberg, & Maes, 1998; I. D. Waldman, Rhee, S.H., Levy, F., & Hay, D.A., 2001) with some evidence for specific associations with dopaminergic, serotoninergic, adrenergic, and GABAergic system genes (Boutwell & Beaver, 2008; Comings et al., 2000).
ADHD, Antisocial Behavior, and Birth Weight

As previously demonstrated, birth weight has been associated with a variety of negative psychological outcomes, although these associations were generally modest in magnitude. In this study, we will examine birth weight as a risk factor for ADHD, ODD, and CD. Thus far, there is evidence to suggest that low birth weight is associated with a small increase in risk for ADHD. Several early studies found significant negative associations between birth weight and attention problems and/or hyperactivity (Botting, Powls, Cooke, & Marlow, 1997; Levy, Hay, McLauglin, Wood, & Waldman, 1996; Mick et al., 2002; Pharoah, Stevenson, Cooke, & Stevenson, 1994), but these associations were generally small and inconsistent across males and females. In 2002, a meta-analysis of research on cognitive and behavioral outcomes of preterm individuals reported an increased risk for ADHD in preterm children (pooled RR = 2.64) (Bhutta et al., 2002). The preterm individuals included in these studies averaged less than 2500 grams at birth, whereas controls across studies averaged greater than 3000 grams (Bhutta et al., 2002). Since these studies were published, additional studies have reported associations between birth weight and levels of inattentive and/or hyperactive symptoms with effect sizes ranging from small (Cohen’s d > 0.2) (Anderson et al., 2011; Heinonen et al., 2010; Linnet et al., 2006; Lund, Vik, Skrane, Brubakk, & Indredavik, 2011; Saigal, Pinelli, Houl, Kim, & Boyle, 2003) to medium (Cohen’s d > 0.5) (Hack et al., 2009) or large (Cohen’s d > 0.8) (Grunau, Whitfield, & Fay, 2004; Indredavik et al., 2010). Other investigations, however, have provided no support for these associations (Buschgens et al., 2009; Hack et al., 2004; Langley, Holmans, van den Bree, & Thapar, 2007; Nigg & Breslau, 2007; Sciberras, Ukoumunne, & Efron, 2011). A more recent meta-analysis of very preterm and/or very low birth weight children (≤33 weeks or ≤1500 grams) reported attention problems to be the most pronounced deficits present in this population (Aarnoudse-Moens, Weisglas-Kuperus, van Goudoever, & Oosterlaan, 2009).

Research designs utilizing birth weight discordance to predict behavioral discordance in ADHD symptoms within monozygotic twin pairs have generally supported a nonshared environmental association between birth weight and these symptoms, with the smaller twin per pair displaying more ADHD symptoms than his or her cotwin (Asbury, Dunn, & Plomin, 2006; Hultman et al., 2007; Sharp et al., 2003). Lehn and colleagues (2007) observed longitudinally that the affected twin within each pair was more likely to have had a lower birth weight and a shorter stature than the unaffected twin at 6 months, 1 year, and 2 years of age. The current investigation will utilize both between- and within-pair phenotypic analyses in order to further examine whether significant associations between birth weight and ADHD symptoms are present across and within families.

Several studies have specifically examined birth weight as a predictor of CD and ODD symptoms. Although there are more studies that have reported null associations between birth weight and ODD or CD symptoms (Botting, Powls, Cooke, & Marlow, 1997; Gatzke-Kopp & Beauchaine, 2007; Langley et al., 2007; Levy, Hay, McLaughlin, Wood, & Waldman, 1996; Saigal et al., 2003) than there are studies that have reported significant associations (Langley et al., 2008; Mankuta, Goldner, & Knafo, 2010; Thapar et al., 2005), several of the studies with null effects may have statistically over-controlled for variables relevant to both child antisocial behavior and birth weight, including parental antisocial...
behavior and child ADHD symptoms (Langley et al., 2007; Gatzke-Kopp & Beauchaine, 2007). Thus, meaningful variance common to these phenotypes may have been excluded in the analyses described by these studies, biasing outcomes toward nonsignificance. Associations between birth weight and later CD and ODD symptoms consequently remain uncertain, and further research is needed to clarify previous findings. Because these symptoms show such strong overlap with ADHD, which has shown fairly consistent negative associations with birth weight, it is hypothesized that low birth weight may be related to increased risk for ODD and CD.

The current investigation built upon this literature in several ways. First, in addition to examining independent associations between birth weight and each of the disruptive behavior disorders (ADHD, ODD, and CD), we examined birth weight as a risk factor for a broader dimension of childhood externalizing problems created by summing the four previously described symptom dimensions (inattention, hyperactive-impulsive, ODD, and CD) for each child. Substantial phenotypic overlap has been found for symptoms of ADHD and antisocial behavior (Caspi et al., 2008), and broad dimensions of externalizing encompassing symptoms across DSM-IV diagnostic categories have shown higher heritability than those based on individual diagnostic categories (Dick et al., 2008). Thus, we used this broad-based externalizing dimension to determine whether the risk conferred by birth weight was specific to each disorder, or more generalized. Based on previous findings and the aforementioned overlap among these symptom dimensions, we predicted that birth weight would be negatively associated with all disruptive disorder symptoms. A related goal was to determine whether the magnitude of birth weight’s effects were appreciable or modest, which would have important translational implications.

Second, because our sample comprised monozygotic (MZ) and dizygotic (DZ) twin pairs, we had the ability to examine these associations both between families and within families. Within-family analyses in twins may be incrementally useful beyond the traditional between-family design, because MZ and DZ twin pairs differ in the extent to which they are genetically similar. DZ twins (who share only 50% of their genes identical-by-descent) may differ in birth weight or disruptive symptoms as a result of genetic or environmental differences, whereas MZ twins (who share 100% of their genes) may differ from one another only due to differing environments. Thus, associations between birth weight differences and disruptive disorder symptom differences within DZ twin pairs may be due to common genetic and/or environmental influences on these phenotypes, but these associations within MZ twin pairs may only be due to common nonshared environmental influences. Consequently, we included zygosity as a moderator of associations in our within-family analyses of birth weight and disruptive symptoms, which allowed us to infer whether common genetic or nonshared environmental influences may play a role in these associations.

