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### Authors

Morgan, Julia E  
Lee, Steve S  
Loo, Sandra K

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Fluid reasoning mediates the association of birth weight with ADHD symptoms in youth from  
multiplex families with ADHD

Julia E. Morgan,<sup>1</sup> Steve S. Lee,<sup>1</sup> & Sandra K. Loo<sup>2</sup>

<sup>1</sup>Department of Psychology, UCLA, 1285 Franz Hall, Box 951563, Los Angeles, CA 90095;

<sup>2</sup>Department of Psychiatry and Biobehavioral Sciences, Semel Institute for Neuroscience and  
Human Behavior, UCLA, 760 Westwood Plaza, Los Angeles, CA 90095.

Correspondence concerning this article should be addressed to Julia E. Morgan, UCLA, 1285  
Franz Hall, Box 951563, Los Angeles, CA 90095. Email: jemorgan@ucla.edu. Telephone:  
310.825.3301, ext. 43. Fax: 310.206.5895.

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#### Abstract

**Objective.** We tested mediation of birth weight and ADHD symptoms by multiple  
biologically plausible neurocognitive functions, and evaluated familiarity of observed indirect  
effects. **Method.** 647 youth from 284 multiplex families with ADHD completed the Arithmetic,  
Digit Span, Vocabulary, and Block Design subtests of the Wechsler Intelligence Scale for

Children (WISC). Multiple mediation tested WISC subtests as mediators of birth weight and multi-informant ADHD symptoms. Familiarity of indirect effects was estimated via moderated mediation comparing conditional indirect effects across siblings concordant and discordant for ADHD. **Results.** Controlling for IQ and demographic factors, Arithmetic uniquely mediated birth weight and ADHD symptoms. Conditional indirect effects through Arithmetic did not differ across ADHD concordant and discordant siblings. **Conclusion.** These cross-sectional findings support previous prospective longitudinal research implicating Arithmetic (i.e., fluid reasoning) as a preliminary causal mediator of birth weight and ADHD symptoms, and suggest that this pathway is independent of genetic influences on ADHD.

**Keywords:** ADHD, birth weight, neurocognitive functioning, multiple mediation, familiarity

Meta-analytic and prospective longitudinal evidence similarly suggest that birth weight is reliably associated with individual differences in attention-deficit/hyperactivity disorder (ADHD; Aarnoudse-Moens, Weisglas-Kuperus, van Goudoever, & Oosterlaan, 2009; Bhutta, Cleves, Casey, Craddock, & Anand, 2002; Halmøy, Klungsøyr, Skjærven, & Haavik, 2012; Martel, Lucia, Nigg, & Breslau, 2007; Morgan, Loo, & Lee, 2016; Nigg & Breslau, 2007). Moreover, there is

replicated evidence that birth weight predicts ADHD symptoms in co-twin control designs, providing quasi-experimental evidence for a causal relation that is independent of environmental and genetic confounds (Groen-Blokhuis, Middeldorp, van Beijsterveldt, & Boomsma, 2011; Pettersson et al., 2014). Thus, birth weight is unlikely to predict ADHD symptoms due to shared variance with other correlates of poor fetal development (e.g., gestational age, teratogen exposure), and is instead a preliminary independent causal factor for the pathogenesis of ADHD symptoms.

If birth weight is a causal predictor of ADHD symptoms, elucidating its mechanisms of influence is necessary to develop early interventions that prevent the onset of symptoms (Sonuga-Barke & Halperin, 2010); surprisingly few studies, however, have examined mediators of this association. To date, predictions of ADHD symptoms from birth weight were statistically mediated by separable neurocognitive functions, including sensorimotor and visuospatial domains in young children (Hatch, Healey, & Halperin, 2014; Martel et al., 2007) and response variability in youth aged 6-17 (Wiggs, Elmore, Nigg, & Nikolas, 2016). To our knowledge, however, only one study evaluated temporally ordered mediators of birth weight and ADHD symptoms, which is necessary to infer causal mediation (Kraemer, Stice, Kazdin, Offord, & Kupfer, 2001). Specifically, baseline scores on the Arithmetic subtest of the Wechsler Intelligence Scale for Children (WISC; ages 5-10) uniquely mediated the association of birth weight with multi-method/informant ADHD symptoms at a 2-year follow-up (ages 7-13), controlling for demographic factors, co-occurring psychopathology, and baseline ADHD symptoms (Morgan et al., 2016). Indirect effects of other WISC subtests (e.g., Digit Span, Vocabulary) were not significant. Although these longitudinal findings implicated fluid reasoning, the primary construct reflected by Arithmetic (Keith, Fine, Taub, Reynolds, &

