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This is a Peer Reviewed Accepted version of the following article, accepted for publication in Journal of Child Psychology and Psychiatry.

2014-07-31

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J Child Psychol Psychiatry. 2015 Apr;56(4):453-9.

<http://doi.org/10.1111/jcpp.12299>

<http://hdl.handle.net/10616/42125>

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Birth weight as an independent predictor of ADHD symptoms:

A within-twin pair analysis

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Word count: 5,265

Disclosure: The authors state no conflicts of interest

Funding/Support: This research was supported by grants from the Swedish Council for Working Life and Social Research and from the Swedish Research Council (2010-3184) and NICHD (HD061817). We also acknowledge financial support from the Swedish Research Council through the Swedish Initiative for Research on Microdata in the Social And Medical Sciences (SIMSAM) framework grant no. 340-2013-5867.

Access to data: Erik Pettersson confirms that he had full access to all the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis.

ABSTRACT

OBJECTIVE: Studies have found an association between low birth weight and ADHD, but the nature of this relation is unclear. First, it is uncertain whether birth weight is associated with both of the ADHD dimensions, inattentiveness and hyperactivity-impulsivity. Second, it remains uncertain whether the association between birth weight and ADHD symptom severity is confounded by familial factors.

METHOD: Parents of all Swedish 9- and 12-year-old twins born between 1992 and 2000 were interviewed for DSM-IV inattentive and hyperactive-impulsive ADHD symptoms by the Autism – Tics, AD/HD and other Comorbidities (A-TAC) inventory (N = 21,775 twins). Birth weight was collected prospectively through the Medical Birth Registry. We used a within-twin pair design to control for genetic and shared environmental factors.

RESULTS: Reduced birth weight was significantly associated with a mean increase in total ADHD ($\beta = -.42$; 95% CI: $-.53, -.30$), inattentive ($\beta = -.26$; 95% CI: $-.33, -.19$), and hyperactive-impulsive ($\beta = -.16$; 95% CI: $-.22, -.10$) symptom severity. These results imply that a change of one kilogram of birth weight corresponded to parents rating their child nearly one unit higher (going from “no” to “yes, to some extent” on a given symptom) on the total ADHD scale. These associations remained within pairs of MZ and DZ twins, and were also present when restricting the analyses to full term births.

CONCLUSIONS: There is an independent association between low birth weight and all forms of ADHD symptoms, even after controlling for all environmental and genetic confounds shared within twin pairs. These results indicate that fetal growth restriction (as reflected in birth weight differences within twin pairs) and/or the environmental factors which influence it is in the casual pathway leading to ADHD.

Keywords: ADHD, DSM, birth weight, behavioral genetics, environmental influences

Birth weight as an independent predictor of ADHD symptoms: A within-twin pair analysis

Attention-Deficit/Hyperactivity Disorder (ADHD) is a prevalent neuropsychiatric disorder that consists of two underlying dimensions, specifically, inattentiveness and hyperactivity-impulsivity (Biederman & Faraone, 2005). In addition to a strong genetic predisposition, environmental influences account for an estimated 10% to 40% of the variance of these dimensions (Faraone, Ericson, Gunnarskog, & Kallen, 1990; Faraone et al., 2005; Burt, 2009). Low birth weight has been recognized as a risk factor that is associated with the development of ADHD (Botting, Powls, Cooke, & Marlow, 1997; Breslau & Chilcoat, 2000; Heinonen et al., 2006; Lahti et al., 2006; Mick, Biederman, Prince, Fischer, & Faraone, 2002; Nigg & Breslau, 2007).