Third, much of the previous research that has examined low birth weight as a predictor of later negative outcomes has not controlled for the confounding of birth weight with gestational age. Low birth weight in full-term infants may be indicative of a different set of potential risks than low birth weight in pre-term infants. We were specifically interested in whether birth weight resulting from being small for one’s gestational age was associated...
with increased psychosocial risk independently of the length of one’s gestation. We therefore included gestational age as a covariate in order to account for this potential confound as well as reduce the extraneous variance in birth weight, potentially augmenting relations between birth weight and symptom levels. It is important to note here that controlling for gestational age allowed us to examine variance in fetal growth rate within our sample, but these norms were not population-based.

Fourth, we replicated all analyses on a second, unrelated twin sample. Thus, we were able to provide further support for the generalization of our findings across children of different ages and backgrounds using different forms of phenotypic measurement. In addition, through the use of meta-analytic techniques, we were able to determine whether the associations of interest were significant and consistent across both samples as well as increase our power to detect small effects that may have gone undetected in the individual samples.

Methods

Participants

The current study utilizes information obtained from birth records and symptom questionnaires for two separate samples of twins. The first sample consisted of 884 twin pairs (407 MZ pairs and 477 DZ pairs) born in the state of Georgia between 1980 and 1991. Participants’ ages during the completion of the questionnaires ranged from 4 to 16 years (M = 8.6, SD = 2.6). The first sample was 51% female and 49% male, with an ethnic composition of 87% European-American, 8% African-American, and 1% Asian or mixed ethnicity. Ethnicity for the remaining 4% of the sample was unknown. The second sample consisted of 2019 twin pairs born in the state of Tennessee who were aged 6–17 years at the time of the study (M = 11.7, SD = 3.3). The second sample was also 51% female and 49% male, but with an ethnic composition of 71% European-American, 24% African-American, and 5% Other.

Method

Georgia sample—Demographic characteristics of the Georgia sample are listed in Table 1. Birth records were obtained for all twins born in the state of Georgia between 1980 and 1991. Between 1992 and 1993, the 5,620 families for whom birth records were available were mailed a request to join the Georgia Twin Registry (GTR) and a Family Information Form (FIF) designed to elicit additional demographic and zygosity information on the twins. Of these families, 1,567 agreed to join the GTR and their FIF data was entered into the GTR database. A substantial number of the original 5,620 families could not be found, as their FIFs were returned to us unopened due to incorrect or outdated addresses. Several years later, the 1,567 twin families who registered were sent an additional set of questionnaires, including a rating scale of symptoms of the common child and adolescent DSM-IV disorders (i.e., the Emory Diagnostic Rating Scale, EDRS), as well as a small monetary compensation ($10) in an effort to increase the response rate, and reminder postcards were sent to families who did not respond. At least 363 questionnaires were returned to the registry due to incorrect addresses, and completed questionnaires were returned for 885 twin pairs, yielding
a 73.5% response rate. Of the 885 twin pairs’ questionnaires returned, complete symptom data was included for 838 pairs and were used in analyses.

A comparison of GTR families who provided data for the current investigation with those who did not yielded no significant between-group differences in parent age or education, family income, or child’s sex, but small group differences were found between samples for several characteristics. There was a slightly higher representation of MZ twin pairs among participants, $\chi^2 = 6.19, p = .03$, and participants were more likely than nonparticipants to report Caucasian ancestry (88% vs. 82%) and less likely to report African-American ancestry (9% vs. 11%) ($\chi^2 = 21.56, p < .001$). In addition, participant families were marginally less likely to be receiving government-provided financial assistance (0.8% vs. 1.7%), $\chi^2 = 6.72, p = .057$, were less likely to be living apart from the twins’ biological father (14.2% vs. 19.2%), $\chi^2 = 7.07, p = .009$, and showed a linear trend for having fewer children (74% vs. 80% of twins had additional siblings), $\chi^2 = 3.02, p = .085$.

Tennessee sample—Demographic characteristics of the Tennessee sample are listed in Table 1. Addresses of twins aged 6–18 years who had been born in Tennessee and still currently resided in the state were provided by the Tennessee Department of Health. A sample of these twins stratified by age and geographic region was selected for inclusion in the present study. Interviews with adult caretakers regarding their children’s dispositions and behavior, including symptom presentation for DSM-IV disorders, were successfully completed for approximately 70% of the eligible families (N = 2,063 families). After excluding families for whom at least one child had been diagnosed with a psychotic disorder or autism and families with incomplete data, the sample consisted of 2,019 families (N = 4,038 children). The caretakers interviewed were predominantly mothers (91%). For more detailed information on this sample, please refer to Lahey et al., 2008.

Measures
Birth weight

Georgia sample: Perinatal data were obtained from state birth records, including information on each participant’s birthdate, gender, ethnic background, parental educational background, gestational age, and birth weight (in grams or pounds). All birth weights were subsequently converted to grams by the investigators.

Tennessee sample: Children’s birth weights and gestational ages were reported by an adult informant, primarily participants’ biological mothers. Retrospective maternal reports of birth weight and gestational age ten to fifteen years following childbirth have been previously demonstrated to correlate strongly with birth weight data obtained from medical records (intraclass correlations = 0.99 for birth weight, 0.90 for gestational age; Yawn, Suman, & Jacobsen, 1998).