Kranzler, 2006; Weiss, Keith, Zhu, & Chen, 2013), as a potential causal mediator, the results require replication. However, the four extant studies on mediators of birth weight and ADHD have evaluated different domains of neurocognitive functioning, precluding direct comparisons across samples. The current study addresses this important gap directly.

Given the need to prosecute indirect effects from birth weight to ADHD symptoms, the present study evaluated higher-order neurocognitive functions as mediators (i.e., performance on WISC Arithmetic, Digit Span, Vocabulary, and Block Design). Although Arithmetic is sensitive to multiple cognitive domains (e.g., working memory, quantitative reasoning), factor analyses suggest that it primarily assesses fluid reasoning (Keith et al., 2006; Weiss et al., 2013). Additionally, Digit Span measures short-term memory and verbal working memory, Vocabulary primarily assesses verbal comprehension (but may also involve crystallized knowledge), and Block Design reflects perceptual reasoning (Keith et al., 2006; Wechsler, 1991; Weiss et al., 2013). We specifically prioritized Arithmetic, Digit Span, Vocabulary, and Block Design based on their (1) previous evaluation as temporally ordered mediators of birth weight and ADHD symptoms within the context of a prospective longitudinal design (with the exception of Block Design), and (2) biological plausibility as causal mediators. That is, all four proposed WISC subtests, and their primary underlying constructs, are reliably correlated with birth weight (Aarnoudse-Moens et al., 2009; Bhutta et al., 2002; Hutchinson, De Luca, Doyle, Roberts, & Anderson, 2013; Lahat, Van Lieshout, Saigal, Boyle, & Schmidt, 2014; Skranes et al., 2013) and with ADHD (Doyle, Biederman, Seidman, Reske-Nielsen, & Faraone, 2005; Martin, Hamshere, Stergiakouli, O'Donovan, & Thapar, 2014; Nigg, 2006; Tamm & Juranek, 2012; Willcutt et al., 2010; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). Moreover, the proposed WISC mediators are associated with neurodevelopmental impairments (e.g., reduced cortical surface

area, thickness, volume) that are secondary to low birth weight (Martinussen et al., 2005; Skranes et al., 2013; Walhovd et al., 2012) and central to ADHD etiology (Narr et al., 2009; Shaw et al., 2012). For example, young adults with low birth weight exhibited reduced cortical surface area that correlated with a composite score from Arithmetic and Digit Span *specifically* in regions where reduced surface area was observed in youth with ADHD (e.g., superior frontal and medial temporal gyri; Shaw et al., 2012; Skranes et al., 2013). Similar results were identified with a composite score from Vocabulary and Block Design (Martinussen et al., 2005). Thus, these four neurocognitive factors are biologically plausible mediators of birth weight and ADHD symptoms.

The present study extends the existing literature on mediators of birth weight and ADHD in several ways. First, this is a relatively large sample ( $n = 647$ ), consisting of affected and unaffected siblings from multiplex families with ADHD. Although a previous study identified significant indirect effects through Arithmetic, but not Digit Span and Vocabulary, the latter tests may have been underpowered given the modest sample size ( $n = 222$ ; Morgan et al., 2016). Second, previous studies on neurocognitive mediators of birth weight and ADHD symptoms did not control for IQ. Given that  $g$  loads substantially across all four hypothesized mediators (.55-.79), and particularly Arithmetic (Keith et al., 2006), control of IQ is necessary to specify indirect effects of birth weight on ADHD symptoms. Third, beyond prosecution of the hypothesized mediators, the present sample affords a unique opportunity to consider familiarity of mediating pathways from birth weight to ADHD symptoms. Birth weight, reasoning/executive function (EF) domains (e.g., fluid reasoning, working memory), and ADHD symptoms are substantially heritable. Fetal and maternal genetic factors accounted for 31% and 22% of the variance in birth weight, respectively (Lunde, Melve, Gjessing, Skjærven, & Irgens, 2007), and