One possible explanation for the association between ADHD and low birth weight is that restricted fetal growth may reflect insufficient energy supply for organ development, leading to an increased susceptibility to a range of suboptimal neurodevelopmental outcomes later in life (Hatch, Healey, & Halperin, in press; Swanson & Wadhwa, 2008). Previous studies examining the association between fetal growth restriction and ADHD have shown that prematurity (Bhutta et al., 2002; Lindstrom, Lindblad, & Hjern, 2011) and low birth weight (Breslau & Chilcoat, 2000; Mick, Biederman, Prince, Fischer, & Faraone, 2002; Nigg & Breslau, 2007) are risk factors for the development of ADHD. Although most researchers have focused on infants with very low (<1,500 g) or extremely low (<1,000 g) birth weights and preterm infants (Breslau & Chilcoat, 2000; Botting, Powls, Cooke, & Marlow, 1997), children with moderately low birth weight (<2,500 g) also appear to have an increased risk for developing ADHD (Mick et al., 2002; Nigg & Breslau, 2007), indicating that the association between ADHD and birth weight might extend beyond the extreme ends of the distributions.

Some evidence indicates that birth weight may influence the inattentive more than the hyperactive subtype (Bhutta, Cleves, Casey, Craddock, & Anand, 2002; Elgen, Sommerfelt, & Markestad, 2002). In one study, whereas 56 adolescents with low birth weight had significantly higher self-reported scores on inattention compared to controls, there was no difference in hyperactivity (Indrevik, Vik, Heyerdahl, Kulseng, Fayers, & Brubakk, 2004). This trend may continue into young adulthood, as parents rated their 20-year old children who were born with very low birth weight (less than 1500 grams) as displaying more problems with inattention, but not behavior, compared to controls (Hack et al., 2004).

Although the association between ADHD and low birth weight appears robust, most prior studies have not been able to rule out potential familial confounding (genetic and environmental; D'Onofrio, Lahey, Turkheimer, & Lichtenstein, 2013; Thapar & Rutter, 2009). A twin design allows for a focused test of the potential influence of genetic and environmental confounds underlying the association between low birth weight and ADHD (McGue, Osler, & Christensen, 2010; Rutter, 2007). Specifically, twin siblings share genes (i.e., monozygotic, MZ, twin pairs have identical genomes, whereas dizygotic, DZ, twin pairs share on the average 50% of their segregating genes), intrauterine exposures, maternal factors, and early environments. Because twin siblings have identical gestational age, birth weight differences within twin pairs reflect factors affecting the growth of each individual fetus. If an association in a cohort of twins remains at the within-twin pair level, then factors specific to each individual must be involved in the underlying causal pathway. In contrast, if the association disappears or substantially attenuates in the within-twin pair comparison, then familial factors (genetic and/or shared environments) must be involved.

Results from a study of about 2,000 MZ twin pairs assessed by their teachers with the Strength and Difficulties Questionnaire hyperactivity subscale (Asbury, Dunn, & Plomin, 2006) and a study of about 15,000 twin pairs assessed by their parents with the Achenbach System of Empirically Based Assessment attention problem scale (Groen-Blokhuis, Middeldorp, van Beijsterveldt, & Boomsma, 2011) suggested that the twin with lower birth weight within a pair tended to have higher scores on the continuously distributed ADHD-related phenotypes. Two studies have tried to use more stringent measures of ADHD based on the Diagnostic Statistical Manual (DSM; American Psychiatric Association, 2000) system, and with less than 20 identical twin pairs discordant for ADHD they demonstrated that the twin with lower birth weight within each pair that tended to receive the diagnosis (Hultman, Torrang, Tuvblad, Cnattingius, Larsson, & Lichtenstein, 2007; Lehn, Derks, Hudziak, Heutink, van Beijsterveldt, & Boomsma, 2007).

Although these studies support the conclusion that low birth weight relates to ADHD even after controlling unmeasured familial confounds, it is difficult to use the twin design to identify a large number of discordant pairs in dichotomously diagnosed disorders with a strong genetic component (Sharp, Gottesman, Greenstein, Ebens, Rapoport, & Castellanos, 2003). Treating ADHD as a continuously distributed (cf., Levy, Hay, McStephen, Wood, & Waldman, 1997) disorder may represent a more fruitful approach to understanding its relation with birth weight (Asbury et al., 2006; Groen-Blokhuis et al., 2011).