Zygosity and demographics

Georgia sample: Zygosity information was collected via parent report on the Family Information Form (FIF) in an initial mailing to Georgia Twin Registry participants. Parents responded to eight questions regarding their twins’ physical likeness. Sample questions
included: “Is it hard for strangers to tell your twins apart based on their physical appearance?” and “Are your twins as alike as two peas in a pod?” Responses were coded as “1” to indicate that the twins were similar on a trait and “0” to indicate that the twins differed. Responses across all eight questions were averaged, resulting in one score per dyad. Dyads with average scores of 0.5 or above were categorized as MZ twin pairs, and dyads with average scores less than 0.5 were categorized as DZ twin pairs, given that this cutoff appeared to maximize the separation between the zygosity scale scores by zygosity group. This method of zygosity determination has been shown to have 96–99% accuracy as compared with direct genotyping techniques (Bonnelykke, Hauge, Holm, Kristoffersen, & Gurtler, 1989; Jackson, Snieder, Davis, & Treiber, 2001; Spitz et al., 1996).

Tennessee sample: Adult caretakers reported on each twin pair’s zygosity status on a short questionnaire containing nine questions about their twins’ physical likeness (Peeters, Van Gestel, Vlietinck, Derom, & Derom, 1998). Most questions overlapped with those used with the Georgia sample. Twin pairs for whom zygosity could not be determined with confidence using this method were assigned to MZ or DZ status based on their similarity across 12 polymorphic genotypic markers.

Disruptive disorder symptom dimensions

Georgia sample: The Georgia twins’ primary caregivers completed the Emory Diagnostic Rating Scale (EDRS), which instructs parents to rate their twins on a series of attributes and behaviors on a Likert scale (with 0 describing the child “not at all” and 4 describing the child “very well”) (I. D. Waldman et al., 1998). The EDRS items reflect symptoms of common DSM-IV childhood psychiatric disorders. The ADHD (inattention, hyperactivity-impulsivity) and antisocial behavior (ODD and CD) symptom dimension scores were derived by averaging each child’s symptom scores across the items within each of these respective scales. Each child’s mean symptom score thus ranged from 0 to 4 per symptom dimension, indicating the severity of his or her symptom presentation. Internal consistency reliability of these scales in the current study was α = .91 for ODD (8 items), .95 for Inattention (9 items), .89 for Hyperactivity-Impulsivity (9 items), and .82 for CD (15 items).

Tennessee Sample: Adult Caretakers in the Tennessee sample completed interviews in which they rated their twins’ disruptive behavior symptoms using the Child and Adolescent Psychopathology Scale (CAPS; Lahey et al., 2004). CAPS items are based on symptoms of common DSM-IV childhood disorders and utilize a Likert scale response format (with 1 describing the child “not at all” and 4 describing the child “very much”). As with the EDRS, ADHD and antisocial behavior symptom dimension scores were derived by averaging each child’s parent-reported symptom scores within each of these scales. Internal consistency reliability of these scales has been previously demonstrated to be high: α = .92 for Inattention (9 items), .94 for Hyperactivity-Impulsivity (9 items), .94 for ODD (8 items), and .86 for CD (15 items) (Lahey et al., 2004).

Family income

Georgia sample: Information on family income was collected via parent report on the FIF. Twelve income categories were provided, with Category 1 containing incomes up to
$10,000 and each successive category increasing by an interval of $10,000. Category 11 included incomes between $100,000 and $150,000, and Category 12 included incomes above $150,000. Parents were instructed to circle the number of the category that corresponded to the best estimate of the family’s income during the past year. The income scale was log-transformed for use as a covariate in all analyses.

Tennessee sample: Parents responded to a single question regarding the total annual household income for the past year. Twenty-three income categories were provided, beginning with Category 00 (“No income”) and each successive category increasing by intervals of $1000 up through Category 10 ($9,000–$9,999). Following Category 10, interval sizes increased exponentially from $2,000 (Categories 11–15) to $15,000 (Category 22) as reported income increased. Income over $100,000 was reported in Category 23. This income scale was also log-transformed for use as a covariate in all analyses.

Analyses

Phenotypic relations between birth weight and disruptive disorder symptoms: In each sample, the ADHD, ODD, CD and composite externalizing symptom dimensions were regressed on birth weight in order to test the hypothesized phenotypic associations between low birth weight and increased disruptive disorder symptomatology. Twins were treated as nested within twin pairs and Generalized Estimating Equation (GEE) methods were used in order to correct for this observational nonindependence and to generate appropriate standard errors and statistical tests. We included the following covariates in all models: child’s age, sex, mother’s age at childbirth (which may influence both prenatal care and her child’s disruptive disorder symptoms), gestational age (discussed previously), family income, and birth weight. Initially, we also included ethnicity, age\(^2\), birth weight\(^2\), age X sex, age\(^2\) X sex, gestational age\(^2\) and income X birth weight interaction terms as covariates, but because these terms were not consistently associated with the twins’ disruptive disorder symptoms across samples, they were not included in the final set of models. The variance explained (\(R^2\)) uniquely by birth weight was estimated from the final model for each symptom dimension following this analytic process. Levels of significance for the main effects of birth weight were determined using one-tailed tests in the direction hypothesized \(a\ priori\) (i.e. in the negative direction). These directional hypotheses were consistent with both the vast majority of findings throughout the extant primary literature and meta-analytic reviews that low birth weight is a risk factor for negative cognitive and emotional outcomes. Accordingly, associations were only reported as significant if they were in the hypothesized direction and any findings in the opposite direction constituted evidence against our hypotheses. Following independent GEE analyses for each sample, meta-analytic procedures were used to calculate composite effect sizes to determine the magnitude and significance of the associations between birth weight and each symptom dimension in between-family analyses in both samples.