heritability estimates for ADHD range from .70-.95 (Hawi et al., 2015; Thapar, Cooper, Eyre, & Langley, 2013). Additionally, genome-wide complex trait analysis highlights a strong additive influence of common single nucleotide polymorphisms on IQ, reasoning, and EF (Loo et al., 2012; Robinson et al., 2015), and polygenic ADHD risk scores predicted IQ and working memory (Martin et al., 2014). Although co-twin control studies suggest that the total effect of birth weight on ADHD symptoms is independent of genetic confounds (Groen-Blokhuis et al., 2011; Pettersson et al., 2015), no study has directly evaluated potential genetic confounding of the corresponding *indirect effects* (although Wiggs et al. controlled for parental ADHD in indirect effects from birth weight to offspring ADHD symptoms). Unlike tests of the total effect, tests of indirect effects are susceptible to bias from unmeasured confounders of mediator-outcome associations (Loeys, Moerkerke, & Vansteelandt, 2015). Thus, genetic factors common to neurocognitive functioning and ADHD (e.g., Martin et al., 2014) may confound indirect effects from birth weight to ADHD symptoms. Crucially, if ADHD and the hypothesized indirect effects are genetically independent, indirect effects will be similar for ADHD concordant siblings and discordant siblings (Schachar et al., 2005; Tsuang, Faraone, & Lyons, 1993). Thus, moderated mediation analysis comparing conditional indirect effects of birth weight on ADHD symptoms across probands, affected siblings, and unaffected siblings is a critical preliminary test of whether effects are independent of or confounded by genetic influences on ADHD. This distinction has key clinical implications, given that environmentally-based pathologies may be more amenable to prevention and intervention compared to genetically driven disorders (Moffitt, Caspi, & Rutter, 2006).

To review, although birth weight may be a causal predictor of ADHD symptoms, the mechanisms underlying this association are largely unknown. We examined biologically

plausible neurocognitive mediators in a sample of affected and unaffected siblings from multiplex families with ADHD. To expand upon prior mediational investigations of birth weight and ADHD symptoms, the present study had two aims: (1) to simultaneously test WISC Arithmetic, Digit Span, Vocabulary, and Block Design as statistical mediators of birth weight and ADHD symptoms in a multiple mediation framework, with stringent control of IQ and relevant demographic factors; and (2) to investigate familiarity of observed indirect effects by comparing conditional indirect effects across siblings concordant and discordant for ADHD.

## Methods

### Participants

Participants were 647 youth aged 5-19 years ( $M = 10.47$ ,  $SD = 3.53$ ; 40.96% female) from 284 families who were assessed within a larger genetic study of multiplex families with ADHD. Complete demographic data and descriptive statistics are presented in Table 1. Families were recruited from a large metropolitan city in California via referrals from local psychiatry, pediatric, and community outlets (see BLINDED FOR REVIEW for additional details regarding recruitment). At least two siblings from each family met criteria for ADHD, with the oldest ADHD youth designated as the proband; unaffected siblings were also included in the sample. ADHD status required a positive diagnosis on the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS; Kaufman et al., 1997), a semi-structured interview with the parent and youth keyed to Diagnostic and Statistical Manual of Mental Disorders-IV criteria (DSM-IV; American Psychiatric Association, 1994). For a small number of families, data were not available for a second affected sibling, such that the sample consisted of ADHD probands ( $n = 284$ ), affected siblings ( $n = 255$ ), and unaffected siblings ( $n = 108$ ). Participants were required to be fluent in English and have biological parents



available to participate in the study. Exclusion criteria consisted of an IQ < 70 or a diagnosis of schizophrenia, autism spectrum disorder, or a known ADHD-linked genetic condition (e.g., tuberous sclerosis, fragile X).

