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

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An abstract of
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Abstract

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

By Courtney A. Ficks

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, findings for associations between birth weight and disruptive disorder symptom dimensions (Attention-Deficit/Hyperactive Disorder, Conduct Disorder, and Oppositional Defiant Disorder) have been inconsistent in the literature, and previous investigations have failed to use genetically-informative methods in examining low birth weight as a risk factor for these disorders. The current investigation examined phenotypic associations between birth weight and symptoms across families (using generalized linear models with generalized estimating equations) as well as within families (using linear and logistic regression). We then utilized univariate and bivariate biometric modeling to examine the extent to which associations between low birth weight and disruptive disorder symptom dimensions were due to common genetic and environmental influences. Small but significant associations between low birth weight and several childhood disruptive disorder symptom dimensions (inattentive, Oppositional Defiant Disorder, and broad externalizing symptoms) were found. Biometric models suggested that these associations were entirely due to common genetic influences, with no contribution of shared and minimal contribution of nonshared environmental risk factors. The current study thus illustrates the importance of using genetically-informative designs to examine putative risk factors of child psychopathology.

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

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). Infants with heightened perinatal risk, including those with low birth weight, now have a better chance at survival. Low birth weight (LBW) is typically defined in human infants as less than 2500 grams, or 5.5 pounds (WHO, 2009). The more extreme categories of low birth weight include very low birth weight (VLBW; less than 1500 grams) and extremely low birth weight (ELBW; less than 1000 grams). Between the years 2000 and 2007, 7% of all infants born in the United States weighed less than 2500 grams (UNICEF, 2007). Because more of these low birth weight individuals have entered and will continue to enter childhood, adolescence, and adulthood as a result of these healthcare improvements, it has become important to understand the challenges that these children may face.

The factors influencing low birth weight and its associated outcomes are numerous. Birth weight is a product of one's gestational age and fetal growth rate. A low birth weight may result from a premature birth in which an infant's weight is appropriate for his or her gestational age, a full-term birth in which the infant experienced intrauterine growth retardation (IUGR) and is small for gestational age, or a combination of preterm birth and IUGR (WHO, 2003). Kramer (1987) reviewed 895 medical publications on singleton pregnancies in healthy women in order to assess the causal impact of seven groups of factors (genetic and constitutional factors, demographic and social factors, obstetric factors, nutritional factors, maternal morbidity during pregnancy, toxic exposures, and antenatal care) on IUGR and preterm birth resulting in low birth weight in infants. Birth weight was associated with a number of predictors, including gender,

race, maternal height, maternal pre-pregnancy weight, paternal height, additional genetic factors including maternal birth weight, parity, intrauterine growth and gestational duration during previous pregnancies, prior spontaneous abortion, in utero exposure to diethylstilbestrol, gestational weight gain, and caloric intake, maternal smoking, and maternal alcohol consumption(Kramer, 1987). The process of examining the specific role of any particular influence, however, is complicated by the complex relations among all the putative influences. The use of genetically-informative methods has yielded heritability estimates for birth weight ranging from 37-43%, though these estimates may differ in individuals exposed to cigarette smoke in utero (Clausson, Lichtenstein, & Cnattingius, 2000; Little & Sing, 1987). The role of the shared uterine environment in birth weight is less clear, and has been estimated to contribute from 3-34% of the variance (Clausson et al., 2000; Little & Sing, 1987). Using birth weight as a proxy for these prenatal genetic , nutritional, and obstetric influences may allow us to predict long-term health outcomes associated with these risk factors.

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 Disorder (Hack et al., 2009), smaller head circumference (Allin et al., 2006), poorer social skills and peer problems (Grunau, Whitfield, & Fay, 2004), decreased academic achievement (Asbury, Dunn, Pike, & Plomin, 2003), 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). It is unclear whether these relations differ in preterm versus small for gestational age individuals, as the inclusion of gestational age as a covariate in these

investigations has yielded inconsistent results (Bohnert & Breslau, 2008; Dahl et al., 2006; Gatzke-Kopp & Beauchaine, 2007). The mechanisms underlying relations between low birth weight and mental health outcomes are not yet fully understood, but low birth weight appears to share common etiological pathways with a variety of psychological, biological, and social developmental influences.

Childhood Disruptive Disorders as Potential Outcomes of Low Birth Weight

Attention-Deficit/Hyperactivity Disorder.

The disruptive behavior disorders are among the most common disorders in children and adolescents and represent psychological outcomes of particular potential relevance to low birth weight. 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. The Predominantly Inattentive Subtype of ADHD is diagnosed when inattentive symptoms (such as distractibility and organizational difficulties) surpass the diagnostic threshold of ≥ 6 of 9 symptoms. The Predominantly Hyperactive-Impulsive Subtype of ADHD is diagnosed when hyperactive or impulsive symptoms (such as fidgeting, interrupting others, and excess motor activity) surpass the diagnostic threshold of ≥ 6 of 9 symptoms. The Combined Subtype of ADHD is diagnosed when criteria are met for both the Predominantly Inattentive and Predominantly Hyperactive-Impulsive Subtypes. 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 (Waldman & Gizer, 2006) with hyperactive-impulsive symptoms showing higher heritability than inattentive symptoms (Goodman & Stevenson, 1989; McLoughlin, Ronald, Kuntsi, Asherson, & Plomin, 2007). Candidate genes that may underlie this genetic influence have been examined primarily in the dopaminergic, serotonergic, and adrenergic systems as well as those involved in the production of catechol-o-methyl-transferase (*COMT*) and monoamine oxidase (*MAOA, MAOB*), enzymes involved in the inactivation of the monoamines (Waldman & Gizer, 2006). A recent meta-analysis of molecular genetic research on ADHD revealed significant but modest associations (Odds ratios from 1.12 to 1.33) with markers in the dopamine transporter gene (*DAT1*),two dopamine receptor genes (*DRD4, DRD5)*, the serotonin transporter genes (*5HTT*), serotonin receptor gene (*HTR1B*), and the synaptosome-associated protein gene (*SNAP25*) (Gizer, Ficks, & Waldman, 2009).

Putative environmental influences on ADHD include perinatal factors such as maternal substance use, pregnancy and delivery complications, and birth weight, socioeconomic status, parental marital status, parenting, abuse, peer treatment, peer characteristics, diet, and exposure to toxins (Banerjee, Middleton, & Faraone, 2007; Buschgens et al., 2009; Cohen, Adler, Kaplan, Pelcovitz, & Mandel, 2002; Daley, 2006; Kim-Cohen et al., 2006; Mick, Biederman, Prince, Fischer, & Faraone, 2002; Sengupta et al., 2006). Prenatal smoke exposure is hypothesized to influence the development of ADHD (perhaps via low birth weight), and the significance of this association has been fairly consistent throughout the literature (Banerjee et al., 2007; Buschgens et al., 2009; Gatzke-Kopp & Beauchaine, 2007; Kahn, Khoury, Nichols, & Lanphear, 2003; Langley et al., 2008; Lehn et al., 2007; Nigg & Breslau, 2007). Although increased symptom levels have been found in children exposed to smoke in utero, controlling for other environmental variables including maternal substance use, education, age, gender,

and IQ has rendered these associations nonsignificant (D'Onofrio et al., 2008; Langley et al., 2008; Nigg & Breslau, 2007). One problem with studying the associations of ADHD with environmental variables (such as prenatal smoke exposure and peer characteristics) associations with ADHD is that one cannot presume that there is a direct, environmental causal link between the measured variable and the disorder. Background environmental or genetic risk factors may be influencing both the predictor and the outcome, or the outcome itself (in this case ADHD), may be influencing the environment. In the present study, we will investigate this concept further by examining possible shared genetic and environmental influences on predictor and outcome variables.

Oppositional Defiant Disorder and Conduct Disorder.

Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD) are disruptive disorders that may also present during childhood and adolescence. ODD is described by diagnostic criteria as a disposition toward anger, negativity, and disrespect for authority coinciding with aggressive behavior and interpersonal difficulties in individuals under 18. ODD is estimated to occur in 2-16% of children in the United States and 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. CD is more often diagnosed in males than females, and an overall prevalence of 1-10% has been estimated (APA, 2000). Symptoms may be present before age 10 (Childhood-Onset Type) or first present later (Adolescent-Onset Type). Childhood-Onset Type CD has been associated with a greater risk for developing Antisocial Personality Disorder in adulthood. CD is more often diagnosed in males than females, and an overall prevalence of 1-10% has been estimated (APA, 2000).

A variety of biological, psychological, and social factors have been associated with the development of these antisocial spectrum disorders. Twin and adoption studies have found substantial genetic influence on ODD and CD (Dick, Viken, Kaprio, Pulkkinen, & Rose, 2005; Karnik, McMullin, & Steiner, 2006; Raine, 2002; Simonoff, Pickles, Meyer, Silberg, & Maes, 1998). Molecular genetic studies have found dopaminergic, serotoninergic, adrenergic , and GABAergic influences on these disorders (Boutwell & Beaver, 2008; Comings et al., 2000). Additional markers on chromosome 19 and chromosome 2 in regions concurrently linked to alcohol dependence have also been associated with CD (Dick et al., 2004; Karnik et al., 2006; Raine, 2002). It is unclear whether genes in these chromosomal regions play a role in the autonomic response deficits (e.g. skin conductance and heart rate) that have been observed in individuals diagnosed with these antisocial behavioral disorders, but it is possible that the decreased arousal that individuals diagnosed with CD and ODD experience in stressful situations plays a pivotal role in the development of these disorders (Karnik et al., 2006).

In addition to genetic influences on CD and ODD, a host of familial and social factors have been implicated. Higher rates of these disorders have been related to family histories of criminal activity, household conflict, family relationships, parental hostility or neglect, antisocial peer groups, low self-control, and growing up in violent neighborhoods (Bird et al., 2001; Boutwell & Beaver, 2008; Karnik et al., 2006). In addition, genetic influences on antisocial behavior may differ according to one's environment. Tuvblad, Grann, & Lichtenstein (2006) found that genetic effects on antisocial behavior may be higher for those raised in low-crime, advantaged neighborhoods, whereas the shared environment may play greater role in the development of these behaviors in less advantaged neighborhoods (Tuvblad, Grann, & Lichtenstein, 2006).It is unclear, however, whether associations between social and environmental factors and child phenotypes are indicative of directional influences. First,

associations may be fully or partially confounded by parental genetic factors accounting for both the child's home and neighborhood environment and their genetic predispositions (Moffitt, 2005). Burt, McGue, Iacono, and Krueger (2006) attempted to control for these genetic confounds and allow for causal inference via a longitudinal monozygotic twin differences design. The investigators found that a high level of discordance in monozygotic twins' levels of parent-child conflict at age 11 was uniquely predictive of the twins' discordant externalizing symptoms several years later (Burt, McGue, Iacono, & Krueger, 2006). Additionally, antisocial behavior in children may evoke more negative parenting in non-biological guardians, indicating that some of these apparent environmental risk factors may actually result from rather than cause these disorders (O'Connor, Deater-Deckard, Fulker, Rutter, & Plomin, 1998). These evocative effects, however, only partially account for the relations between aspects of parenting behavior and childhood antisocial behavior, and additional research has shown that marital turmoil and parental psychopathology within the adoptive home environment is related to behavioral outcomes in children independently of the children's biological predispositions (Cadoret, Yates, Troughton, Woodworth, & Stewart, 1995; O'Connor et al., 1998; Tully, Iacono, & McGue, 2008). It appears that environmental factors do play a role in the development of antisocial behavior in children, but the true nature and magnitude of these associations may only be revealed through more rigorous methodological approaches.