To date, only one study to our knowledge has assessed the relation between DSM-based continuous ADHD inattentiveness and hyperactivity, and low birth weight using a twin design. Across two independent American samples consisting of over 1,500 and 4,000 twins, respectively, a primary care taker rated the twin with the lighter birth weight within a pair as displaying more DSM-based ADHD problems in childhood and adolescence (Ficks, Lahey, &

Waldman, 2013). However, birth weight did not account for more than one percent of the variance in ADHD, prompting the conclusion that “birth weight does not represent a major risk factor in the development of ADHD...” (pp. 848). Potential reasons for the small amount of variance accounted for may include that the larger sample relied on retrospective reports of birth weight, which may have introduced error that attenuated the association, and a selection bias involving families of lower socio-economic status (SES) declining to participate, which might have led to a truncation of range of birth weight. We circumvent these potential issues by relying on a large population-based twin study with a high participation rate and prospective birth weight reports.

The aims of the present study were to:

- 1) Examine if birth weight was uniformly related to all forms of DSM-based ADHD symptoms, including continuous total score, inattention, and hyperactivity-impulsivity.
- 2) Examine if these associations held up within twins pairs, that is, after controlling unmeasured genetic and shared environmental confounds.

METHOD

PARTICIPANTS

Parents of all Swedish twins were identified through the Swedish Twin Registry and contacted for interviews as part of the Child and Adolescent Twin Study in Sweden (CATSS; Anckarsäter et al., 2011). The study is ongoing, and focused on parents of 9- and 12-year olds from July 1992 through June 1995, and on 9-year olds from July 1995 and onward. This age range was the focus because potential neurodevelopmental disorders tend to have stabilized by then, whereas disorders more common of adolescence and adulthood (such as depression and

drug abuse) have usually not surfaced yet. Interviewers from a professional company, who received a brief introduction to child and adolescent psychiatry and twin research, carried out the interviews over the phone. The study started in July 2004 and is ongoing. Over 80% of the parents in the cohorts born before May 2000 have responded. The mother was interviewed in 88% and the father in the remaining cases except for 30 cases (0.4%) in which another member of the family was interviewed. The total study group consisted of 21,775 consenting and assessed individuals. The data collection was approved by the Ethics Committee at Karolinska Institutet.

MEASURES

ADHD. Child ADHD symptoms were assessed using the Autism – Tics, ADHD, and other Comorbidities inventory (A-TAC; Hansson, Svanstrom Rojwall, Rastam, Gillberg, & Anckarsater, 2005), which is designed for large-scale epidemiological research as an easy-to-administer, dimensional, and comprehensive interview for administration by lay persons over the phone. The A-TAC covers 96 specific child psychiatric symptoms, such as ADHD and autism spectrum disorder, and the instrument has high reliability and validity (Hansson et al., 2005; Larson et al., 2010). ADHD was assessed using 18¹ items corresponding to the specific DSM-IV symptom criteria using three response categories: “no” (0), “yes, to some extent” (0.5), and “yes” (1.0). All items were answered with a life-time perspective and in comparison to similarly aged peers. A continuous inattention scale was created from the sum of 9 DSM-IV symptoms of inattention (coefficient alpha = .90), and a continuous hyperactivity-impulsivity scale was created from the sum of the 9 DSM-IV items related to hyperactivity-impulsivity (coefficient alpha = .86).

¹ Note that the A-TAC ADHD scale contains 19 items. However, in order to remain consist with the DSM-IV, we only used the 18 items that directly corresponded to those criteria.

Birth weight. Information regarding birth weight was obtained from the Medical Birth Registry, which contains prospective data from more than 99% of births in Sweden since 1973. The validity of variables in the Medical Birth Registry is high (Cnattingius et al., 1992; Centre for Epidemiology, 2003). Data from the CATSS interview were linked to the Medical Birth Registry through personal identification numbers. The parental reports of birth order and birth weight in CATSS were compared with the information in the Medical Birth Registry as a means of ascertaining that the correct birth weight was assigned to the correct twin with a pair. We retained participants for whom the difference was less than 100 grams, leading to a total of 18,359 twins. Birth weight was analyzed as a continuous variable.