### **Procedures**

All study procedures were approved by the Institutional Review Board. After receiving verbal and written explanations of study requirements, parents and youth provided written informed consent/assent. The K-SADS interview was administered to parents (95% mothers), and then separately to youth (if  $\geq 8$  years of age). Additionally, mothers reported birth weight data, youth completed a neurocognitive assessment, and rating scales were mailed to teachers. All youth completed the neurocognitive assessment free of stimulant medication for at least 24 hours. Informants were asked to assign ratings according to youth unmedicated behavior, if possible. All assessments were conducted by intensively trained clinical psychologists or master's degree-level research assistants. "Best estimate" diagnoses were determined by senior clinicians after individual review of diagnostic data. Multi-informant ADHD symptom counts were generated across parent and youth K-SADS ratings for each symptom; teacher ratings were used to supplement the interview data to achieve "best estimate" symptom counts using all available data. Inter-rater reliability among senior clinicians is reflected by a kappa of 1.0 for ADHD diagnoses and a mean weighted kappa of .84 across all diagnoses with > 5% occurrence in the sample. See BLINDED FOR REVIEW for additional details regarding assessment procedures and reliability.

### **Measures**

**Birth weight.** Mothers retrospectively reported youth birth weights in pounds and ounces, which were converted to ounces for all analyses ( $M = 119.55$ ,  $SD = 20.41$ ,  $range = 26-$

176). Maternal recall of offspring birth weight is highly correlated with medical record data into offspring adulthood (e.g.,  $ICC = .99$  in Yawn, Suman, & Jacobsen, 1998; also see Buka, Goldstein, Spartos, & Tsuang, 2004; Jaspers, de Meer, Verhulst, Ormel, & Reijneveld, 2010; O'Sullivan, Pearce, & Parker, 2000; Rice et al., 2007; Walton et al., 2000).

**Neurocognitive functioning.** Neurocognitive functioning was assessed using the Arithmetic, Digit Span, Vocabulary, and Block Design subtests of the WISC-III (Wechsler, 1991), which demonstrates excellent psychometric properties (Wechsler, 1991). The primary constructs assessed by these tests are fluid reasoning (Arithmetic), short-term memory and verbal working memory (Digit Span), verbal comprehension (Vocabulary), and perceptual reasoning (Block Design; Keith et al., 2006; Wechsler, 1991; Weiss et al., 2013), although they may also tap other domains of functioning. We used scaled scores for each subtest. Full Scale IQ was also derived from the WISC to be used as a covariate in analyses.

**ADHD.** As described above, ADHD diagnostic status and “best estimate” symptom counts were generated from parent and youth ratings on the K-SADS (Kaufman et al., 1997) and informed by teacher ratings on the Teacher Report Form (TRF; Achenbach & Rescorla, 2001). The TRF is a normed 113-item rating scale yielding eight narrowband syndrome scales, including an Attention Problems scale with both inattention and hyperactivity/impulsivity items. Both the K-SADS and TRF have been extensively validated and demonstrate excellent psychometric properties (Achenbach & Rescorla, 2001; Kaufman et al., 1997).

### **Statistical Analysis**

**Missing data.** Approximately 20% of youth were missing data on at least one key study variable (e.g., birth weight). Thus, we used full information maximum likelihood (FIML) estimation to maximize sample size for all analyses described below. FIML optimally remediates

missing data when the amount of missingness is up to 50% and data are missing at random or missing completely at random (MCAR; Schlomer, Bauman, & Card, 2010). Evaluation of missing data patterns via Little's MCAR Test (Little, 1988) indicated that data were indeed MCAR in the present sample ( $\chi^2(176) = 190.60, p = .21$ ).