Comorbidity among ADHD, ODD, and CD

Diagnoses of antisocial behavior in children and adolescents (i.e. ODD and CD) overlap considerably with ADHD diagnoses. 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 et al., 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).

It is perhaps unsurprising then that molecular genetic studies have focused on similar markers in the dopamine, norepinephrine, and serotonin systems for both ADHD and the childhood antisocial disorders (Boutwell & Beaver, 2008; Caspi et al., 2008; Langley et al., 2008; Retz & Rosler, 2009; Sengupta et al., 2006). Nonetheless, few molecular genetic studies have examined these disorders together (Thapar et al., 2006). A recent study by Caspi and colleagues (2008) reported that ADHD-diagnosed children homozygous for the valine allele of the 22q11 COMT Val/Met polymorphism were more likely to display symptoms of CD and aggression than those carrying at least one methionine allele (Caspi et al., 2008). A followup by Monuteaux and colleagues (2009) on a smaller ADHD sample found support for an association between the Val/Val genotype and aggression, but not CD (Monuteaux, Biederman, Doyle, Mick, & Faraone, 2009). Zhou and colleagues (2008) found two markers in the dopamine transporter (*DAT1*) that were only associated with ADHD in cases in which no CD diagnosis was present (Zhou et al., 2008). Overall, ADHD appears to be closely related to both CD and ODD, and the search for common genetic influence on these disorders continues.

ADHD, Antisocial Behavior, and Birth Weight

As previously demonstrated, low birth weight has been associated with a variety of negative psychological outcomes. In this study, we will examine low birth as a risk factor for ADHD, ODD, and CD. Thus far, evidence for associations between low birth weight and ADHD has been mixed. Pharoah and colleagues (1994) found higher levels of hyperactivity in low birth

weight males, but not females (Pharoah, Stevenson, Cooke, & Stevenson, 1994). Levy and colleagues (1996) found that both male and female twins were on average 900 grams lighter at birth than their singleton siblings and had higher ADHD scores. Although the association was significant, birth weight explained very little variance in ADHD symptoms (Levy, Hay, McLaughlin, Wood, & Waldman, 1996). Botting and colleagues (1997) found support for an association between birth weight and ADHD in a sample of 12-year-old very low birth weight (<1500 grams) children. More individuals in the very low birth weight group exhibited behavioral difficulties and psychopathology, particularly attention deficit and hyperactive symptoms (23%), than in the matched control group (6%) (Botting, Powls, Cooke, & Marlow, 1997). Further, in the very low birth weight group the boy-to-girl ratio of symptoms was nearly equal, whereas boys in the matched control group were much more likely than girls to exhibit ADHD symptoms (7:2 ratio) (Botting et al., 1997). Mick and colleagues (2002) also found support for an association between ADHD symptoms and low birth weight in school-aged children. ADHD cases in this study were 3.1 times more likely to have been born with a low birth weight (<2500 grams) than controls (Mick et al., 2002). In 2002, a meta-analysis of research on cognitive and behavioral outcomes of preterm individuals by Bhutta and colleagues reported an increased risk for ADHD in low birth weight children (pooled RR = 2.64) (Bhutta et al., 2002). Since these studies were published, several additional studies have found associations between low birth weight and increased levels of inattention and hyperactive symptoms (Grunau, Whitfield, & Fay, 2004; Hack et al., 2009; Hack et al., 2004; Linnet et al., 2006; Saigal, Pinelli, Hoult, Kim, & Boyle, 2003). Other findings, however, have not supported these associations (Buschgens et al., 2009; Langley, Holmans, van den Bree, & Thapar, 2007; Nigg & Breslau, 2007).

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 low birth weight and symptoms. Lehn and colleagues (2007) observed differences in birth weight within monozygotic twin pairs discordant for ADHD symptoms in late childhood and adolescence. 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. This effect, however, was small (Cohen's d = 0.32), and these differences usually disappeared by the child's 3rd year (Lehn et al., 2007). Similarly, Asbury and colleagues (2006) found modest associations between birth weight and hyperactivity in 7-year old twin pairs (r = -.10, p < .01); the smaller twin in each pair was more likely to display symptoms, and these associations were strongest in females (Asbury, Dunn, & Plomin, 2006). Hultman et. al (2007) reported the lighter twin within same-sex discordant pairs to consistently have an average ADHD score 12-13% higher than his or her cotwin across two separate waves of data collection (time 1 at 8-9 years old; time 2 at 13-14 years old). Further, Sharp and colleagues (2003) found that within monozygotic twin pairs aged 6-16 years discordant for ADHD diagnoses, the lighter twin was more likely to be diagnosed (Sharp et al., 2003).

Several studies have examined the interactive effects of low birth weight with other genetic and environmental influences on ADHD outcomes. Langley et al. (2008) found no evidence of interactions between low birth weight and several genetic markers in the dopaminergic and serotonergic systems previously associated with ADHD (Langley et al., 2008). In a sample of very low birth weight individuals (<1500 grams), Dahl and colleagues (2006) found that relations between birth weight and attention problems in a sample of adolescents from 13-18 years of age were moderated by symptom reporter. Although very low birth weight adolescents (males and females) self-reported fewer attention problems than their normative birth weight peers, parents of the very low birth weight adolescents reported more attention problems in their children than parents of average birth weight peers (Dahl et al., 2006).

Although intrauterine growth retardation (small for gestational age) status was associated with parent-reported symptoms, low birth weight due to preterm birth was not discussed (Dahl et al., 2006). In a longitudinal investigation of low birth weight and psychiatric outcomes, Bohnert & Breslau (2008) reported a nearly threefold risk for attention problems in low birth weight individuals across ages 6, 11, and 17, but only for children in urban areas; children with low birth weight in suburban areas did not have significantly more attention problems than their peers (Bohnert & Breslau, 2008). These findings were consistent regardless of whether the low birth weight had resulted from intrauterine growth retardation or preterm birth (Bohnert & Breslau, 2008).

Although few studies have examined low birth weight as risk factor for CD and ODD symptoms, many have sought to establish broad associations between birth weight and later externalizing or problem behavior. Pharoah and colleagues (1994) found higher overall rates of behavioral disorders (conduct, emotional, or undifferentiated) in a sample of low birth weight (<2000 grams) 8-9 year-old children when compared with normal birth weight controls (Pharoah et al., 1994). These findings were supported by McCormick et al. (1996) using a behavioral outcome measure inclusive of disobedience, fighting, impulsiveness, and destruction of belongings in children aged 5-12 years (McCormick, Workman-Daniels, & Brooks-Gunn, 1996). Further, associations between low birth weight and problem behavior appear to be consistent within monozygotic (MZ; identical) and dizygotic (DZ; fraternal) twin pairs discordant for birth weight, which may be indicative of environmental influences on these associations (van Os et al., 2001). Bhutta and colleagues' (2002) review on cognitive and behavioral outcomes in preterm individuals noted higher rates of externalizing in preterm children; nonetheless, it is unclear whether these associations between preterm birth and symptoms were due to the children's decreased birth weights or other characteristics of preterm birth (Bhutta et al., 2002).

More recently, findings of associations between low birth weight and externalizing have been mixed. Although very low birth weight young adults were more likely to have repeated grades in school and less likely to have graduated high school, these individuals actually exhibited less alcohol and drug use, had lower rates of pregnancy, and less police contact than their normal birth weight peers (Hack et al., 2002). Rates of self-reported externalizing behavior in this sample were similar across both groups (Hack et al., 2004). According to Grunau and colleagues (2004), however, parents of extremely low birth weight teens (800 grams or less) reported more externalizing behavior in their teens, including more delinquent and aggressive behavior (Grunau et al., 2004). In contrast, the extremely low birth weight teens' reports of behavioral self-conduct were similar those of their normative peers (Grunau et al., 2004). To further complicate matters, in a study by Dahl and colleagues (2006), very low birth weight teens (1500 grams or less) actually reported fewer externalizing symptoms than their peers, though parents reported no differences in externalizing between the two groups of teens (Dahl et al., 2006). In addition, a recent study by Mankuta, Goldner, & Knafo (2010) found that within a sample of Israeli twin pairs, it was more common for the *larger* twin within the pair to show higher levels of conduct problems than his or her cotwin than it was for the smaller twin within the pair to show higher levels of conduct problems (Mankuta, Goldner, & Knafo). Asbury and colleagues (2006) reported no associations between discordance in birth weight and discordance in conduct problems in a sample of monozygotic twins, even in the most extreme 10% of discordant pairs (Asbury et al., 2006). A longitudinal study by Greenley et al. (2007) revealed an interactive association between low birth weight and perceived family conflict on externalizing problems, such that adolescent-perceived family conflict at age 11 was related to teacher-reported externalizing and behavior problems at age 17, but only in individuals weighing less than 750 grams at birth (Greenley, Taylor, Drotar, & Minich, 2007). Further

supportive of an association, Bohnert and colleagues (2008) found higher rates of externalizing problems in low birth weight individuals in both urban and suburban communities (Bohnert & Breslau, 2008). Recent findings by Buschgens et al. (2009), however, reported no associations between low birth weight and externalizing problems (Buschgens et al., 2009). Similarly, Fowler and colleagues (2009) did not find relations between birth weight and adolescent psychopathy (Fowler et al., 2009).

Several studies have examined the value of low birth weight as a predictor of CD and ODD symptoms. Botting and colleagues (1997) reported similar rates of CD and ODD across low birth weight and control groups. However, greater overlap was found between antisocial and ADHD symptoms in the control group (Botting et al., 1997). In a comparison of twins and their singleton siblings, although twins' average birth weights were 900 grams lighter than singletons, they were not more likely to exhibit CD or ODD symptoms (Levy et al., 1996). Saigal et al. (2003) also found no differences in CD or ODD symptoms among extremely low birth weight (501-1000 g) teens and controls according to parent or self-report (Saigal et al., 2003). In contrast, findings by Thapar and colleagues (2005) on a sample of children with ADHD indicated main effects of low birth weight on CD symptom levels as well as an interaction between low birth weight and the COMT Val/Val genotype to produce higher symptom levels (Thapar et al., 2005). A follow up by Sengupta and colleagues (2006), however, did not replicate these results (Sengupta et al., 2006). Langley et al. (2007) found evidence for an association between low birth weight and CD, but not ODD symptoms, yet these associations were only a trend when covariates, such as gender and ADHD symptoms, were included in the analysis (Langley et al., 2007). Similarly, birth weight did not emerge as a significant predictor of CD when entered simultaneously in a multiple regression with parental antisocial personality disorder, maternal smoking, and several related predictors (Gatzke-Kopp & Beauchaine, 2007). Most recently, Langley and colleagues

(2008) found several GXE interactions between birth weight and dopaminergic system genes on CD and ODD. Birth weight interacted with DRD4 and DRD5 in the production of ODD symptoms and with DAT1 in the production of CD symptoms (Langley et al., 2008). Associations between birth weight and later CD and ODD symptoms thus remain uncertain, and further research is needed to replicate and extend previous findings.