Within-family analyses of birth weight and disruptive disorder symptoms: In addition to phenotypic relations between birth weight and disruptive disorder symptoms across the sample (i.e. between families), within-pair associations between these variables were also investigated separately for each sample. Continuous difference scores for both birth weight
and the ADHD, ODD, CD, and composite externalizing symptom dimensions were assigned to each twin pair by calculating the signed difference in these scores within cotwins for each variable. Thus, the terms for birth weight included in the within-family analyses describe intrapair variation in birth weight (the extent to which one’s birth weight is lower or higher than that of one’s cotwin), which is not necessarily indicative of whether the individuals’ birth weights are actually “low” or “high” with respect to other individuals in the sample. Twin differences in symptoms were regressed on the twin differences in birth weight as well as the previously mentioned covariates in the following manner: First, child’s age, ethnicity, and gestational age were included as covariates in order to control for their potential effects on the magnitude of intrapair differences in symptom levels and/or birth weight. Next, in order to account for sex differences in symptom expression and birth weight, two contrast terms were entered: a) male pairs compared to female pairs, and b) same-sex pairs compared to opposite-sex pairs. Third, the birth weight difference scores were entered into the model followed by (fourth) the birth weight X twin sex contrast interaction terms in order to test for moderation of the association between birth weight differences and symptom differences by sex composition of the twin pairs. Fifth, zygosity was entered into the model and sixth, a zygosity X birth weight interaction term was entered to test for zygosity as a moderator of the association between birth weight differences and symptom differences. Lastly, we included family income and an income X birth weight interaction term in each model in order to test whether the predictive value of birth weight may differ by level of economic hardship.

Following the linear regressions, meta-analytic procedures were utilized once again in the calculation of composite effect sizes in order to determine 1) the overall strength of the associations between birth weight and each symptom dimension across both samples, and 2) whether zygosity emerged as a significant moderator of these putative associations across both samples. Levels of significance for associations with birth weight were again determined using one-tailed tests in the hypothesized direction (i.e. the twin with the lower birthweight showing greater symptom levels), and thus associations were only reported to be significant if in the hypothesized direction.

**Results**

**Descriptive statistics and demographic analyses**

**Georgia sample**—The distribution of birth weight for both samples is listed in Table 1. Although birth weight was measured and analyzed continuously in the current investigation, information regarding the traditional cutoffs in each sample (i.e. low birth weight, VLBW, and ELBW) is also provided. Birth weight was normally distributed with a mean of 2546.87 grams (SD = 585.79). On average, males weighed 147 grams more than females, a significant difference, \( t(1718.26) = 5.35, p < .001 \). Significant differences in the distribution of birth weight by ethnicity were also observed, \( F(4,1678) = 4.45, p = .001 \). On average, European-American newborns weighed 188 grams more than African-American newborns and 389 grams more than Asian newborns. In addition, DZ twins weighed 54.26 grams more than MZ twins (\( M = 2568.17 \) and \( M = 2513.91 \), respectively), a difference that only approached significance, \( t (1733.79) = 1.88, p = .06 \).
The mean difference in birth weight within twin pairs was 292.66 grams ($SD = 263.90$). Within pairs, MZ twins on average exhibited smaller differences in birth weight than DZ twins [$M = 245.97$ grams and $M = 332.35$ grams, respectively; $t (851.20) = 4.94, p < .001$]. In addition, contrasts revealed significantly greater differences in birth weight within opposite-sex twin pairs ($M = 332.35$ grams, $SD = 286.97$) than within same-sex twin pairs ($M = 245.97$ grams, $SD = 225.02$), $t (355.01) = 2.87, p = .004$, with boys weighing more than their female cotwins.

**Tennessee sample**—The mean and distribution of birth weight in the Tennessee sample was similar to that of the Georgia sample ($M = 2434.66$ grams, $SD = 602.17$), but individuals in the Tennessee sample had a significantly shorter length of gestation, (34.6 versus 37.6 weeks, $t(5712) = 30.29, p < .001$). Males weighed an average of 112.83 grams more than females at birth, a significant difference, $t(4007.47) = 5.97, p < .001$. On average, African-American newborns weighed 149.97 grams less than other ethnic groups. DZ twins weighed 121.62 grams more than MZ twins, a significant difference, $t(3287.59) = 6.32, p < .001$.

Within twin pairs, the average difference in birth weight was 270.74 grams ($SD = 251.18$), with MZ twin pairs exhibiting smaller differences in birth weight than DZ pairs [$M = 231.51$ grams and $M = 294.06$ grams, respectively; $t (1890.379) = 5.82, p < .001$]. Again, contrasts revealed greater differences in opposite-sex twin pairs ($M = 314.73$ grams, $SD = 278.1$) than in same-sex pairs ($M = 252.27$ grams, $SD = 236.6$), with boys weighing more than their female cotwins.

**ADHD, ODD, CD, and Broad Externalizing Symptoms**

**Georgia sample**—Symptom dimension scores on the ECRS range from 0–4. Average inattentive, hyperactive-impulsive, ODD, and CD symptoms scores for the Georgia sample are listed in Table 2. A broad externalizing symptom dimension was calculated as the mean of each child’s z-scores across all disruptive symptom dimensions. The distributions of symptom scores were positively skewed, indicating that parents of most children reported few symptoms. Within twin pairs the distribution of symptom differences was highly leptokurtic, indicating that within-pair differences tended to be small. For all symptom dimensions, Mann-Whitney U tests indicated significantly higher symptom scores for boys than girls (see Table 2).

**Tennessee sample**—Symptom dimension scores on the CAPS range from 1–4. Average disruptive symptom scores for the Tennessee sample are listed in Table 2. Again, a broad externalizing symptom dimension was calculated from the means of the other z-transformed symptom dimensions. Symptom distributions were similar to those reported within the Georgia sample and Mann-Whitney U tests confirmed higher symptom scores for boys than girls across all dimensions (see Table 2).