**Multiple mediation.** Intraclass correlations (ICCs) indicated substantial between-family variation on the key study variables: birth weight ( $ICC = .47$ ), Arithmetic ( $ICC = .33$ ), Digit Span ( $ICC = .24$ ), Vocabulary ( $ICC = .38$ ), Block Design ( $ICC = .28$ ), and ADHD symptoms ( $ICC = .04$ ). Thus, we used multilevel structural equation modeling (MSEM; Preacher, Zyphur, & Zhang, 2010) in Mplus 7.0 (Muthén & Muthén, 1998-2015). Unlike traditional multilevel modeling approaches to mediation that conflate within- and between-level indirect effects (i.e., produce a single mean slope that combines the within- and between-level coefficients), MSEM separates within- and between-level effects into their orthogonal components and calculates separate coefficients for each level (Preacher et al., 2010). This distinction is nontrivial given that the former approach often produces biased estimates (Preacher et al., 2010). Moreover, in simulation studies, MSEM was superior to conflated and unconflated multilevel modeling-based mediation with respect to bias, power, and efficiency (Preacher, Zhang, & Zyphur, 2011). Thus, to evaluate Arithmetic, Digit Span, Vocabulary, and Block Design as statistical mediators of birth weight and ADHD symptoms, we constructed an MSEM path analysis that simultaneously tested direct effects from birth weight to all mediators and ADHD symptoms, and from all mediators to ADHD symptoms, controlling for age, sex, race-ethnicity, socioeconomic status (SES), and IQ. Given that this analysis stringently controlled for IQ and intercorrelations among the WISC mediators (bivariate correlations ranged from  $r = .17-.46, p < .001$  for all tests), demographic covariates unrelated to ADHD symptoms were dropped from the analysis to preserve power.

Because bootstrapped confidence intervals (CIs) cannot be computed with multilevel data, 95% CIs for the total and specific indirect effects of the mediators were calculated using 20,000 Monte Carlo simulations (Preacher & Selig, 2012; statistical significance is assumed when the interval excludes zero). Monte Carlo CIs for indirect effects are superior to other methods that are compatible with multilevel data (e.g., delta method) with respect to power, Type I error, and robustness to non-normal data (Mackinnon, Lockwood, & Williams, 2004; Preacher & Selig, 2012). Effect sizes were calculated for significant indirect effects using the *completely standardized indirect effect* (Preacher & Kelley, 2011), which can be interpreted on a scale of .01 = small, .09 = medium, and .25 = large. Tests of observed indirect effects were repeated but with mediator and outcome reversed to improve directional inferences derived from cross-sectional data.

**Moderated mediation.** We also evaluated moderation of observed indirect effects by proband, affected sibling, or unaffected sibling status to estimate familiarity. Specifically, we calculated conditional indirect effects (i.e., an indirect effect conditioned on a particular value of the moderator) for probands ( $n = 284$ ), affected siblings ( $n = 255$ ), and unaffected siblings ( $n = 108$ ), and calculated post hoc differences between these effects (Hayes, 2015). Moderated mediation calculations were based on addition of two dummy codes for the sibling status variable as well as two dummy codes for a sibling status x birth weight interaction term to the full multiple mediation model described above, such that conditional indirect effects were identically adjusted for covariates and the other WISC mediators.