Although common genetic influences among birth weight, antisocial behavior, and ADHD have yet to be explored using a genetically-informed design, we have several hypotheses about the outcomes of the phenotypic and behavior genetic analyses and how these outcomes will influence our findings. Based on the previous literature, we hypothesize 1) that there will be considerable phenotypic overlap among CD, ODD, and ADHD symptoms (Caspi et al., 2008). Children exhibiting higher levels of inattention, impulsivity, and hyperactivity will display more antisocial behavior than their peers. Further, associations between birth weight and later ADHD, CD, and ODD have been mixed. However, there is evidence that low birth weight relates to increased risk for psychopathology, and several studies report negative relations between birth weight and externalizing symptoms, including ADHD, ODD, and CD. We thus predict that 2) birth weight will emerge as a significant *environmental* predictor of these disorders. Specifically, low birth weight will be related to higher symptom levels in the sample as a whole as well as within twin pairs discordant for birth weight. In addition, because 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), the four symptom dimensions (inattention, hyperactive-impulsive, ODD, and CD) will be summed to create a more broad dimension of child externalizing problems for use in these analyses.

Relations between birth weight and these disruptive behavior disorders may depend upon other gestational factors. A low birth weight in full-term infants (small for gestational age) may be indicative of a different set of potential risks than low (but gestationally-appropriate) birth weight in pre-term infants. It is unclear how gestational age may affect relations between low birth weight and behavioral outcomes, as findings in this area have been mixed (Bohnert & Breslau, 2008; Dahl et al., 2006). Including gestational age as a covariate may reduce the extraneous variance in birth weight and thus augment relations between birth weight and symptom levels.

Univariate behavior genetic models will be used to estimate the relative influences of genetic, shared environmental, and nonshared environmental factors on each predictor and outcome variable (i.e. ADHD, ODD, CD, broad externalizing, and birth weight). Because moderate to high heritability for ADHD and antisocial behavior has previously been established (Waldman & Gizer, 2006), we hypothesize 3) that these findings will be further supported in this sample. Nonshared environmental influences will also contribute to symptom levels. Further, birth weight has been previously found to have a moderate genetic influence in nonsmoking mothers (Clausson et al., 2000; Little & Sing, 1987). We predict that 4) these findings will be supported in our sample, with genes playing at least a small to moderate role in birth weight in addition to shared and nonshared environmental influences.

The hypothesized relations between birth weight, ADHD, antisocial behavior, and broad externalizing will be further explored using multivariate behavior genetic models. Genetic overlap has been found between ADHD and antisocial behavior (Dick et al., 2005; Kendler et al., 2003; Nadder et al., 2002; Thapar et al., 2006; Waldman, Rhee, S.H., Levy, F., & Hay, D.A. , 2001), and it is thus predicted 5) that these variables will share at least a moderate amount of genetic and nonshared environmental influence and minimal common environmental influence.

Although it has not previously been explored, it is also predicted that 6) common genetic risk between low birth weight and ADHD and the other disruptive disorders will account for some of the previously found phenotypic associations, if only to a small extent. Finally, we hypothesize that 7) common non-shared environmental influences also will play a role in these phenotypic associations, based on studies of discordant MZ twins.

Methods

Participants

The current study utilizes information obtained from birth records and symptom questionnaires for 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 = 8.57, SD = 2.58). The sample was 50.7% female and 49.3% male, with an ethnic composition of 87.1% European-American, 8.1% African-American, and 0.9% Asian or mixed ethnicity. Ethnicity for the remaining 3.9% of the sample was unknown.

Method

Birth records were obtained for all twins born in the state of Georgia between 1980 and 1991. Between 1992 and 1993, the 5,260 families for whom birth records were available were mailed Family Information Forms designed to elicit additional demographic and zygosity information on the twins. Of these families, 1,567 responded, and their information was entered into the Georgia Twin Registry. Several years later, registered families 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). Of this second set of mailed questionnaires, 885 were returned by the twins' mothers or fathers and ~95% (838) of these questionnaires were complete.

Measures.

Birth records.

Information on the population of twins born in the state of Georgia between 1980 and 1991 was obtained from state hospitals, including the children's birthdates, gender, location, race, parental education, gestational age, and birth weight in grams or pounds. All birth weights were subsequently converted to grams by the investigators. In the extant literature, discussion of birth weight less than 2500 g typically has been considered Low Birth Weight; 1500 g or less, Very Low Birth Weight; and 1000 g or less, Extremely Low Birth Weight (Hack et al., 2002; Saigal et al., 2003). Nonetheless, the prenatal growth curve for twins differs from that of singletons according to a recent examination of almost 18 million birth records across the United States, with the low optimal birth weight for twins about 152 grams lighter than that of singletons (Joseph et al., 2009).

Zygosity and demographics.

Zygosity information was collected via parent report on the Family Information Form (FIF) in the first mailing to 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 across the zygosity measure were categorized as MZ, and dyads with average scores less than 0.5 were categorized as DZ. This method of zygosity determination has been shown to have 96-99% accuracy as compared with genotyping techniques (Bonnelykke, Hauge, Holm, Kristoffersen, & Gurtler, 1989; Jackson, Snieder, Davis, & Treiber, 2001; Spitz et al., 1996).

***Psychopathology symptoms*.**

The twins' primary caregiver completed the Emory Diagnostic Rating Scale (EDRS), which instructs parents to rate their twins on a series of attributes and behaviors using a 0-4 likert scale (with 0 describing the child "not at all" and 4 describing the child "very well") (Waldman et al., 1998). The assessment tool includes items that compose symptom dimensions of the common DSM-IV childhood psychiatric disorders, and averaging items within a symptom scale results in scores that represent the degree to which the child displays symptoms characteristic of that particular disorder. The ADHD (inattention as well as hyperactivity/impulsivity) and Antisocial Behavior (ODD and CD) symptom dimension scores were thus derived by averaging each child's symptom scores on these respective scales. Each child's mean symptom score 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 (ODD), .95 (Inattention), .89 (Hyperactivity-Impulsivity), and .82 (CD).

Analyses.

Phenotypic relations between birth weight and disruptive disorder symptoms.

In the full sample, the ADHD, ODD, CD and composite externalizing symptom dimensions were regressed on birth weight in order to confirm or refute hypothesized phenotypic associations between low birth weight and increased levels of disruptive disorder symptoms. Twins were treated as nested pairs and Generalized Estimating Equation (GEE) methods were used in order to correct for this observational nonindependence within the data and generate appropriate standard errors and statistical tests. Because birth weight is at least partially dependent upon an infant's gestational age, which may have independent associations with externalizing symptoms (Bhutta et al., 2002; Dahl et al., 2006; Hack et al., 2009; Hack et al., 2004; Linnet et al., 2006), gestational age was included in these analyses as a covariate. Kramer and colleagues (1987) reported sex and ethnicity differences in birth weight, thus sex and

ethnicity were entered as covariates in order to account for additional variance in birth weight. Further, because child's age at the time of questionnaire completion likely accounts for variance in symptom ratings and because parents' ages at childbirth may affect both prenatal care and the children's psychopathology, these variables were also included as covariates in the models.

Discordance twin analyses of birth weight and disruptive disorder symptoms.

In addition to phenotypic relations between birth weight and disruptive disorder symptoms across the sample, within-pair associations between these variables were investigated using a twin discordance design. Difference scores for both birth weight and the ADHD, ODD, CD, and composite externalizing symptom dimensions were assigned to each pair by calculating the signed difference in these scores between twins for each variable. Twin differences in symptoms were regressed on the twin differences in birth weight, in addition to the previously mentioned covariates. Zygosity (MZ or DZ) and a zygosity X birth weight interaction term were entered as covariates in order to determine whether hypothesized relations differ according to the twins' levels of genetic similarity.

The Cotwin Control Method.

The Cotwin Control Method contrasts Odds Ratios (OR's) for MZ and DZ pairs in order to determine to what extent associations between dichotomous variables are due to nonshared genetic or environmental influences (Kendler et al., 1993). Individuals were assigned to birth weight categories ("low birth weight" = 2350 g; "normal birth weight" > 2350 g). Within pairs discordant for low birth weight, OR's were estimated to determine if low birth weight twins display more symptoms than their normal birth weight cotwins (using a cutoff of ≥ 1 standard deviation above their cotwin's symptom level to establish discordance for each disorder). Because DZ twins only share of 50% of their genes on average, associations between discordance in birth weight and discordance in symptoms in DZ twin pairs could indicate genetic

or nonshared environmental influences, or both. Thus, if the difference in disruptive symptoms for individuals discordant in birth weight is equal across MZ and DZ twins but greater than 1 (MZ=DZ>1), it is likely that these associations result solely from nonshared environmental influences. If the OR is greater in DZ twins than MZ twins (DZ>MZ>1 or DZ>MZ=1), there may be genetic influences on these associations. In contrast, because MZ twins share 100% of their genes, associations between discordance in birth weight and discordance in symptoms within MZ pairs would result from nonshared environmental influences.

Genetic and environmental influences on low birth weight and disruptive disorder symptoms.

In order to more comprehensively examine the role of genetic and environmental influences on the variables of interest (i.e., low birth weight and disruptive disorder symptoms), univariate behavior genetic analyses were utilized. As previously mentioned, MZ twins are genetically identical whereas DZ twins share only 50% of their genes identical-by-descent. If MZ twins are more similar than DZ twins on a particular trait (i.e. MZ twins are more likely to share similar birth weight), the trait is likely to be heritable. Univariate models utilize this differential similarity by examining the correlation of each variable within and across twin pairs in the sample. Behavior genetic models estimate what proportions of variance in the trait or disorder are accounted for by genetic (a^2), shared environmental (c^2) and nonshared environmental (e^2) influences. Alternatively, nonadditive genetic influences (d^2) may be tested instead of shared environmental influences, and a parameter representing direct sibling effects and/or rater contrasts may also be included. In this sample, separate analyses were conducted for birth weight, inattentive symptoms, hyperactive-impulsive symptoms, ODD symptoms, CD symptoms, and the externalizing symptom composite.

Common and unique genetic or environmental influences on low birth weight and disruptive disorder symptoms.

In addition to estimating genetic and environmental influences on each individual phenotype, we utilized bivariate Cholesky decomposition models to investigate the genetic and environmental influences common to birth weight and each disruptive disorder symptom dimension. A series of nested models was utilized to determine to what extent each etiological influence contributing to the variance in birth weight [i.e. additive genetic (a^2), shared environmental (c^2) and nonshared environmental influences (e^2)] also contributed to variance in disruptive symptoms. In addition, genetic and environmental influences contributing *uniquely* to disruptive disorder symptoms were estimated. Separate models were run for each disruptive disorder symptom dimension and a parameter representing sibling effects/rater contrasts on disruptive disorder symptoms was also estimated. In. addition, a parallel set of nested models were fitted allowing for nonadditive genetic effects (d^2) instead of shared environmental influences (c^2), and fit statistics were compared between the best-fitting models including shared environmental or non-additive genetic influences in order to determine the best-fitting, most parsimonious model for each symptom dimension.

Results

Descriptive statistics and demographic analyses

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* = .061.

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* (851.204) = 4.936, *p* < .001]. In addition, contrasts revealed significantly greater differences in birth weight within opposite-sex twin pairs (*M* = 332.35, *SD* =286.98) than within same-sex twin pairs (*M* = 245.97, *SD* =225.02), *t* (355.01) = 2.87, *p* = .004.

ADHD, ODD, CD, and Broad Externalizing Symptoms

Scale scores on the ECRS range from 0-4. Average inattentive, hyperactive-impulsive, ODD, CD, and broad externalizing symptoms scores are listed in Table 1. Symptom score distributions are shown in Figures 1-5. For all symptom dimensions, scores were significantly higher in boys than girls, *t* (1757) = 7.23, *p* < .001, Cohen's *d* = 0.34 for inattention; *t* (1754) = 5.71, *p* < .001, Cohen's *d* = 0.28 for hyperactivity-impulsitivity; *t* (1761) = 3.48, *p* = .007, Cohen's *d* = 0.18 for ODD; *t* (1753) = 3.83, *p* < .001, Cohen's *d* = 0.27 for CD; and *t* (1656.39) = 6.65, *p* < .001, Cohen's *d* = 0.32 for broad externalizing. The distributions of these scores were positively skewed, indicating that parents of most children reported few symptoms. Within twin pairs the distribution of symptom differences was highly kurtotic, indicating that within-pair differences tended to be small.