**Between-Family Analyses of Birth Weight and Disruptive Disorder Symptoms**

An outlier analysis was first performed for the between-family analyses to eliminate cases exerting disproportionate influence on the magnitude of associations. Pearson residuals were
calculated from generalized linear models with generalized estimating equations. For nearly all analyses, cases with Pearson residuals exceeding the recommended cutoff > 2 were removed. Following the outlier analysis, approximately 4–9% of cases were removed from the Georgia sample and 3–4% of cases were removed from the Tennessee sample.

The results of the between-family analyses of birth weight and disruptive disorder symptoms are shown in Table 3. After controlling for significant covariates, birth weight was negatively associated with inattentive symptoms in both samples. Birth weight was also associated with hyperactive-impulsive symptoms and broad externalizing symptoms in the predicted direction in both samples, but these associations were only trends in the smaller Georgia sample. Although birth weight was significantly associated with CD symptoms in the Georgia sample in the predicted direction, this association was non-significant in the Tennessee sample. Further, non-significant associations were found between birth weight and ODD in both samples. Following meta-analytic procedures, significant negative associations emerged in the combined sample for all symptom dimensions. All effects observed within the combined sample were extremely small, with birth weight contributing to less than 1% of the variance in any symptom dimension.

In order to test whether traditional cutoffs for low birth weight (<2500 grams) might provide additional predictive utility, all generalized linear models for each sample were reanalyzed with birth weight modeled as a dichotomous predictor. In the Georgia sample, the categorical term for low birth weight emerged as a significant predictor of CD symptoms in the hypothesized direction, \( \chi^2 = 4.40, p = 0.018 \), but was not associated with any other symptom dimension. In the Tennessee sample, the categorical term for low birth weight emerged as a significant predictor of inattentive and broad externalizing symptoms in the hypothesized direction (for inattention, \( \chi^2 = 4.60, p = 0.016 \); for externalizing, \( \chi^2 = 6.76, p = 0.005 \)). Overall, based on the observed patterns of significance for the continuous and categorical birth weight terms across both samples, the categorical term appeared to be a somewhat weaker predictor of disruptive disorder symptoms than birthweight considered as a continuous variable.

Within-Family Analyses of Twin Differences in Birth Weight and Disruptive Disorder Symptoms

An outlier analysis was also performed for the within-family analyses to check for cases that might be exerting disproportionately large influence. Symptom differences were regressed on birth weight differences using the previously described process after selecting out cases for which regression diagnostics were greater than the conventionally recommended values (i.e., a Cook’s D cutoff ≥4/N) (Rawlings, Pantula, & Dickey, 1998). As a result, approximately 8–10% of cases were removed from the Georgia sample and 4–6% of cases were removed from the Tennessee sample. The results of these regressions sans outliers are listed in Table 4. In the Georgia sample, twin differences in birth weight significantly predicted twin differences in CD symptoms only. In contrast, in the larger Tennessee sample, the twin with lower birth weight showed small but significant increases in risk for inattentive, hyperactive-impulsive, and broad externalizing symptoms, but non-significant
increases in ODD and CD symptoms. Zygosity did not emerge as a significant moderator of associations within either sample.

Following meta-analytic procedures, across both samples combined continuous within-pair differences in birth weight emerged as a significant predictor of within-pair differences in inattentive, hyperactive-impulsive, and CD symptoms, and a marginally significant predictor of within-pair differences in broad externalizing symptoms, all in the hypothesized direction (i.e., the twin with lower birth weight exhibited significantly elevated symptoms). Nonetheless, these associations were again very small, contributing less than 1% of the variance in within-pair disruptive disorder symptom differences. There were no significant zygosity X birth weight interactions for any disruptive disorder symptom dimension in the meta-analytically combined samples.

**Discussion**

In the current study we examined birth weight as a risk factor for childhood disruptive disorder symptoms. Phenotypic associations between birth weight and ADHD, ODD, CD, and broad externalizing symptom dimensions were examined within and between families. Overall, we found support for our hypotheses regarding associations between childhood disruptive disorder symptom dimensions and birth weight. We proposed that there would be phenotypic associations between birth weight and later ADHD, ODD, and CD between families. Evidence for associations between birth weight and ADHD in the previous literature has been mixed (Botting et al., 1997; Levy et al., 1996; Mick, Biederman, Prince, Fischer, & Faraone, 2002; Pharoah, Stevenson, Cooke, & Stevenson, 1994), likely owing to the modest effects of birth weight, although it appears that more studies have reported significant negative associations between birth weight and ADHD than null or positive associations. We did find that birth weight was negatively associated with risk for inattentive, hyperactive-impulsive, and broad externalizing symptoms in both the within- and between-family analyses. Despite their consistency, however, all of the reported effects were very small (i.e., explaining < 1% of the variance), suggesting that low birth weight does not represent a major risk factor in the development of ADHD or other externalizing symptoms in the general population.

In addition, prior to the current investigation few studies had examined associations between birth weight and childhood antisocial behavior. Based on the overlap of ADHD with ODD and CD symptoms in the literature as well as in the current sample, we predicted that birth weights at the lower end of the continuum would be related to greater symptoms of ODD, CD, and externalizing. Although some significant associations were reported between birth weight and CD symptoms, there was no consistent pattern of associations between birth weight and risk for ODD across both sets of analyses, suggesting that birth weight may not be a substantial or consistent risk factor for common childhood behavior problems. Further, the use of a broad externalizing dimension comprising inattentive, hyperactive-impulsive, ODD, and CD dimensions did not yield larger effect sizes than those found for the inattentive and hyperactive-impulsive symptom dimensions alone, suggesting that birth weight is not better represented as a general risk factor for externalizing behavior. These findings are surprising given the previously described overlap between ADHD symptoms.
and antisocial behavior, but they are consistent with the null findings and small effect sizes reported in several studies thus far.