## Results

### WISC Subtests as Mediators of Birth Weight and ADHD Symptoms

We first evaluated multiple mediation of birth weight and ADHD symptoms by Arithmetic, Digit Span, Vocabulary, and Block Design simultaneously, controlling for age, sex, and IQ (Figure 1). Race-ethnicity and SES were not controlled given they were unrelated to ADHD symptoms ( $p > .17$  for each). At the within level (i.e., individual youth within families), birth weight was positively associated with Arithmetic ( $B = .03$ ,  $SE = .01$ ,  $p = .01$ ) and Block Design ( $B = .04$ ,  $SE = .01$ ,  $p < .001$ ), but unrelated to Digit Span ( $B < .01$ ,  $SE = .01$ ,  $p = .77$ ) and Vocabulary ( $B = .01$ ,  $SE = .01$ ,  $p = .53$ ). In turn, Arithmetic was inversely associated with ADHD symptoms ( $B = -.22$ ,  $SE = .10$ ,  $p = .02$ ), but Digit Span ( $B = -.06$ ,  $SE = .10$ ,  $p = .53$ ), Vocabulary ( $B = -.03$ ,  $SE = .14$ ,  $p = .84$ ), and Block Design were not ( $B = -.17$ ,  $SE = .10$ ,  $p = .12$ ). Neither the total effect of birth weight on ADHD symptoms nor its corresponding direct effect (i.e., controlling for the mediators) was significant (respectively,  $B = -.01$ ,  $SE = .02$ ,  $p = .45$ ;  $B > -.01$ ,  $SE = .02$ ,  $p = .98$ ). However, the within-level total indirect effect of birth weight on ADHD symptoms through the mediators (i.e., the difference between the total effect and direct effect) was significant, such that Arithmetic mediated the association of birth weight with ADHD symptoms (Table 2). Specific indirect effects of Digit Span, Vocabulary, and Block Design were not significant (Table 2). The effect sizes for the total indirect effect and the specific indirect effect of Arithmetic were  $-.05$  and  $-.03$ , respectively, indicating small to medium effects. When the observed indirect effect through Arithmetic was tested with mediator and outcome reversed, there was no significant indirect effect of birth weight on Arithmetic through ADHD symptoms ( $B = -.001$ ,  $SE = .001$ ,  $95\% CI = -.004, .002$ ). Given that data were cross-sectional, the absence of a reverse indirect effect additionally supports Arithmetic as a mediating pathway. No between-level direct or indirect effects among birth weight, mediators, and ADHD symptoms were

observed (results available upon request), suggesting that mediation by Arithmetic was present across individuals (i.e., youth within families), but not across families.

### **Moderation of the Indirect Effect Through Arithmetic by Sibling Status**

We additionally evaluated moderation of the indirect effect of birth weight on ADHD symptoms through Arithmetic by sibling status to estimate potential genetic influences on this mediating pathway. Conditional indirect effects for each sibling group were significant: probands ( $B = -.009$ ,  $SE = .004$ ,  $p = .03$ ), affected siblings ( $B = -.011$ ,  $SE = .005$ ,  $p = .02$ ), and unaffected siblings ( $B = -.014$ ,  $SE = .005$ ,  $p = .01$ ). Post hoc tests of differences among the conditional indirect effects revealed that the indirect effect through Arithmetic did not differ significantly between probands and affected siblings ( $B = -.001$ ,  $SE = .002$ ,  $p = .39$ ) or between probands and unaffected siblings ( $B = -.004$ ,  $SE = .002$ ,  $p = .08$ ). Thus, the indirect effect through Arithmetic was similar across siblings concordant and discordant for ADHD.

### **Discussion**

We evaluated mediation of birth weight and ADHD symptoms by biologically plausible neurocognitive functions in a sample of youth from multiplex families with ADHD. WISC Arithmetic statistically mediated the association of birth weight with ADHD symptoms, controlling for IQ and relevant demographic factors; Digit Span, Vocabulary, and Block Design were not significant mediators. Additionally, the indirect effect of birthweight on ADHD symptoms through Arithmetic did not differ between siblings concordant and discordant for ADHD. Although cross-sectional, these findings (1) support previous prospective longitudinal research implicating individual differences in Arithmetic as a preliminary causal mediator of birth weight and ADHD symptoms, and (2) provide preliminary evidence that this mediating pathway is independent of genetic influences on ADHD.