Generalized linear models with generalized estimating equations were used to examine the relations of ODD and CD symptoms with ADHD symptoms, given that the symptom dimensions were highly positively skewed and were thus better represented by a negative binomial distribution. In addition, the nesting of data within twin pairs allowed by generalized estimating equations made it possible to analyze associations within the full sample without

selecting for one twin per pair. As hypothesized, considerable phenotypic overlap was found between ADHD and ODD and CD symptoms, as inattentive and hyperactive-impulsive symptoms accounted for unique, significant proportions of the variance in ODD symptoms, $R^2 = 0.26$, $b = 0.02$, $p < 0.001$ and $R^2 = 0.47$, $b = 0.04$, $p < 0.001$, respectively. Inattentive and hyperactive-impulsive symptoms were also predictive of variance in CD symptoms, but to a lesser extent; $R^2 = 0.13$, $b = 0.002$, $p < 0.001$ and $R^2 = 0.19$, $b = 0.004$, $p < 0.001$, respectively.

Birth Weight and Disruptive Disorder Symptoms

Associations between birth weight and each disruptive disorder symptom dimension were modeled using generalized linear modeling (to address the non-normality of the symptom scale distributions) with generalized estimating equations (which allow for the nesting of twins within pairs). Because lower birth weight was hypothesized to predict increased symptom levels in children, one-tailed significance tests were conducted. The previously mentioned covariates were entered in a series of steps, and if a covariate was not predictive of symptom scores in the step in which it was entered, it was dropped from the equation in the following step. Linear and quadratic terms for birth weight were entered in the final step. If the quadratic term was nonsignificant, it was then dropped from the equation.

The results of these analyses are shown in Table 2. Child sex and age at the time of the symptom ratings were consistently predictive of child symptom levels. In addition, the age of a child's mother (but not father) at the child's birth was predictive of the child's inattentive, hyperactive-impulsive, ODD, and broad externalizing symptom levels, with younger mothers reporting more symptoms in their children. After controlling for significant covariates, low birth weight emerged as a significant predictor of higher inattentive, ODD, and broad externalizing symptoms, and there was a trend toward significant prediction of hyperactive-impulsive symptoms.

Discordant Twin Analyses of Birth Weight and Disruptive Disorder Symptoms

Difference scores for birth weight and symptom presentation were created for each twin pair by subtracting one twin's scores from the other twin's scores for birth weight and each symptom dimension. Because the distributions of the symptom difference scores were highly kurtotic (indicating twins within pairs were in general very similar), box-cox transformations were performed on the difference scores to help approximate normality. Linear regressions were then conducted in a five step process. First, 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 versus opposite-sex pairs. Second, the birth weight difference score was entered. Third, the birth weight X twin sex contrast interaction terms were entered in order to test for moderation of the association between birth weight differences and symptom differences by sex composition of the twin pairs. Fourth, zygosity was entered into the model to test for heritable influences on symptom differences, and fifth, 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. The results of these analyses are shown in Table 3. Differences in birth weight did not significantly predict differences in symptoms. Within twin pairs, the twin with the lower birth weight was no more likely to exhibit disruptive symptoms than his or her cotwin.

An outlier analysis was next performed to check for cases that might be exerting a disproportionately large influence on the regression analysis. Symptom differences were regressed on birth weight using the previously performed five-step process after selecting out cases in which residuals were greater than conventionally recommended values (i.e. Cook's D cutoff of 4/N). The results of these regressions sans outliers are also listed in Table 3. Although the magnitude of the standardized regression coefficients increased for nearly all symptom

dimensions after the removal of outlying cases, no significant associations emerged between differences in birth weight and differences in disruptive symptoms.

Cotwin Control Analyses of Discordance in Birth Weight and in Disruptive Disorder Symptoms.

Birth weight and symptom difference scores were recoded into dichotomous categories in order to compare the OR's across MZ and DZ twin pairs for the purpose of examining genetic and environmental influences underlying the phenotypic associations,. A twin pair was dummy coded as 1 for "discordant" in birth weight if the absolute difference in individual birth weights within the pair was greater than or equal to one sample standard deviation (*SD* = 585.79 grams). The remaining twin pairs were coded as 0 for "concordant." In this sample, 12.1% of twin pairs met criteria for discordance in birth weight. Symptom measures were dichotomized similarly, with discordance indicative of greater than or equal to one standard deviation of difference in each symptom dimension.

Logistic regressions were performed (controlling for the two previously discussed dyad sex contrasts) in order to determine whether discordance in birth weight predicted discordance in symptoms. Only cases in which the Cook's D values fell within the guidelines in the previous analysis were included. Birth weight was entered as the first predictor in the model, followed by zygosity, then a zygosity X birth weight interaction term was entered to test whether associations between birth weight discordance and symptom discordance differed for MZ and DZ pairs. Because DZ twin pairs may differ in birth weight and symptoms due to both differing genetic and environmental influences, whereas MZ pairs may differ due only to environmental influences, greater associations in DZ pairs may be indicative of shared genetic influences on these associations. Results of these logistic regressions are displayed in Table 4. Although discordance in birth weight predicted discordance in hyperactive-impulsive symptoms, however,

this association was in the opposite direction than predicted in that twin pairs discordant for birth weight were actually *less* likely to be discordant for hyperactive-impulsive symptoms. No other main effects of birth weight discordance emerged. In contrast, zygosity emerged as a significant predictor of discordance across all symptom dimensions, indicating a main effect of genetic similarity on similarity in symptoms. This is not surprising in that these symptom dimensions have been consistently found to be highly heritable. Further, although zygosity moderated the association between birth weight discordance and discordance for ODD symptoms, contrary to our hypotheses, the association between birth weight and symptom discordance was actually *weaker* in the DZ pairs than in MZ pairs.

G***enetic or environmental influences on low birth weight and disruptive disorder symptoms and their overlap.***

Prior to biometric model fitting, within-pair correlations for the disruptive disorder symptoms and birth weight data were estimated separately for MZ and DZ twin pairs. The symptom scales utilized for these within-pair correlations were first residualized on each child's sex and age, the quadratic term for the child's age, and the interaction of child's sex with his or her linear and quadratic terms for age. Birth weight was residualized on the child's sex, gestational age at birth, the quadratic term for gestational age, and the interaction of sex with these linear and quadratic terms. As illustrated in Table 5, the disruptive disorder symptoms correlated more strongly within MZ twin pairs than within DZ pairs. For inattentive, hyperactive-impulsive, Conduct Disorder, and broad externalizing symptoms, MZ twin correlations were greater than twice the magnitude of DZ twin correlations, suggesting the possibility of nonadditive genetic influences on these dimensions. For ODD symptoms and birth weight, MZ twin correlations were greater than DZ twin correlations but less than twice their magnitude, suggesting both genetic and shared environmental influences on these phenotypes.

Univariate biometric models were then utilized to better understand the etiology of each disruptive disorder symptom dimension and birth weight by decomposing the phenotypic variances into heritable and environmental components. First, two competing baseline models were tested: the ACE model, which allows for genetic (A), shared environmental (C), and nonshared environmental (E) influences, and the ADE model, which differs from ACE in that it estimates nonadditive genetic influences (D) instead of shared environmental influences (C). In addition, a version of each model was estimated including a parameter that reflects direct sibling interaction or rater contrasts (S). Within each competing model, a series of nested models were tested by dropping the A(only for ACE), C, or S parameters in order to yield the best-fitting, most parsimonious model for each phenotype.

Fit statistics for the models tested are displayed in Table 6. Model fit was judged primarily using the Bayesian Information Criterion (BIC), which takes into account both the probability of the observed data given the specified model (the likelihood) and the number of parameters estimated in the model (its parsimony) (Schwarz, 1978). The BIC has the advantage of allowing comparisons between both nested and non-nested models. Lower BIC values suggest better model fit and/or greater parsimony. Additional fit indices that were considered in selecting the best-fitting model for each phenotype included the Comparative Fit Index (CFI; P. M. Bentler, 1990)and Tucker-Lewis Index (P.M. Bentler & Bonett, 1980). For each of these two indices, values approaching 1 indicate excellent model fit, whereas values greater than 0.90 are recommended. Further, like the Chi-Square statistic (χ^2), the Root Mean Square Error of Approximation (RMSEA) provides a goodness-of-fit index based on the discrepancy between observed and expected values given the specified model, but the RMSEA is less influenced by sample size than the Chi-Square statistic. Values closer to zero (less than 0.08) indicate excellent fit and values.

Parameter estimates for the best-fitting univariate models are listed in Table 7. For both ADHD symptom dimensions (inattention and hyperactivity-impulsivity) and ODD symptoms, additive genetic influences accounted for the largest proportion of the variance (64-72%), with no shared environmental influences. These additive genetic influences were even stronger for the broad externalizing symptom dimension, accounting for 84% of the total variance in this composite phenotype. In contrast, variance in CD symptoms was primarily due to nonadditive genetic effects (89%). Birth weight appeared to be influenced by a combination of additive genetic (37%), shared environmental (32%), and nonshared environmental influences (31%), with genetic influences accounting for only a slightly larger proportion of the variance than the other two factors. Sibling interaction/rater contrast effects were found for ADHD and broad externalizing symptoms, but not for CD or ODD, and these effects were negative and small in magnitude.

Bivariate Cholesky decomposition models were used to estimate common and unique genetic and environmental influences on birth weight and each disruptive disorder symptom dimension. Nested models estimated the extent to which genetic, shared environmental, and nonshared environmental influences on birth weight were shared with each of the disruptive disorder symptom dimensions in addition to unique genetic and environmental influences on the symptom dimensions. As in the univariate models, each phenotype was residualized on the relevant covariates prior to model-fitting. Fit statistics for the bivariate models are presented in Table 8. In all cases, the ACE-AE models resulted in the best fit for birth weight and disruptive disorder symptoms, respectively. As hypothesized, common additive genetic influences were found for birth weight and three of the five disruptive disorder symptom dimensions (i.e. hyperactive-impulsive, ODD, and broad externalizing symptoms). These common genetic influences were small in magnitude, accounting for 1-2% of the genetic variance and ~1% of the

total variance in each disruptive disorder symptom dimension (see Figures 6-10 for squared standardized parameter estimates). Although dropping the parameter for common genetic influences from each of these three models resulted in a slightly lower BIC value due to increased parsimony, all of the other fit indices (i.e. the CFI, TLI, and RMSEA) suggested worse fit. No common shared or nonshared environmental influences were found for birth weight and any of the disruptive disorder symptom dimensions. Direct sibling influences/rater contrast effects were found for all disruptive disorder symptom dimensions with the exception of ODD. The magnitudes of standardized parameter estimates for these sibling interaction effects were small, ranging from -.14 to -.10. Common genetic influences on birth weight and the disruptive disorder symptom dimensions accounted for 1.1%, 1.2%, and 1.3% of the total genetic influences on hyperactive-impulsive, ODD, and broad externalizing symptoms, respectively, but did not contribute to variance in internalizing or CD symptoms.