We used one-tailed p-values to evaluate the evidence for the birth weight – disruptive disorders associations based on the a priori hypothesis that it is lower birth weight that is a risk factor. We feel this is justified for several reasons. First, the extant literature bears out this direction of association, as the vast majority of studies find that it is lower birth weight that is related to later behavior problems, including several meta-analyses that have documented this relation across many studies and thousands of participants. Second, an important concern regarding the use of one-tailed tests is that there is no assurance that the direction of the test was set a priori, as opposed to post-hoc after the analyses were conducted and the results were obtained. We steadfastly avoided this problem of ad hoc hypotheses by counting as evidence against our a priori hypotheses the rare findings that went in the opposite direction from what we predicted. For example, if the association between birth weight and inattention was positive, such that inattention was higher in children who had greater birthweight, we calculated the one-tailed p-value as 1 − p/2, rather than p/2. So if the obtained two-tailed p-value was .05, instead of reporting it as .025 we reported it as .975, thus it constituted strong evidence against our directional predictions. Nonetheless, it should be acknowledged that two of the results that were reported as significant using one-tailed p-values only would be considered marginally significant if two-tailed p-values were used (i.e., p = .06 for CD in the between-family analysis of the Georgia sample and p = .06 for broad externalizing in the within-family analysis of the Tennessee sample). Further, no associations would have emerged as significant or even approached significance in the direction opposite what we predicted if we had instead chosen to conduct two-tailed tests.

The pattern of associations between birth weight and the disruptive disorder symptom dimensions differed somewhat across the within- and between-family analyses. Although it may be interpreted as a sign of inconsistency or as an indication that these associations lack robustness, this observation may actually inform us about the etiology of these associations. Between-family associations for two phenotypes of interest may result from common genetic influences, shared environmental influences (such as family income or parenting practices), or nonshared environmental influences (such as pre- or peri-natal complications experienced by one but not the other twin in a pair) that contribute to both phenotypes. Within-family associations, in contrast, may only result from genetic influences (in nonidentical twins or siblings) or nonshared environmental influences (in identical twins) common to the phenotypes, because shared environmental influences by definition do not differ within families and thus cannot contribute to twin or sibling differences. The presence of significant associations between birth weight and CD in the within-family but not between-family analyses suggests that nonshared environmental influences may contribute to the overlap between birth weight and more serious antisocial behavior. Because associations between birth weight and the ADHD symptom dimensions were significant both within- and between-families, this suggests that both shared and nonshared environmental influences are present.
Further, because genetic differences may contribute to within-pair differences in both birth weight and disruptive disorder symptoms in DZ but not MZ twins, we tested whether within twin-pair associations differed by zygosity, as stronger associations in DZ than MZ pairs may indicate common genetic influences on birth weight and disruptive symptoms. No significant interactions were found by zygosity in the associations between the differences in birth weight and the differences in symptom dimensions, reducing the likelihood that the phenotypic associations found are due to common genetic influences on birth weight and disruptive disorder symptoms. Nonetheless, it is possible that the present analyses are not the most powerful for revealing common genetic influences on birth weight and later disruptive disorder symptoms, and other methods such as multivariate behavior genetic analyses using biometric model fitting may afford greater power to detect such influences.

After controlling for the effects of gestational age, birth weight was negatively associated with risk for later disruptive disorder symptoms, suggesting that factors within the prenatal environment contributing to a slower rate of growth may have a negative impact on later psychological outcomes. Factors that have previously been found to contribute to intrauterine growth have included maternal nutrition (Belkacemi, Nelson, Desai, & Ross, 2010; Imdad & Bhutta, 2011) and placental development (Belkacemi et al., 2010), physical activity during pregnancy (Takito, Benicio, & Neri Lde, 2009), psychosocial stress (Littleton, Bye, Buck, & Amacker, 2010), and tobacco exposure (Suter, Abramovici, & Aagaard-Tillery, 2010), among others. Indeed, it appears that there may be complex relations between prenatal smoking exposure and the phenotypes of interest in the current investigation. Little and Sing (1987) found that the pattern of genetic and environmental influences on infant birth weight differed for smoking and nonsmoking mothers, and other investigations have reported associations between prenatal cigarette smoke exposure, low birth weight, and behavioral problems in children (Buschgens et al., 2009; Kramer, 1987; Langley et al., 2007), though these associations may be confounded by factors such as maternal ADHD symptoms (Thapar, et al., 2009). Because smoking during pregnancy was reported by very few mothers in the current investigation, we were unable to examine whether prenatal cigarette exposure moderated or accounted for the associations between birth weight and disruptive disorders. In further examining the mechanisms underlying the reported associations between birth weight and disruptive disorder symptoms, it will be important to take these factors into consideration.

While our primary goal was to test for associations between birth weight and the disruptive disorder symptom dimensions, a related goal was to characterize the magnitude of those associations. If those associations are of appreciable magnitude this has obvious translational implications for developing preventive interventions that may mitigate low birth weight and its sequelae. Perhaps less obvious, but no less important, is the finding that – while significantly associated with later externalizing problems – the observable effects of a slower than average fetal growth rate are only minimal. This finding was consistent with much of the previous research indicating that low birth weight is associated with very small increases in ADHD symptoms (Anderson et al., 2011; Heinonen et al., 2010; Linnet et al., 2006; Lund et al., 2011; Saigal et al., 2003). We hope that these findings may prevent needless worry among the parents of infants born with low birth weight in the absence of other serious pre- or perinatal complications, as the evidence suggests that these infants will
not likely exhibit any major differences in attentional functioning, impulsivity, or behavioral problems as children. Indeed, there is evidence to suggest that these infants may “catch up” developmentally with their peers, as they display normative patterns of cognition (Paulson, Chauhan, Hill, & Abuhamad, 2012), language acquisition (Stolt, Lehtonen, Haataja, & Lapinleimu, 2012) and emotional functioning (Hall & Wolke, 2012) later in childhood.