The significant indirect effect through Arithmetic and absence of indirect effects through Digit Span and Vocabulary in this study converge with prior prospective longitudinal research (Morgan et al., 2016), including a nearly identical effect size for the indirect effect through Arithmetic; this is especially notable given important differences between these samples. In particular, the previous study investigated WISC mediators at ages 5-10 and ADHD at ages 7-13 in unrelated youth with and without ADHD as well as controlled for co-occurring internalizing and externalizing symptoms (Morgan et al., 2016). In contrast, the present study extended hypotheses to a larger sample consisting of siblings from a broad age range with high genetic load for ADHD (although age was controlled in all analyses), and controlled for IQ. Contrary to Morgan et al. (2016) as well as the larger literature on birth weight and ADHD, but consistent with other mediational studies of birth weight and ADHD symptoms (e.g., Wiggs et al., 2016), we did not observe a significant total effect of birth weight on ADHD symptoms (i.e., association of birth weight with ADHD symptoms unadjusted for the mediators). This may be attributable to several factors, including higher power to detect indirect effects relative to the total effect (Loeys et al., 2015), or the elevated ADHD symptom severity of this high-risk sample relative to case-control or population-based samples previously used to establish birthweight-ADHD associations. Thus, future studies should investigate whether the association between birth weight and ADHD severity relates to heterogeneity *within* youth with ADHD.

Whereas Arithmetic loads moderately onto working memory and modestly onto verbal reasoning domains in traditional four-factor WISC models, there is replicated evidence that it loads strongly onto fluid reasoning in superior five-factor models (Keith et al., 2006; Weiss et al., 2013). Thus, although Arithmetic may recruit additional neurocognitive functions, it appears to primarily reflect fluid reasoning. That fluid reasoning statistically mediated the association of

birth weight with ADHD symptoms converges with prior evidence of fluid reasoning deficits in youth born with low birth weight (e.g., Lahat et al., 2014), and with evidence for fluid reasoning deficits and hypoactivation in relevant brain regions in youth with ADHD (Tamm & Juranek, 2012). However, given the complexity of the constructs underlying Arithmetic, we await studies that disentangle these separable components to further improve traction on fluid reasoning pathways from birth weight to ADHD. In this regard, follow-up mediation analyses employing other measures of fluid reasoning and the Arithmetic Process Approach, which involves administration of the subtest in multiple formats that decrease working memory, attentional, quantitative, and oral expressive demands, are promising avenues. Although stringent control of IQ in the present study lends critical precision to inferences regarding Arithmetic, distillation of cognitive components underlying Arithmetic that are *most* critical to birth weight and ADHD will further enhance the clinical utility of the present findings.

Several key limitations should be noted. First, whereas this study was cross-sectional, temporally ordered predictors, mediators, and outcomes are necessary to infer causal mediation (Kraemer et al., 2001). However, that secondary analysis using a reverse mediation framework did not identify a significant indirect effect of birth weight on Arithmetic through ADHD symptoms, coupled with convergence of these findings with prior prospective longitudinal research, provides key support for the mediated pathway. Second, because the featured WISC subtests may tap other domains of functioning in addition to fluid reasoning, working memory, verbal comprehension, and perceptual reasoning, replication with more specific measures of these constructs is necessary; this is especially true not only for fluid reasoning but also working memory given evidence that Digit Span may reflect only short-term memory and not working memory (e.g., Colom, Abad, Rebollo, & Shih, 2005). Third, birth weight was assessed via



maternal recall, which although highly correlated with medical record data (e.g., Yawn et al., 1998), is less accurate. Fourth, despite the relatively large sample ( $n = 647$ ), which significantly exceeds that required to adequately power product-of-coefficients tests of mediation using resampling methods for path coefficients of even small effect (Fritz & Mackinnon, 2007; Mackinnon et al., 2004), larger samples may be required to tests the complex models examined herein (e.g., moderated mediation with multiple mediators). For example, the indirect effect for Block Design was of the same magnitude as that for Arithmetic, but was not significant.

Additionally, due to the relatively low number of unaffected siblings ( $n = 108$ ), the analysis to detect a difference between probands and unaffected siblings on the indirect effect of Arithmetic may have been underpowered. Thus, further evaluation of these hypotheses in large prospective longitudinal samples is warranted. Fifth, while comparison of ADHD concordant and discordant siblings affords insight into potential genetic influences (Schachar et al., 2005; Tsuang et al., 1993), and indeed was a novel feature of this study, follow-up with additional behavioral genetic designs that estimate heritability (e.g., co-twin control) will provide further clarification of whether the mediated effect through Arithmetic is truly independent of genetic influences on ADHD. Finally, whereas we found that fluid reasoning statistically mediated the pathway from birth weight to ADHD symptoms, substantial variance remained unexplained given the small effect observed. That is, additional neurocognitive functions (e.g., response variability) may mediate parallel pathways from birth weight (Wiggs et al., 2016), and even from other risk factors. For example, working memory and response inhibition are potential endophenotypes for ADHD from dopaminergic genes (Kamradt, Nigg, Friderici, & Nikolas, 2016; Loo et al., 2008). Thus, evaluation of diverse biologically plausible causal mediators for ADHD symptoms must be a continued priority.