Discussion

The current study examined low birth weight as a risk factor for childhood disruptive disorder symptoms. Phenotypic associations between birth weight and ADHD, ODD, CD, and broad externalizing symptoms were examined within and between families, and biometric models were then used to estimate the extent to which these associations were influenced by common genetic and/or environmental influences. Overall, we found mixed support for our hypotheses regarding the associations between childhood disruptive disorder symptom dimensions and birth weight. We proposed that there would be phenotypic associations between birth weight and later ADHD, CD, and ODD in the full sample. Evidence for associations between low birth weight and ADHD in the previous literature has been mixed (Botting et al., 1997; Levy et al., 1996; Mick et al., 2002; Pharoah et al., 1994), although it appears that more studies have reported negative associations between low birth weight and ADHD than null or

positive associations. Prior to the current investigation, few studies had examined associations between low birth weight and childhood antisocial behavior. Based on the overlap between ADHD and ODD and CD symptoms in the literature as well as in this sample, we predicted that low birth weight would be related to greater symptoms of ODD, CD, and externalizing in general. Our findings were supportive of these hypotheses in that low birth weight significantly predicted increased risk for inattentive, ODD, and broad externalizing symptoms, with a trend toward significant prediction of increased hyperactive-impulsive symptoms. However, these associations were small, with birth weight generally accounting for less than 1% of the variance in each symptom dimension after controlling for relevant covariates such as sex and age. Birth weight did not emerge as a significant predictor of CD symptoms, suggesting that birth weight may not be associated with this more extreme dimension of antisocial behavior; however, because our sample was community-based, the variability in CD symptoms reported in this sample was very small. Our failure to detect an association between birth weight and CD symptoms may thus be due to restricted phenotypic range. Future investigations should examine these associations in high-risk samples in order to more reliably detect small effects that may be present and stronger at the extremes.

It was also hypothesized that nonshared environmental influences would largely account for the associations between birth weight and disruptive disorder symptoms, and thus within-pair differences in birth weight would be associated with within-pair differences in symptoms, with the smaller twin in each pair exhibiting greater disruptive symptoms. We explored this possibility by examining within-pair differences in two ways, using signed twin difference scores as well as by assigning twin pairs to concordant or discordant status based on their categorical phenotypic similarity. In general, findings did not support our hypotheses. Although we found previously that smaller twins showed increased levels of disruptive disorder

symptoms, differences in birth weight *within* twin pairs were not associated with differences in their symptom scores. In other words, associations between birth weight and disruptive disorder symptoms that were found across families did not hold true within families. There was one puzzling exception to this general finding, however, in that twins discordant for birth weight (at least one standard deviation apart) were *less* likely to be discordant for hyperactive-impulsive symptoms. Although this finding is counterintuitive and may be an artifact of multiple testing, it is possible that there may be processes in utero contributing to imbalances in nutrition that result in long-term detriment to both individuals within a twin pair. Further investigation is needed to determine the meaning of this finding. Overall it appears that associations between low birth weight and disruptive disorder symptoms may be less due to nonshared environmental influences than to shared genetic or shared environmental influences.

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 phenotypic 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 magnitude of difference in symptoms, reducing the likelihood that the phenotypic associations found are due to common genetic influences on birth weight and disruptive disorder symptoms. Only one interaction by zygosity was found for ODD symptoms, but contrary to our hypothesizes, this interaction reflected stronger associations among MZ rather than DZ twins, providing further evidence that the phenotypic associations may not be due to common genetic influences.

Consistent with previous research, the univariate biometric models revealed significant additive genetic influences (nonadditive for CD symptoms) across all phenotypes, including birth

weight. In addition, shared environmental influences were found only on birth weight, and not on any disruptive disorder symptoms. Based on previous literature and phenotypic associations found in the current study, we hypothesized that there are common genetic and environmental influences between low birth weight and symptoms of disruptive disorders. Bivariate Cholesky Decomposition models provided partial support for this hypothesis. Although no common environmental influences were found for birth weight and any symptom dimension, common additive genetic influences were found for birth weight and hyperactive-impulsive symptoms, ODD symptoms, and overall externalizing. Paralleling the phenotypic associations, the magnitude of these common genetic influences was very small, generally contributing to only 1% of the variance in each disruptive disorder symptom dimension. This may explain why previous studies, as well as the current investigation, have found inconsistent evidence for phenotypic associations between birth weight and childhood ADHD or antisocial behavior. In order to have adequate statistical power to detect associations as small as those found in the present study, very large sample sizes are needed. Further, because phenotypic associations were found to be due to common genetic influences, discordant MZ twin designs are likely to detect no effects.

Several implications for future research in developmental psychopathology should be noted. First, although associations between birth weight and disruptive disorder symptoms were detected between families using generalized linear modeling and latent variable modeling strategies, within-family methods utilizing difference scores or within-pair discordance for MZ and DZ twins did not yield significant findings. Given the heritable nature of the associations, it is not surprising that discordance in symptoms and discordance in birth weight were not associated within MZ pairs given that MZ pairs are genetically identical and thus any discordance may only result from environmental differences. Nonetheless, it is surprising that discordance in

these phenotypes was not associated within the nonidentical twin pairs. This failure to detect an effect may be due to the reduction in sample size resulting from examining only DZ twin pairs, or further, the use of difference scores, which may decrease reliability and reduces one's power to detect small associations due to an increased standard error (Edwards, 1995). It is thus important that we use multiple statistical methods in examining phenotypic associations in addition to within-family discordance designs. In addition, many prior investigations have examined low birth weight as a putative environmental risk factor for later negative outcomes, including child psychopathology. Our findings appear to contradict this assumption that birth weight and disruptive disorder symptoms share common teratogenic environmental influences; bivariate models revealed that common genetic influences accounted for 100% of the phenotypic relations between birth weight and each associated disruptive disorder symptom dimension, suggesting that low birth weight may not result in an increased risk for disruptive symptoms through any causal environmental mechanism. Rather, low birth weight may simply serve as a weak indicator of an individual's increased *genetic* risk for developing behavioral problems in childhood. These findings underscore the importance of biometric modeling in studying the development of child psychopathology longitudinally, as these methods allow us to determine to what extent associations between putative risk factors and later phenotypes are actually due to common genetic or environmental influences operating within an individual over time. Future research should examine other putative indicators of perinatal environmental risk in order to further understand the nature of their associations with later behavioral problems and aid in our conceptualization of the early development of these disorders.

It is important to note that associations found within the current sample may not be generalizable to all individuals. Little & 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). Because smoking during pregnancy was reported by very few mothers in the current sample, we were unable to examine whether prenatal cigarette exposure moderated associations between birth weight and disruptive disorders. It is plausible that common environmental influences on birth weight and disruptive disorder symptoms may emerge only in samples with greater variability in smoking or prenatal exposure to other toxins, and thus it is important that future investigations examine these associations in populations with greater environmental risk.

In addition, because the current investigation utilized a twin sample, we should be cautious in generalizing results to singleton 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 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, low birth weight may have a qualitatively 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 summary, this investigation used multiple statistical methods, including univariate and bivariate biometric modeling, to examine associations between low birth weight and disruptive disorder symptoms in children. These associations have previously been inconsistent in the literature, and our findings suggest that small but significant associations exist between low birth weight and childhood externalizing behavior problems. These associations appear to be primarily due to common genetic influences on these phenotypes rather than shared environmental risk factors. Although the nature of our twin sample may limit the generalizability of findings, this investigation exemplifies the necessity of genetically-informative designs in the examination of putative risk factors for behavioral problems in children.

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Table 1

Average Symptom Scores

	M (*SD*)	
Symptom Type	Males	Females
Inattention	.95 (1.03)	.63 (0.83)
Hyperactivity-impulsivity	.80 (0.87)	.58 (0.71)
ODD	.98 (0.86)	.83 (0.80)
CD	.05 (0.12)	.02 (0.10)
Broad Externalizing	.16 (1.10)	-.16 (0.87)

Notes: ODD = Oppositional Defiant Disorder; CD = Conduct Disorder.

Table 2

Birth weight as a predictor of disruptive disorder symptoms

Symptom Type	Predictor	*Wald* χ^2	R^2	*p*
Inattentive	Age	21.47		0.00
	Sex	0.02		0.44
	Age x Sex	6.28		0.01
	Age^2	14.13		<0.01
	Mother Age @ Birth	4.55		0.02
	Birth Weight	2.70	0.003	0.05
Hyp.-Impulsive	Age	16.55		<0.01
	Sex	34.48		<0.01
	Mother Age @ Birth	6.31		0.01
	Birth Weight	2.02	0.002	0.08
ODD	Age	4.95		0.02
	Sex	18.17		<0.01
	Age^2	4.16		0.02
	Mother Age @ Birth	5.83		0.01
	Birth Weight	2.89	0.003	0.05
CD	Age	17.63		<0.01
	Sex	12.69		<0.01

	Birth Weight	1.70	0.002	0.10
Externalizing sum	Age	2.96		0.05
	Sex	0.62		0.22
	Age x Sex	2.70		0.05
	Mother Age @ Birth	5.75		0.01
	Birth Weight	6.03	0.007	<0.01

Notes: critical value at p < .05, one-tailed; Mother Age @ Birth indicates the mother's age at the birth of the twins in the sample; Hyp.-Impulsive indicates hyperactive-impulsive symptoms; ODD indicates Oppositional Defiant Disorder symptoms; CD indicates Conduct Disorder symptoms; Externalizing sum indicates the sum of inattentitive, hyperactive-impulsive, Oppositional Defiant Disorder, and Conduct Disorder symptom z-scores.

Table 3

Within-pair differences in disruptive phenotype regressed on differences in birth weight

Symptom Type	Predictor	R^2		*p*	
		full sample	outliers removed	full sample	outliers removed
Inattentive	Male vs. female	0.01	0.07	0.39	0.26
	Same vs. opposite	0.10	0.55	0.20	0.05
	BW	0.01	0.02	0.18	0.11
	BW X 1	0.01	0.08	0.40	0.25
	BW X 2	0.08	0.53	0.22	0.05
	Zygosity	0.08	0.45	0.25	0.08
	BW X Zygosity	0.06	0.28	0.29	0.14
Hyp.-Impulsive	Male vs. female	0.02	0.10	0.35	0.23
	Same vs. opposite	0.00	0.44	0.45	0.07
	BW	0.00	0.01	0.33	0.20
	BW X 1	0.01	0.06	0.37	0.28
	BW X 2	0.01	0.35	0.42	0.09
	Zygosity	0.03	0.16	0.35	0.21
	BW X Zygosity	0.02	0.13	0.37	0.24
ODD	Male vs. female	0.12	0.18	0.18	0.15
	Same vs. opposite	0.01	0.44	0.38	0.06
	BW	0.00	0.00	0.34	0.33
	BW X 1	0.12	0.16	0.17	0.17
	BW X 2	0.02	0.36	0.35	0.08

	Zygosity	0.05	0.05	0.29	0.32
	BW X Zygosity	0.06	0.04	0.30	0.34
CD	Male vs. female	0.05	0.05	0.27	0.29
	Same vs. opposite	0.06	0.03	0.26	0.33
	BW	0.00	0.02	0.30	0.10
	BW X 1	0.07	0.05	0.25	0.29
	BW X 2	0.05	0.04	0.28	0.31
	Zygosity	0.00	0.09	0.47	0.25
	BW X Zygosity	0.00	0.10	0.45	0.25
Broad	Male vs. female	0.00	0.00	0.43	0.44
Externalizing	Same vs. opposite	0.01	0.42	0.41	0.07
	BW	0.01	0.00	0.23	0.49
	BW X 1	0.00	0.00	0.45	0.49
	BW X 2	0.00	0.41	0.47	0.07
	Zygosity	0.04	0.01	0.33	0.41
	BW X zygosity	0.03	0.01	0.35	0.44

Notes: critical value at p < .05, one-tailed; Hyp.-Impulsive = hyperactive-impulsive; CD = conduct disorder; ODD = oppositional defiant disorder; for predictor, Male vs. female = Contrast: both male versus both female twin pairs; Same vs. opposite = Contrast 2: same sex versus opposite sex twin pairs; BW = birth weight; BW X 1 = Contrast: both male versus both female twin pairs X birth weight interaction term; BW X 2 = Contrast 2: same sex versus opposite sex twin pairs X birth weight interaction term; BW X zygosity = zygosity X birth weight interaction term.