Zygoty. Zygoty determination for 11,392 individuals was based on a panel of 48 SNPs (Hannelius et al., 2007). For the remaining participants, we applied an algorithm based on 5 items concerning twin similarity that were maximally correlated with DNA-determined zygoty. Only twins with more than 95% probability of being correctly classified were assigned a zygoty. Complete information from both twins on ADHD, birth weight, and zygoty was available for 17,909 twins, 5,084 of whom were MZ, 6,423 were DZ, and 6,402 were DZ opposite sexed (DZOS) twins.

STATISTICAL ANALYSES

In a first set of analyses, we examined associations between birth weight and ADHD over twin pairs using standard linear regression models. These analyses quantify the association between birth weight and ADHD on a population level (i.e., not within twin pairs), and are thus not adjusted for shared environmental and genetic factors. We regressed total ADHD, inattentive, and hyperactive-impulsive scores on birth weight. All variables were treated as continuous, and all three regressions were adjusted for sex and gestational age (continuous). To

account for the clustering of data, we used clustered (“sandwich”) standard errors. Subsequently, we refitted these three regressions after restricting the analysis to the term-born children (gestational age \geq week 37), instead of adjusting for gestational age in the models.

In a second set of analyses, we examined associations between birth weight and ADHD within twin pairs using conditional linear regression models. In these models, each twin pair was entered as a separate stratum, analogous to standard conditional logistic regression analyses of matched pairs with binary outcomes (Allison, 2009). Because these conditional analyses quantify the association between birth weight and ADHD on a within twin pair level, they adjust for shared environmental and genetic factors. We fitted the same six regression models described above, separately for the MZ and DZ twin pairs, with the exception that we did not adjust for gestational age because it is constant within twin pairs. Because sex is associated with both birth weight and ADHD (and therefore potentially an important confounder), opposite-sexed DZ twin pairs were excluded from the within twin pair analyses.

RESULTS

Across all individuals, birth weight was significantly associated with total ADHD symptoms ($\beta = -.42$, 95% CI: $-.53, -.30$), inattention symptoms ($\beta = -.26$, 95% CI: $-.33, -.19$), and hyperactivity-impulsivity symptoms ($\beta = -.16$, 95% CI: $-.22, -.10$). The association with total ADHD implies that a change of one kilogram of birth weight corresponded to being rated nearly one unit higher (e.g., going from “no” to “yes, to some extent” on a given symptom) on one of the ADHD symptoms. These results remained the same when examining birth weight based on only term-born babies (Table 1). Figure 1 plots binned ADHD scale scores against the mean birth weights corresponding to each bin, and shows that the association appears to exist across the full range of ADHD symptoms and not just at the extreme end.

Subsequently, we proceeded to examine if the associations remained at a within-twin level. Within MZ pairs, birth weight remained significantly related to total ADHD symptoms ($\beta = -.74$, 95% CI: $-.97, -.51$), inattention symptoms ($\beta = -.50$, 95% CI: $-.66, -.34$), and hyperactivity-impulsivity symptoms ($\beta = -.24$, 95% CI: $-.35, -.12$). Within DZ pairs, birth weight remained significantly related to total ADHD symptoms ($\beta = -.81$, 95% CI: $-1.12, -.51$), inattention symptoms ($\beta = -.47$, 95% CI: $-.66, -.27$), and hyperactivity-impulsivity symptoms ($\beta = -.35$, 95% CI: $-.52, -.18$). Similar results emerged when examining only term-born babies (Table 1). This implies that if two identical twins differed in birth weight by one kilogram, we would expect the lighter twin to score about a symptom and half higher on the total ADHD scale. Furthermore, it suggests that the association cannot be attributed to unmeasured familial or genetic factors. A sensitivity analyses was conducted to investigate the extent to which the within-pair results remained stable after excluding the most extreme cases (515 twin pairs) with a birth weight difference of more than 40% or more than 1000 grams. We obtained similar results (the estimates changed by an average of $-.02$, min = $-.11$, max $.07$), suggesting that the observed pattern of within-pair associations is robust even after controlling for the potential influence of the twin to twin transfusion syndrome.