Our study had several limitations. First, there was a significant difference in the mean gestational age between the GA and TN samples, which may indicate differences in underlying levels of prenatal risk that should be considered when comparing these findings. In addition, because the current investigation utilized non-referred twin samples, we should be cautious in generalizing results to singleton or clinically-referred populations. Healthy growth differs for twins and singletons (van Dommelen, de Gunst, van der Vaart, van Buuren, & Boomsma, 2008), as illustrated by the fact that nearly 50% of our twin sample could be categorized as low birth weight under the typical cutoffs (<2500 grams). Differences in size between twins and singletons at birth are not entirely accounted for by their shorter than average gestation, and it appears that these differences are reduced in the first few years of life as twins start to “catch up” in size (van Dommelen et al., 2008). Consequently, birth weight may have somewhat different meaning in twins than in singletons, and thus replication in an adoptive sample may provide similar genetically-informative findings without the limited generalizability. On a positive note, although physical growth in twin samples shows large deviation from singleton norms, a recent investigation found that the trajectories of externalizing symptoms across twins and singletons during middle and late childhood were very similar (Robbers et al., 2010). These findings suggest that research on the development of externalizing psychopathology in twins may be generalizable to nontwin populations.

In addition, a major strength of the current investigation was its utilization of two unrelated twin samples in all analytical procedures. It is noteworthy that we provided evidence for the replicability and consistency of our findings, given that the associations between birth weight and disruptive disorder symptoms have been inconsistent in the literature thus far. Indeed, the presence of similar patterns and magnitudes of effects across both samples is testament to the robustness of our findings, particularly because different methodologies were utilized for data collection and phenotypic measurement across both samples. Further, the use of meta-analytic procedures allowed us to conduct more powerful tests of association, allowing us to infer the presence or absence of associations across both samples with greater confidence despite marginal significance in one or both samples considered individually.

In summary, this investigation used multiple statistical methods, including both between-family phenotypic analyses and within-family genetically-informative analyses, to examine associations between birth weight and disruptive disorder symptoms across two independent samples of twins. These associations have previously been inconsistent in the literature, and our findings suggest that very small but significant associations exist between birth weight and childhood disruptive disorder symptoms. These associations appear to be primarily due to common shared and non-shared environmental influences on these phenotypes, rather than to common genetic risk factors. Although the nature of our twin samples may limit the
generalizability of findings somewhat, this investigation exemplifies the necessity of genetically-informative designs in the examination of putative environmental risk factors for behavioral problems in children.

Acknowledgments

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References


Langley K, Holmans PA, van den Bree MB, Thapar A. Effects of low birth weight, maternal smoking in pregnancy and social class on the phenotypic manifestation of Attention Deficit Hyperactivity Disorder and associated antisocial behaviour: investigation in a clinical sample. BMC Psychiatry. 2007; 7:26. 1471-244X-7-26 [pii]. 10.1186/1471-244X-7-26 [PubMed: 17584500]


# Table 1

Basic demographics and distribution of birth weight in each sample

<table>
<thead>
<tr>
<th></th>
<th>Georgia Sample</th>
<th>Tennessee Sample</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Basic Demographics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age (SD) in years</td>
<td>8.6 (2.6)</td>
<td>11.7 (3.3)</td>
</tr>
<tr>
<td>% Male</td>
<td>49%</td>
<td>49%</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>87% Caucasian, 8% African American</td>
<td>71% Caucasian, 24% African American</td>
</tr>
<tr>
<td>Mean mother’s age at twins’ birth (SD) in years</td>
<td>29.21 (4.47)</td>
<td>28.01 (5.34)</td>
</tr>
<tr>
<td>Zygosity</td>
<td>54% DZ, 46% MZ</td>
<td>63% DZ, 37% MZ</td>
</tr>
<tr>
<td>Mean gestational age (SD) in weeks</td>
<td>37.55 (3.35)</td>
<td>34.62 (3.32)</td>
</tr>
<tr>
<td><strong>Distribution of Birth Weight</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean birth weight (SD) in grams</td>
<td>2546.87 (585.79)</td>
<td>2434.66 (602.17)</td>
</tr>
<tr>
<td>25th percentile (grams)</td>
<td>2211</td>
<td>2070</td>
</tr>
<tr>
<td>50th percentile (grams)</td>
<td>2579</td>
<td>2466</td>
</tr>
<tr>
<td>75th percentile (grams)</td>
<td>2948</td>
<td>2835</td>
</tr>
<tr>
<td>% ELBW (&lt;1000 grams)</td>
<td>1.3%</td>
<td>2.1%</td>
</tr>
<tr>
<td>% VLBW (&lt;1500 grams)</td>
<td>4.7%</td>
<td>7.8%</td>
</tr>
<tr>
<td>% LBW (&lt;2500 grams)</td>
<td>45.7%</td>
<td>52.6%</td>
</tr>
</tbody>
</table>

Notes: ELBW indicates extremely low birth weight; VLBW indicates very low birth weight; LBW indicates low birth weight; MZ indicates monozygotic; DZ indicates dizygotic.
## Table 2