Table 4

The Cotwin Control Method: within-pair discordance in disruptive phenotype regressed on discordance in birth weight

Symptom Type	Predictor	*Wald* χ^2	*p*	OR (MZ)	OR (DZ)
Inattention	Male vs. female	1.50	.11		
	Same vs. opposite sex	1.29	.13		
	BW	1.39	.12		
	Zygosity	22.20	<.01		
	BW X zygosity	0.00	.48		
Hyperactive-imp	Male vs. female	8.33	<.01		
	Same vs. opposite sex	0.15	.45		
	BW	4.87	.01		
	Zygosity	25.62	<.01		
	BW X zygosity	0.07	.39		
ODD	Male vs. female	.28	. 30		
	Same vs. opposite sex	.58	.22		
	BW	1.06	.30		
	Zygosity	13.80	<.01		
	BW X zygosity	6.12	.01*	1.57	

			0.33
CD	Male vs. female	3.65	.03
	Same vs. opposite sex	0.29	.30
	BW	.95	.17
	Zygosity	1.49	.11
	BW X zygosity	.11	.38
Externalizing	Male vs. female	3.12	.04
	Same vs. opposite sex	0.04	.42
	BW	0.01	.47
	Zygosity	18.01	<.01
	BW X zygosity	0.44	.26

*Notes: critical value at p < .05, one-tailed; OR = Odds Ratio; MZ = monozygotic pairs; DZ = dizygotic pairs; Hyp.-Impulsive = hyperactive-impulsive; CD = conduct disorder; ODD = oppositional defiant disorder; for predictor, 1 = Contrast: both male versus both female twin pairs; 2 = Contrast 2: same sex versus opposite sex twin pairs; 3 = birth weight, 4 = zygosity; 5 = zygosity X birth weight interaction term; *indicates a significant birth weight X zygosity interaction.*

Table 5

Within-pair correlations for disruptive symptoms and birth weight

Phenotype	Zygosity	
	MZ	DZ
Inattention	.55	.11
Hyperactive-Impulsive	.71	.20
ODD	.60	.37
CD	.89	.23
Externalizing	.75	.27
Birth Weight	.66	.53

Notes: MZ = monozygotic pairs; DZ = dizygotic pairs.

Table 6

Fit statistics for univariate models of disruptive symptoms and birth weight

Phenotype	Model	χ^2	df	p	CFI	TLI	RMSEA	90% CI	BIC
Inattention	ACES	18.32	5	0.0026	0.81	0.92	0.08	0.04-0.12	4579.47
	ACE	28.26	6	0.0001	0.68	0.89	0.09	0.06-0.13	4596.35
	ADES	14.31	5	0.0002	0.86	0.95	0.07	0.06-0.13	4580.36
	ADE	18.16	6	0.0000	0.83	0.94	0.07	0.17-0.24	4579.69
	AES	**17.17**	**6**	**0.0087**	**0.84**	**0.95**	**0.07**	**0.03-0.10**	**4573.58**
	AE	32.96	7	0.0000	0.63	.89	0.09	0.06-0.13	4589.57
	CES	No convergence achieved							
	CE	66.45	7	0.0000	0.15	.76	0.14	0.11-0.17	4640.00
					1.00				
Hyp.-Imp.	ACES	2.14	5	0.8294	0	1.01	0.00	0.00-0.04	3869.54
	ACE	14.09	6	0.0000	0.9	.98	0.06	0.02-0.09	3884.82

					3				
	ADES			0.8743	1.0			0.00-0.03	
		1.81	5		0	1.01	0.00		3869.80
	ADE			0.6366	1.0			0.00-0.05	
		4.30	6		0	1.01	0.00		3866.31
	AES			**0.90**	**1.0**			**0.00-0.03**	
		2.18	**6**		**0**	**1.01**	0.00		**3863.11**
	AE			0.021	0.9			0.02-0.09	
		16.44	7		2	0.98	0.06		3878.05
	CES				No convergence achieved				
	CE			0.0000	0.3			0.13-0.19	
		79.74	7		5	0.81	0.15		3991.40
ODD	ACES				No convergence achieved				
	ACE			0.18	0.9			0.00-0.08	
		8.89	6		8	0.99	0.03		4101.41
	ADES			0.1540	0.9			0.00-0.08	
		8.04	5		8	0.99	0.04		4108.78
	ADE			0.25	0.9			0.00-0.07	
		7.83	6		8	1.00	0.03		4102.80
	AES			0.14	0.9			0.00-0.08	
		9.65	6		7	0.99	0.04		4102.00
	AE			**0.2435**	**0.9**			**0.00-0.07**	
		9.13	**7**		**8**	1.00	**0.03**		**4095.31**

	CES			No convergence achieved					
	CE			0.0000	0.7			0.06-0.13	
		34.36	7		7	0.93	0.09		4132.31
					1.0				
CD	ACES	6.72	5	0.2424	0	1.00	0.03	0.00-0.08	-3258.58
	ACE			0.1999	1.0			0.00-0.07	
		8.56	6		0	1.00	0.03		-3232.38
	ADES			0.4209	0.9			0.00-0.07	
		18.59	5		8	0.99	0.08		-3260.73
	ADE			**0.4580**	1.0			**0.00-0.06**	
		5.70	**6**		0	1.00	0.00		**-3267.37**
	AES			0.2335	1.0			0.04-0.12	
		8.06	6		0	1.00	0.03		-3265.36
	AE			.1894	1.0			0.00-0.07	
		9.99	7		0	1.00	0.03		-3239.15
	CES			No convergence achieved					
	CE			0.0000	0.9			0.12-0.18	
		72.05	7		0	.97	0.15		-2918.78
					1.0				
Broad Ext.	ACES	4.96	5	0.4209	0	1.00	0.00	0.00-0.07	32361.90
	ACE			0.1241	0.9			0.00-0.08	
		10.01	6		9	1.00	0.04		32373.71
	ADES			0.5444	1.0			0.00-0.06	
		4.04	5		0	1.00	0.00		32364.00

	ADE			0.3972	1.0			0.00-0.06	
		6.24	6		0	1.00	0.01		32361.49
	AES			**0.5642**	1.0			**0.00-0.06**	
		4.84	**6**		0	**1.00**	0.00		**32357.22**
	AE			0.1115	0.9			0.00-0.08	
		11.68	7		9	1.00	0.04		32366.93
	CES				No convergence achieved				
	CE			0.0000	0.7			0.12-0.18	
		78.81	7		6	0.93	0.15		32508.13
B. Weight	ACES				No convergence achieved				
	ACE			**.0061**	**0.9**			**0.03-0.11**	
		18.03	**6**		**6**	**0.99**	**0.07**		**24931.71**
	ADES			.0020	0.9			0.04-0.12	
		18.91	5		5	0.98	0.08		24942.76
	ADE			.0001	0.9			0.06-0.13	
		28.98	6		1	0.97	0.10		24951.48
	AES			.0000	0.9			0.07-0.14	
		31.22	6		1	0.97	0.10		24955.12
	AE			.0000	0.0			0.28-0.35	
		302.60	7		0	0.68	0.31		25296.02
	CES			.0000	0.9			0.07-0.14	
		31.22	6		0	0.97	0.10		24955.12
	CE			.0000	0.8			0.07-0.13	
		36.42	7		9	0.97	0.10		24948.37

Notes: Hyp.-Imp = hyperactive-impulsive symptoms; ODD = oppositional defiant disorder; CD = conduct disorder; B. Weight = birth weight; for Model, A = additive genetic influences, C = shared environmental influences, D = nonadditive genetic influences, E = nonshared environmental influences, and S = direct sibling influence or rater contrast.

Table 7

Parameter estimates for best-fitting univariate models of disruptive symptoms and birth weight

Phenotype	A (% total)	C (% total)	D (% total)	E (% total)	S
inattention	0.68	-	-	0.32	-0.14
hyperactivity-impulsivity	0.72	-	-	0.28	-0.12
ODD	0.64	-	-	0.36	-
CD	0.00	-	0.89	0.12	-
Broad externalizing	0.84	-	-	0.16	-0.10
Birth weight	0.37	0.32	-	0.31	-

Note: A, C, D, and E parameter estimates are displayed in terms of percentage of total variance (% total) explained; standardized S parameter values are given.

Table 8

Fit statistics for bivariate models of disruptive symptoms and birth weight

Phenotype	Model	χ^2	df	p	CFI	TLI	RMSEA	90% CI	BIC
Inattent.	Full	44.68	16	.000	.933	.950	.064	0.042-0.086	29526.29
	-c2	51.38	17	.000	.920	.944	.068	0.047-0.089	29522.04
	-c3	43.35	17	.000	.939	.957	.059	0.038-0.081	29520.05
	-c2, c3	47.00	18	.000	.933	.955	.060	0.040-0.082	29516.81
	-s, c2, c3	64.87	19	.000	.894	.933	.074	0.055-0.094	29532.39
	-e2, c2, c3	48.24	19	.000	.932	.957	.059	0.039-0.080	29510.67
	-a2, e2, c2, c3*	49.85	20	.000	.931	.958	.058	0.038-0.079	29505.42
	-a3, e2, c2, c3	67.76	20	.000	.889	.933	.074	0.055-0.093	29526.52
Hyp-Imp.	Full	24.24	16	.084	.983	.987	.034	0.000-0.060	28815.39

	-c2	24.43	1	.108	.98	.98	.031	0.000-	28808.6
			7	3	5	9		0.057	1
	-c3	23.67	1	.128	.98	.99	.030	0.000-	28808.8
			7	6	6	0		0.056	8
	-c2, c3	29.99	1	.155	.98	.99	.027	0.000-	28802.1
			8	3	8	2		0.054	3
	-s, c2, c3	40.66	1	.002	.95	.97	.051	0.029-	28817.1
			9	7	5	2		0.073	3
	-e2, c2, c3*	25.15	1	.155	.98	.99	.027	0.000-	28796.5
			9	8	7	2		0.053	0
	-a2, e2, c2, c3	29.64	2	.075	.98	.98	.033	0.000-	28794.8
			0	9	0	8		0.057	6
	-a3, e2, c2, c3	43.51	2	.001	.95	.97	.052	0.031-	28812.4
			0	7	1	1		0.073	6
ODD	Full	28.66	1	.026	.97	.98	.042	0.014-	29049.9
			6	3	4	0		0.067	6
	-c2	29.54	1	.029	.97	.98	.041	0.013-	29043.6
			7	9	4	2		0.065	1
	-c3	33.91	1	.008	.96	.97	.048	0.023-	29048.1
			7	6	5	5		0.071	9
	-c2, c3	34.40	1	.011	.96	.97	.045	0.021-	29041.6
			8	2	6	8		0.068	3
	-s, c2, c3	33.47	1	.021	.97	.98	.042	0.016-	29034.9
			9	2	0	1		0.064	4