Consistent with prior prospective longitudinal research, we found that Arithmetic (i.e., fluid reasoning) uniquely mediated the association of individual differences in birth weight with ADHD symptoms. Additionally, these data suggest that the observed indirect effect through Arithmetic was independent of genetic risk for ADHD. If replicated further, fluid reasoning will reflect a single step in a multilevel neurodevelopmental pathway from birth weight to ADHD. It will therefore be important to characterize the proximal mechanisms that mediate the associations of birth weight with fluid reasoning and fluid reasoning with ADHD symptoms. To this end, deficient in utero nourishment preceding birth weight and postnatal complications arising from birth weight (e.g., neonatal malnutrition; De Curtis & Rigo, 2004) are promising mechanisms underlying neurodevelopmental impairments that elicit fluid reasoning deficits and ADHD (Georgieff, 2007; Groen-Blokhuis et al., 2011). Also, deep phenotyping across multiple levels of analysis (e.g., cellular, neural, behavioral) should be prioritized (Bilder, Howe, Howe, & Sabb, 2013). Ultimately, delineation of causal risk processes underlying ADHD symptoms will highlight precise targets for early interventions to reduce the burden associated with ADHD.

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Table 1. Sample demographics and descriptive statistics

	<i>% of sample</i>		<i>M (SD), range</i>
Sex (female)	40.96		
Ethnicity:			
Caucasian	71.52	Age, years	10.47 (3.53), 5-19
African American/Black	4.80	SES	2.63 (0.91), 1-5
Hispanic/Latino	8.51	Birth weight, ounces	119.55 (20.41), 26-176

Asian	2.17	WISC Arithmetic	10.94 (3.42), 1-19
Mixed	10.22	WISC Digit Span	10.31 (2.94), 3-19
Other	2.79	WISC Vocabulary	11.44 (3.18), 1-19
ADHD diagnosis	83.44	WISC Block Design	11.07 (3.42), 1-19
ODD diagnosis	40.19	Full Scale IQ	108.87 (15.65), 71-152
CD diagnosis	1.86	Total ADHD symptoms	11.17 (5.00), 0-18

*Note:* ADHD = attention-deficit/hyperactivity disorder; ODD = oppositional defiant disorder; CD = conduct disorder; SES = socioeconomic status assessed with the Hollingshead scale on an ordinal scale from 1 = highest to 5 = lowest; WISC = Wechsler Intelligence Scale for Children

Table 2. Indirect effects of birth weight on ADHD symptoms through the WISC subtests

	<i>Point Est.</i>	<i>SE</i>	<i>95% Monte Carlo CI</i>	
			<i>Lower</i>	<i>Upper</i>
<b>Total</b>	<b>-.013</b>	<b>.006</b>	<b>-.028</b>	<b>-.002</b>
<b>Arithmetic</b>	<b>-.006</b>	<b>.003</b>	<b>-.015</b>	<b>-.002</b>
Digit Span	>-.001	.001	-.003	.002

Vocabulary	>-.001	.001	-.005	.004
Block Design	-.007	.005	-.017	.002

*Note:* Boldface indicates significant mediation; ADHD = attention-deficit/hyperactivity disorder;

WISC = Wechsler Intelligence Scale for Children; Point est. = point estimate of the indirect

effect; CI = confidence interval

Figure 1. Multiple mediation of birth weight and ADHD symptoms by Wechsler Intelligence Scale for Children neurocognitive functions, controlling for age, sex, and IQ. \* $p < .05$  \*\* $p < .001$