DISCUSSION

In our study, lower birth weight was significantly associated with an increase in all types of DSM-IV ADHD symptom severity, including total score, inattention, and hyperactivity-impulsivity, indicating that the effect of birth weight is uniform across all ADHD symptoms. These results remained after controlling for gestational age, and shared environmental and genetic confounds. This effect of low birth weight is in line with results from two smaller

(Hultman et al., 2007; Lehn et al., 2007) and one large (Ficks et al., 2013) twin study of DSM-based ADHD and with the fetal programming hypothesis (Swanson & Wadhwa, 2008).

Whereas previous studies have reported that inattention may be more influenced than hyperactivity-impulsivity by low birth weight (Bhutta et al., 2002; Elgen et al., 2002; Hack et al., 2004; Indrevik et al., 2004), such studies have been hampered by relatively small samples and the inability to control for unmeasured familial and genetic factors. In contrast, we relied on a large population-based twin sample, which afforded adequate power to test the differential hypothesis. The absence of a difference between inattention and hyperactivity-impulsivity indicates that the fetal growth restriction influences all forms of ADHD along similar pathways.

In a previous large twin study of within-pair differences, birth weight accounted for less than one percent of the variance in DSM-based ADHD symptoms, leading the authors to suggest that birth weight is not a major risk factor (Ficks et al., 2013). It is important to keep in mind, however, that variance accounted for depends on the variance in birth weight (i.e., the predictor). One possibility is that families of lower SES, which may be related to lower birth weight, chose not to participate in their study, which in turn may have truncated the range and thereby the variance accounted for. Focusing on unstandardized regression weights may be preferable (Tukey, 1969) because they are untethered to the variance of the predictor, which varies depending on sample characteristics. Nevertheless, given that statistical significance is not only a function of the estimate but also the sample size, studies with many observations may identify associations of limited clinical relevance. Although the effect in this study was in line with other environmental exposures after controlling genetic and shared environmental confounding such as parental income (cf., Larsson, Sariaslan, Långström, D'Onofrio, & Lichtenstein, 2014), it may not inform clinical decisions; rather, it could highlight mechanisms of action through which

ADHD develops. For example, investigations into differences in brain function between children of low and normal birth weight may reveal mediating pathways, which could represent fruitful targets for future research and intervention.

Although the twin design is less powerful than randomized controlled trials in establishing causality, it can rule out a number of alternative explanations for the observed association. First, twin pairs raised together are matched for socioeconomic status, maternal stress, and an unfavorable lifestyle during pregnancy (e.g., maternal smoking during pregnancy), which rule out shared environments as a plausible explanation for the observed association. Likewise, twin siblings have identical gestational age, implying that birth weight differences within twin pairs reflect factors that influenced the growth of each individual fetus. Second, genetic confounding is virtually impossible because MZ twin pairs are genetically matched. Thus, even though uncertainty remains regarding the mechanism of action, our results highlight that restricted fetal growth (as reflected in birth weight differences within MZ twin pairs) is likely in the causal pathway to all forms of ADHD. One may speculate that this association may be mediated through differential in utero nourishment, leading to stymied brain development and subsequently increased neurodevelopmental problems during childhood (de Bie, Oostrom, & Delemarre-van de Waal, 2010; Schlotz & Phillips, 2009).

The present study suggests that the association between reduced birth weight and ADHD symptoms extend beyond the extreme end of the ADHD distribution, including the sub-diagnostic threshold range. This result is in line with accumulating evidence that ADHD exists on a severity continuum (Lubke, Hudziak, Derks, van Bijnsterveldt, & Boomsma, 2009; Pluess & Belsky, 2011; Shaw et al., 2011), and further implies that its relation to risk factors might also exist across the full ADHD spectrum. It may be beneficial to evaluate whether other potential

risk factors aside from birth weight, such as pre-term births and advancing paternal age, may be involved in the transition from milder to more severe levels of ADHD symptoms.