	-e2, s, c2, c3	33.74	20	.027 9	.97 2	.98 3	.039	0.013-0.062	29028.19
	-a2, e2, s, c2, c3*	38.89	21	.010 1	.96 3	.97 9	.044	0.021-0.065	29027.14
	-a3, e2, s, c2, c3	52.54	21	.000 2	.93 5	.96 3	.058	0.039-0.078	29043.81
CD	Full	23.13	16	.110 4	.99 3	.99 5	.032	0.000-0.058	21688.77
	-c2	24.49	17	.106 7	.99 3	.99 5	.032	0.000-0.058	21682.72
	-c3	24.57	17	.104 7	.99 2	.99 5	.032	0.000-0.058	21681.99
	-c2, c3	25.93	18	.101 3	.99 2	.99 5	.032	0.000-0.057	21675.94
	-s, c2, c3	28.29	19	.078 0	.99 1	.99 4	.033	0.000-0.058	21701.70
	-e2, c2, c3	27.34	19	.097 0	.99 2	.99 5	.032	0.000-0.056	21669.89
	-a2, e2, c2, c3*	29.46	20	.079 1	.99 1	.99 4	.033	0.000-0.056	21666.48
	-a3, e2, c2, c3	34.22	20	.024 7	.98 6	.99 2	.040	0.014-0.063	21685.91
Broad ext.	Full	26.92	16	.042 4	.98 5	.98 8	.039	0.007-0.065	57306.32

-c2	27.45	17	.051 8	.98 5	.99 0	.037	0.000-0.062	57299.76
-c3	24.91	17	.096 7	.98 9	.99 2	.033	0.000-0.058	57301.45
-c2, c3	26.34	18	.092 2	.98 8	.99 2	.032	0.000-0.057	57295.93
-s, c2, c3	35.91	19	.010 8	.97 6	.98 5	.045	0.021-0.067	57312.18
-e2, c2, c3*	26.99	19	.104 9	.98 9	.99 3	.031	0.000-0.056	57289.18
-a2, e2, c2, c3	32.21	20	.041 1	.98 3	.99 0	.037	0.008-0.060	57289.05
-a3, e2, c2, c3	42.40	20	.002 5	.96 8	.98 1	.050	0.029-0.072	57304.52

*Notes: Inattent. = inattentive symptoms; Hyp.-Imp = hyperactive-impulsive symptoms; ODD = oppositional defiant disorder; CD = conduct disorder; Broad ext. = broad externalizing symptoms; "-" indicates the following parameters have been dropped from the model; c2 = parameter for common shared environmental influences; c3 = parameter for unique shared environmental influences on disruptive behavior; s = parameter for bidirectional influences of sibling phenotype; e2 = parameter for common nonshared environmental influences; e3 = parameter for unique nonshared environmental influences on disruptive behavior; a2 = parameter for common genetic influences; a3 = parameter for unique genetic influences on disruptive behavior; * indicates best fitting model.*

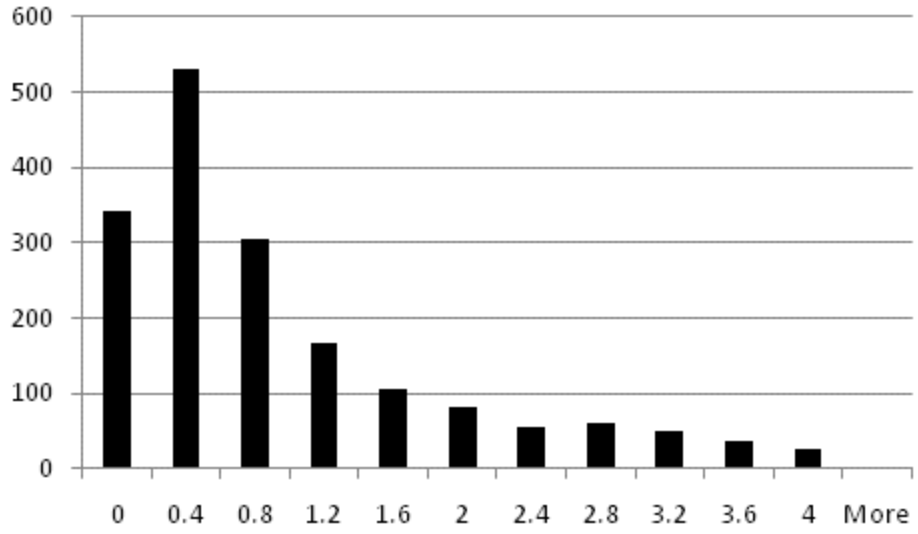

Figure 1. Histogram of inattentive symptom scores.

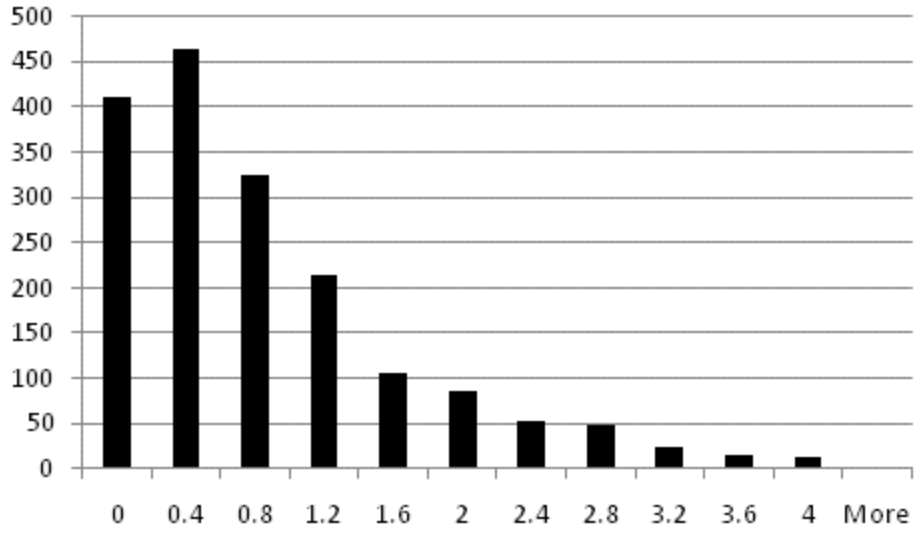

Figure 2. Histogram of hyperactive-impulsive symptom scores.

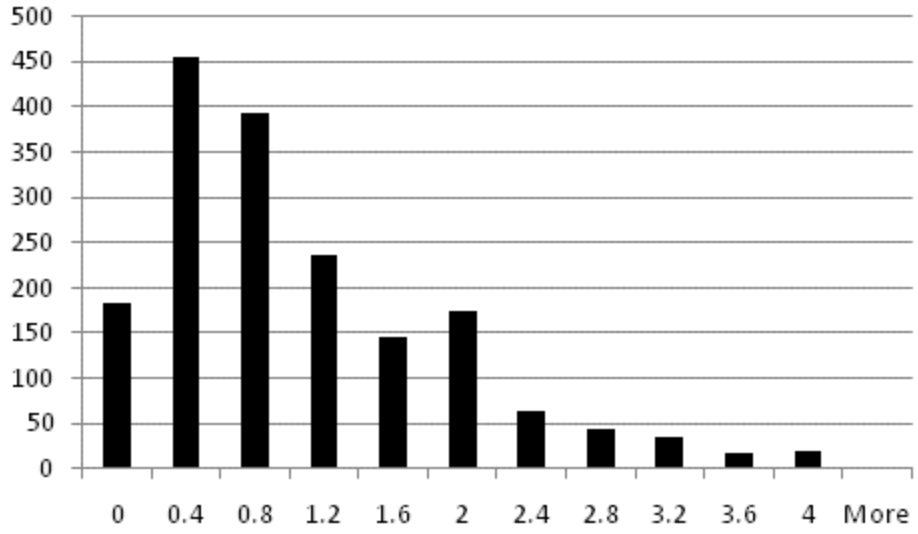

Figure 3. Histogram of ODD symptom scores.

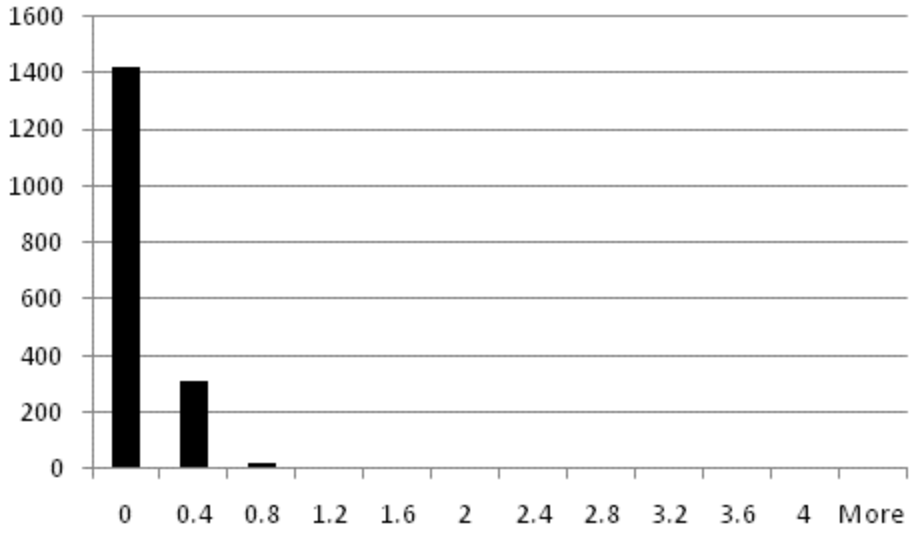

Figure 4. Histogram of CD symptom scores.

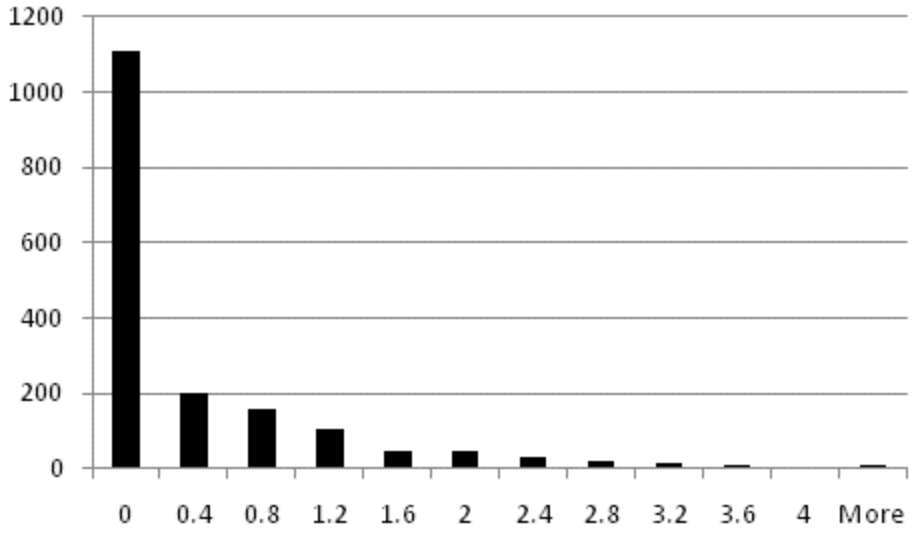

Figure 5. Histogram of broad externalizing symptom scores.