### Average Symptom Scores

<table>
<thead>
<tr>
<th>Symptom Type</th>
<th>M (SD) Georgia Sample</th>
<th>Z</th>
<th>p</th>
<th>Cohen's d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inattention</td>
<td>Males: .95 (.10)</td>
<td>Females: .63 (.83)</td>
<td>7.07</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hyperactivity-Impulsivity</td>
<td>.80 (.87)</td>
<td>.58 (.71)</td>
<td>5.41</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ODD</td>
<td>.98 (.86)</td>
<td>.83 (.80)</td>
<td>3.64</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CD</td>
<td>.05 (.12)</td>
<td>.02 (.10)</td>
<td>5.87</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Broad Externalizing</td>
<td>.16 (1.10)</td>
<td>−.16 (.87)</td>
<td>6.70</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Symptom Type</th>
<th>M (SD) Tennessee Sample</th>
<th>Z</th>
<th>p</th>
<th>Cohen's d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inattention</td>
<td>.84 (.66)</td>
<td>.61 (.53)</td>
<td>11.52</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hyperactivity-Impulsivity</td>
<td>.66 (.58)</td>
<td>.50 (.48)</td>
<td>9.10</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ODD</td>
<td>.63 (.50)</td>
<td>.54 (.45)</td>
<td>6.11</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CD</td>
<td>.07 (.15)</td>
<td>.04 (.09)</td>
<td>8.17</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Broad Externalizing</td>
<td>.15 (90)</td>
<td>−.14 (.70)</td>
<td>10.77</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Notes: ODD = Oppositional Defiant Disorder; CD = Conduct Disorder; Z statistics reported for Mann-Whitney U tests of sex differences.
### Table 3

Birth weight as a predictor of disruptive disorder symptoms

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Georgia Sample</th>
<th>Tennessee Sample</th>
<th>Combined Samples</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Wald ( \chi^2 )</td>
<td>( R^2 )</td>
<td>( p )</td>
</tr>
<tr>
<td>Inattention</td>
<td>7.80</td>
<td>0.010</td>
<td>0.003</td>
</tr>
<tr>
<td>Hyp.-Imp.</td>
<td>2.24</td>
<td>0.003</td>
<td>0.067</td>
</tr>
<tr>
<td>ODD</td>
<td>.99</td>
<td>0.001</td>
<td>0.160</td>
</tr>
<tr>
<td>CD</td>
<td>3.41</td>
<td>0.004</td>
<td>0.033</td>
</tr>
<tr>
<td>Externalizing</td>
<td>2.17</td>
<td>0.003</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Notes: All Wald \( \chi^2 \) and \( R^2 \) values presented are estimates of the unique effects of birth weight on each symptom dimension adjusted for covariates. Critical value of \( p < .05 \), one-tailed; Hyp-Imp indicates hyperactive-impulsive symptoms; ODD indicates Oppositional Defiant Disorder symptoms; CD indicates Conduct Disorder symptoms; Externalizing indicates the sum of inattentive, hyperactive-impulsive, Oppositional Defiant Disorder, and Conduct Disorder symptom z-scores. Predictors and covariates included in each model were as follows: age, sex, mother’s age at the twins’ birth, gestational age, family income, and birth weight.
Table 4

Within-pair differences in disruptive disorder phenotypes regressed on differences in birth weight

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Predictor</th>
<th>GA Sample</th>
<th></th>
<th>TN Sample</th>
<th></th>
<th>Combined Samples</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>t</td>
<td>p</td>
<td>R²</td>
<td>t</td>
<td>z</td>
<td>p</td>
</tr>
<tr>
<td></td>
<td>BW</td>
<td>−0.52</td>
<td>&lt;0.01</td>
<td>−2.35</td>
<td>0.01</td>
<td>−2.40</td>
<td>0.009</td>
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<tr>
<td></td>
<td>Zyg.</td>
<td>−2.48</td>
<td>0.01</td>
<td>−0.51</td>
<td>0.61</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BW X Zyg.</td>
<td>0.23</td>
<td>0.82</td>
<td>0.94</td>
<td>0.35</td>
<td>0.97</td>
<td>0.17</td>
</tr>
<tr>
<td>Inattention</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hyperactive-Impulsive</td>
<td>BW</td>
<td>0.09</td>
<td>&lt;0.01</td>
<td>−2.45</td>
<td>0.007</td>
<td>−2.10</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Zyg.</td>
<td>−1.43</td>
<td>0.15</td>
<td>−1.26</td>
<td>0.21</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BW X Zyg.</td>
<td>0.86</td>
<td>0.39</td>
<td>1.08</td>
<td>0.28</td>
<td>1.22</td>
<td>0.11</td>
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<tr>
<td>ODD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Externalizing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>BW X Zyg.</td>
<td>0.26</td>
<td>0.40</td>
<td>&lt;0.01</td>
<td>−0.19</td>
<td>0.48</td>
<td>−0.29</td>
<td>0.39</td>
</tr>
<tr>
<td></td>
<td>Zyg.</td>
<td>0.34</td>
<td>0.74</td>
<td>−0.74</td>
<td>0.46</td>
<td>&lt;0.01</td>
<td></td>
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<tr>
<td></td>
<td>BW X Zyg.</td>
<td>−0.26</td>
<td>0.80</td>
<td>1.64</td>
<td>0.10</td>
<td>1.56</td>
<td>0.12</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>BW X Zyg.</td>
<td>−2.43</td>
<td>0.008</td>
<td>&lt;0.01</td>
<td>−0.01</td>
<td>0.50</td>
<td>−2.27</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>Zyg.</td>
<td>−0.91</td>
<td>0.37</td>
<td>0.05</td>
<td>0.96</td>
<td>&lt;0.01</td>
<td></td>
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<tr>
<td></td>
<td>BW X Zyg.</td>
<td>1.25</td>
<td>0.21</td>
<td>0.31</td>
<td>0.19</td>
<td>&lt;0.01</td>
<td></td>
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</tbody>
</table>

Notes: All values presented are adjusted for covariates. Covariates included in all models but not reported in the table include child’s age, ethnicity, gestational age, dyad sex constellation, dyad sex constellation X birth weight interactions, and log of family income. Significance is reported for main and interactive effects of birth weight only; critical value of p < .05 (one-tailed test for main effects of birth weight; two-tailed test for zygosity and birth weight X zygosity interaction); Zyg. = zygosity; CD = conduct disorder symptoms; ODD = oppositional defiant disorder symptoms; BW = birth weight; BW X zygosity = zygosity X birth weight interaction term.