Limitations

The strength of this study includes the use of data from a large population-based sample of twins with a high response rate assessed using a psychometrically sound and well-validated instrument (Hansson et al., 2005; Larson et al., 2010). Birth weight information was retrieved from original birth records, which precludes recall bias, and the dimensional treatment of birth weight and ADHD symptoms allowed us to explore the effect throughout the distribution.

However, the results should be interpreted in light of some limitations.

First, in this very large epidemiological study, complete clinical evaluations were not feasible and therefore we had to rely on parental report. Although the items used herein closely mirrored the DSM-IV criteria, parental interviews are not equivalent to a psychiatric evaluation. Second, it is not obvious that our results, which are based on twins, can be generalized to singletons. Twins have higher risk for very low birth weight and complications before and around birth than singletons (MacGillivray, Campbell, & Thompson, 1988; Phillips, 1993). However, differences in birth weight observed in singletons may reflect familial factors, whereas differences in birth weight within twin pairs effectively control for such potential confounding (D'Onofrio et al., 2013; Shadish, Cook, & Campbell, 2001). Third, many markers of prenatal adversity (e.g., smoking during pregnancy and maternal stress during pregnancy) cannot be studied in the twin design, simply because there is no variation within twin pairs on such variables. Future research could address this important issue (Swanson & Wadhwa, 2008; Lahey, D'Onofrio, & Waldman, 2009) by analyzing adversity markers in a sibling design.

In conclusion, we have shown that reduced birth weight is associated with an increase in DSM-IV total ADHD, inattentive, and hyperactive-impulsive symptom severity. The association between birth weight and ADHD symptom severity remained after controlling unmeasured shared environmental and genetic factors, which lends support to the hypothesis that fetal growth restriction is in the causal pathway to ADHD.

Key points

- We examined the association between birth weight and parental ratings of DSM ADHD symptoms in a Swedish sample of 9 and 12 year old twins ($N = 17,909$)
- There was an association between low birth weight and ADHD, inattentive, and hyperactive-impulsive symptom severity in childhood, indicating that fetal growth restriction influences all forms of ADHD along similar pathways
- These associations appeared to exist across the entire ADHD range, including the sub-threshold range
- The associations remained after controlling for unmeasured shared environmental and genetic confounds, implying that fetal growth restriction, as reflected in birth weight differences within twin pairs, is in the casual pathway leading to ADHD

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Table 1. Twin study analyses of continuous birth weight (kg) continuous ADHD scores.

Outcome type	Full range of gestational age			Term-born (Gestational age => 37 weeks)		
	All ^a	MZ pairs	DZ pairs	All ^b	MZ pairs	DZ pairs
Total ADHD symptoms	-.42 (-.53,-.30)	-.74 (-.97,-.51)	-.81 (-1.12,-.51)	-.39 (-.52,-.26)	-.44 (-.72,-.15)	-.69 (-1.05,-.33)
Inattention symptoms	-.26 (-.33,-.19)	-.50 (-.66,-.34)	-.47 (-.66,-.27)	-.21 (-.28,-.13)	-.29 (-.47,-.10)	-.42 (-.65,-.19)
Hyperactivity/impulsivity symptoms	-.16 (-.22,-.10)	-.24 (-.35,-.12)	-.35 (-.52,-.18)	-.18 (-.25,-.11)	-.15 (-.30,.01)	-.27 (-.48,-.07)

Note. All = Regressions across all individuals. MZ pairs = Regressions within monozygotic twins. DZ pairs = Regressions within dizygotic twin pairs. The table shows estimates with 95% confidence intervals in parentheses. ^aAdjusted for gestational age and sex. ^bAdjusted for sex.

Figure 1. Relation between ADHD symptom severity and mean birth weight in grams.