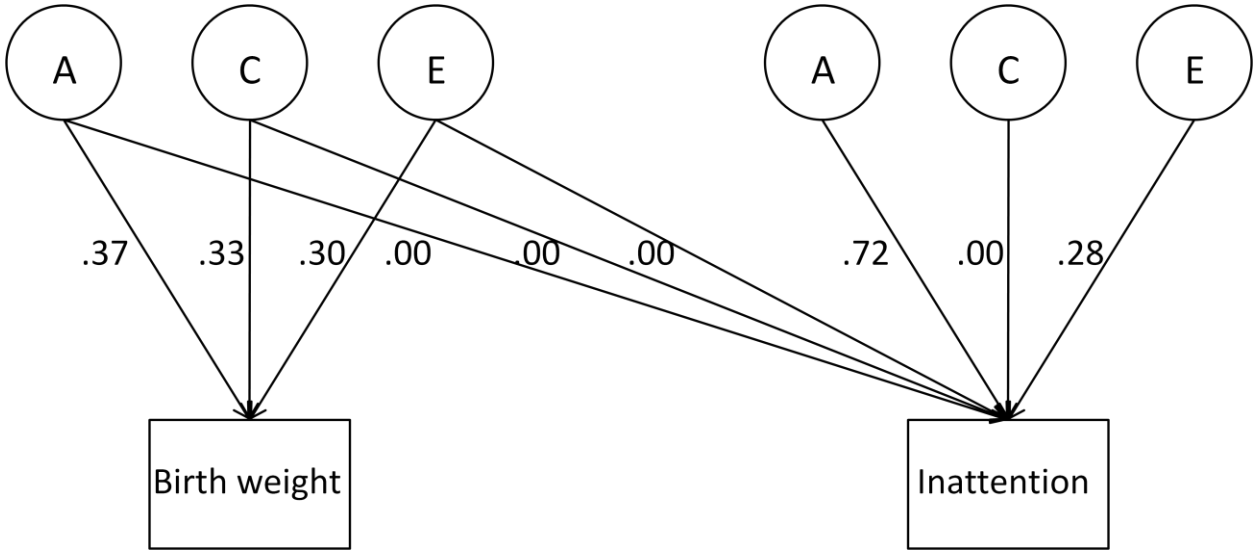

Figure 6. Bivariate Cholesky model for birth weight and inattentive symptoms.

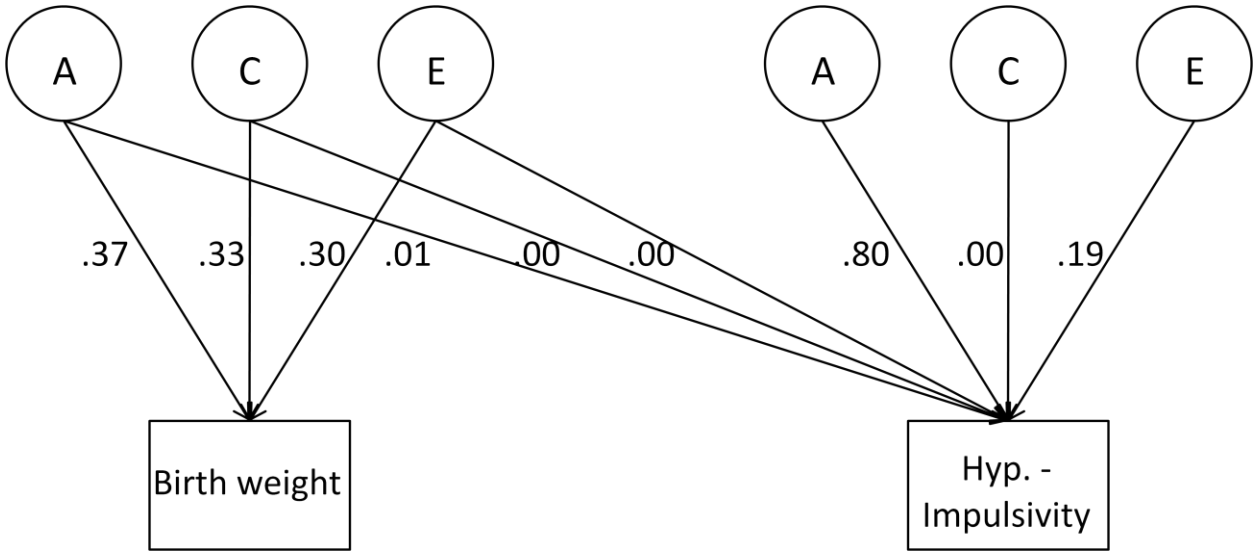

Figure 7. Bivariate Cholesky model for birth weight and hyperactive-impulsive (hyp.-impulsivity) symptoms.

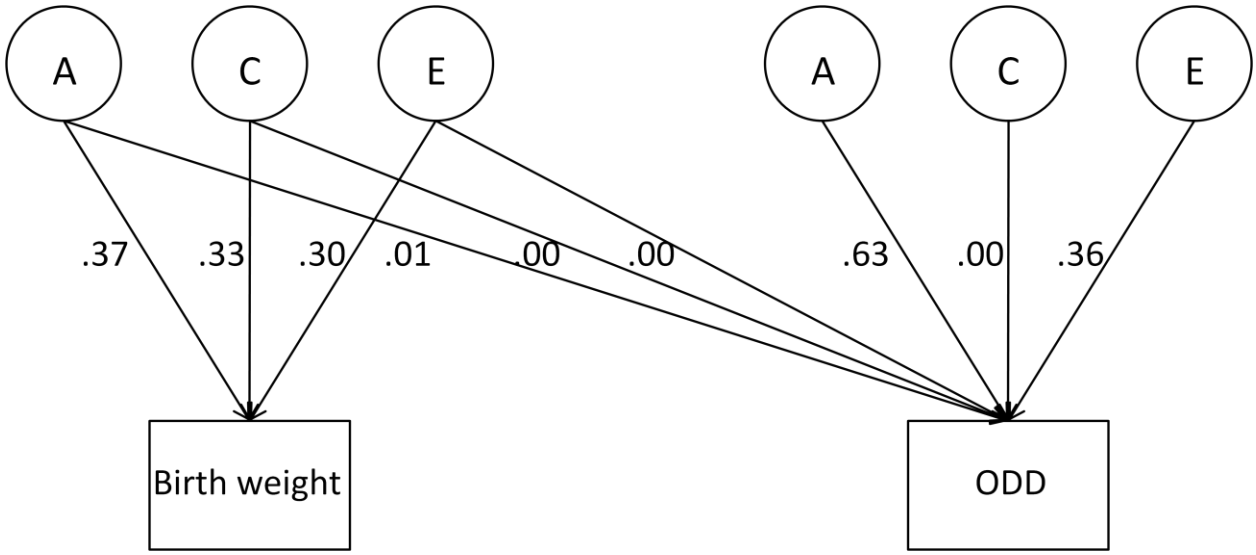

Figure 8. Bivariate Cholesky model for birth weight and oppositional defiant disorder (ODD) symptoms.

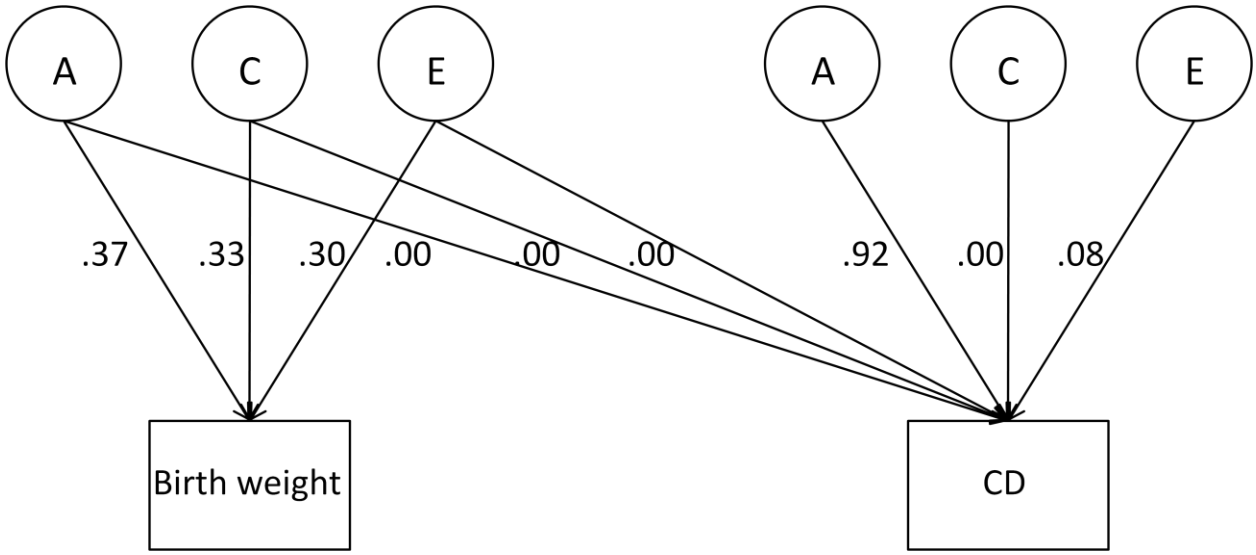

Figure 9. Bivariate Cholesky model for birth weight and conduct disorder (CD) symptoms.

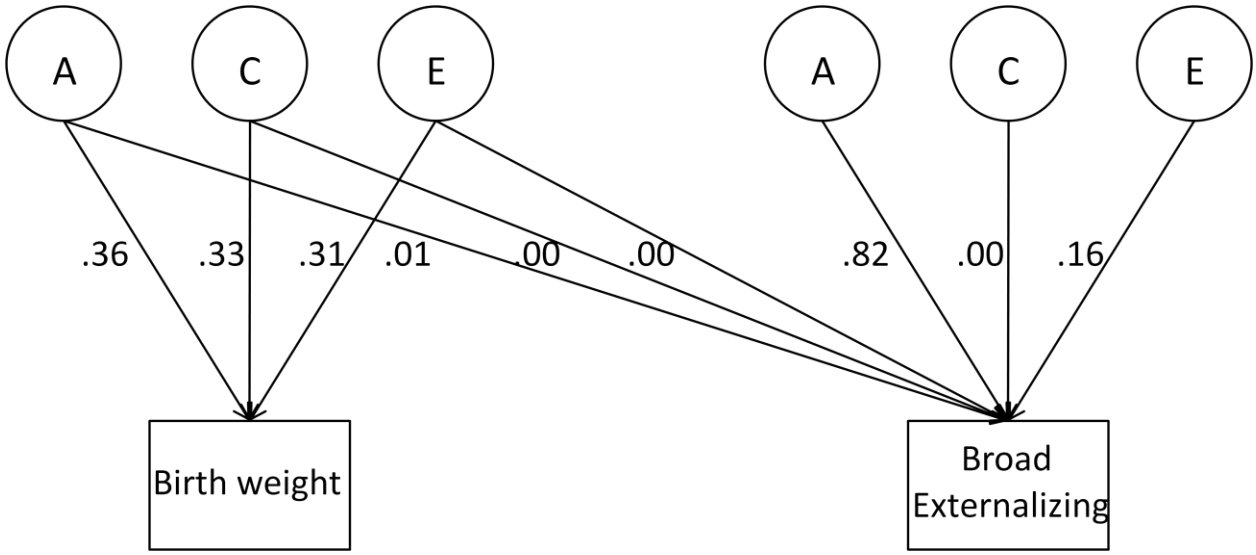

Figure 10. Bivariate Cholesky model for birth weight and broad externalizing symptoms.