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COMT and DAT1 polymorphisms moderate the indirect effect of parenting behavior on youth ADHD symptoms through neurocognitive functioning

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Pathways from Birth Weight to ADHD Symptoms through Fluid Reasoning in Youth with or without Intellectual Disability

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Abstract Although individual differences in fluid reasoning reliably mediate predictions of attention-deficit/hyperactivity disorder (ADHD) symptoms from birth weight in youth with typical cognitive development (TD), it is unknown if this indirect effect operates similarly in the development of ADHD symptoms secondary to intellectual disability (ID). Thus, we evaluated mediation by fluid reasoning in a longitudinal sample of 163 youth (45% female) with (n = 52) or without (n = 111) ID who were followed prospectively from age 5 to age 13. At age 9, youth completed the Arithmetic subtest of the Wechsler Intelligence Scale for Children, a measure of fluid reasoning. At ages 9 and 13, mothers and teachers separately rated youth ADHD symptoms and mothers completed a diagnostic interview. Mediation was tested via path analysis with bootstrapped confidence intervals, and moderated mediation estimated whether indirect effects differed between ID and TD youth or based on youth IQ. Controlling for demographic factors and age 9 ADHD symptoms, age 9 Arithmetic mediated birth weight and multi-method/informant age 13 ADHD symptoms, such that birth weight positively predicted Arithmetic, which negatively predicted ADHD symptoms. Neither ID status nor IQ moderated the observed indirect effect through Arithmetic, suggesting that it was similar for ID and TD youth as well as across the range of youth IQs. These findings support previous evidence that fluid reasoning, as measured by Arithmetic, may causally mediate birth weight and ADHD symptoms, and suggest that this pathway operates similarly with respect to the development of ADHD symptoms in youth with ID.

Keywords ADHD · Intellectual disability · Birth weight · Fluid reasoning · Mediation

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Attention-deficit/hyperactivity disorder (ADHD) is a highly prevalent and consequential condition in the United States, affecting 11% of American youth and resulting in annual societal costs of $143 to $266 billion (Doshi et al. 2012; Visser et al. 2014). ADHD is also the most common co-occurring condition among youth with intellectual disability (ID), occurs more frequently in youth with ID compared to typically developing (TD) youth, and confers significant impairment beyond ID alone (Dekker and Koot 2003; Neece et al. 2011; Neece et al. 2013a). Despite its substantial public health impact, relatively little is known about the etiology of ADHD, especially in youth with ID. This gap in knowledge prevents innovations in ADHD prevention, given that identification of causal factors, and their mechanisms of influence, will highlight precise targets for early resilience-promoting interventions (Sonuga-Barke and Halperin 2010). Thus, elucidation of biologically plausible risk processes underlying the development of ADHD is a critical priority.

Meta-analytic, prospective longitudinal, and quasi-experimental research converge to suggest that birth weight is a causal predictor of ADHD symptoms in TD youth (Aarnoudse-Moens et al. 2009; Bhutta et al. 2002; Groen-Blokhuis et al. 2011; Martel et al. 2007; Nigg and Breslau 2007; Pettersson et al. 2015). For example, birth weight has reliably predicted ADHD symptoms in co-twin control studies, which provide quasi-experimental evidence for causal

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effects that are independent of other potential causal factors for ADHD (e.g., genetic and family influences; Groen-Blokhuis et al. 2011; Pettersson et al. 2015). There is also preliminary evidence that fluid reasoning mediates the pathogenesis of ADHD symptoms from birth weight. Fluid reasoning consists of logical thinking and problem solving under novel circumstances (Cattell 1987), and is central to, or may even subsume, other neurocognitive domains that are more commonly associated with ADHD (i.e., executive functions; Cho et al. 2010; Conway et al. 2002; Tamm and Juranek 2012). Various measures of fluid reasoning are reliably correlated with birth weight (Hutchinson et al. 2013; Lahat et al. 2014; Skranes et al. 2013) and with ADHD diagnosis and symptoms (Biederman et al. 2009; Doyle et al. 2005; Tamm and Juranek 2012). Moreover, fluid reasoning deficits are associated with neural abnormalities (i.e., hypoactivation in fronto-striato-parietal networks; reduced cortical surface area, thickness, and volume; Hobeika et al. 2016; Skranes et al. 2013) that are sequelae of low birth weight (Griffiths et al. 2013; Martinussen et al. 2005; Skranes et al. 2013; Walhovd et al. 2012) and implicated in the etiology of ADHD (Cortese et al. 2012; Narr et al. 2009; Shaw et al. 2012). Thus, causal mediation is biologically plausible.

Beyond its biological plausibility, fluid reasoning uniquely mediated (i.e., beyond other neurocognitive constructs) predictions of dimensionally-measured ADHD symptoms from birth weight in two prior studies, although both studies focused on youth with IQs above 70. First, the Arithmetic subtest of the Wechsler Intelligence Scale for Children (WISC; Wechsler 2003), a measure of fluid reasoning (Keith et al. 2006; Weiss et al. 2013), mediated birth weight and multi-method/informant ADHD symptoms in a prospective longitudinal study of 222 youth with and without ADHD (ages 5–10 years at baseline, 7–13 years at follow-up; *M* IQ = 106.88, *SD* = 14.55, *range* = 73–144), controlling for demographic factors and co-occurring internalizing and externalizing psychopathology (Morgan et al. 2016b). Indirect effects of other WISC subtests tested alongside Arithmetic (i.e., Digit Span, Vocabulary, Symbol Search) were not significant. Notably, this study featured temporally ordered predictors, mediators, and outcomes, which is necessary to infer causal mediation (Kraemer et al. 2001). Second, in a separate cross-sectional study of 5- to 19-year-old youth from multiplex families with ADHD (*n* = 647), WISC Arithmetic, but not Digit Span, Vocabulary, or Block Design, mediated birth weight and multi-informant ADHD symptoms, controlling for IQ (*M* = 108.87, *SD* = 15.65, *range* = 71–152) and demographic factors (Morgan et al. 2016a). Thus, there is strong evidence for an intermediary role of fluid reasoning in pathways from birth weight to ADHD symptoms, at least among youth with cognitive abilities in the typical range.

Although evidence that fluid reasoning, as assessed by WISC Arithmetic, constitutes an indirect pathway from birth weight to ADHD symptoms is promising, this finding requires expansion into diverse samples to improve traction on fluid reasoning as a causal mediator. Additionally, because prior mediational studies focused on youth with cognitive abilities in the typical range, it remains unclear if the observed indirect effect through fluid reasoning generalizes to the development of ADHD symptoms in youth with ID. ADHD is a valid diagnosis in youth with ID, and presents similarly to ADHD in TD youth (e.g., severity, factor structure, and developmental course of symptoms; frequency of specific symptoms; Neece et al. 2011; Neece et al. 2013a). Moreover, there is preliminary evidence that ADHD symptoms in ID and TD youth share common risk factors (e.g., genetic, environmental; Neece et al. 2013b). However, no study has evaluated ADHD risk *processes* in youth with ID (i.e., mediation), including from birth weight, and it therefore is unknown if ADHD develops via convergent or divergent pathways in ID and TD youth. Thus, formal evaluation of indirect pathways from birth weight to ADHD symptoms in youth with ID is warranted. Crucially, identification of biologically plausible ADHD risk processes in youth with ID will inform prevention and intervention efforts to reduce the augmented burden conferred by ADHD symptoms in this population.

To review, the indirect pathway from birth weight to ADHD symptoms through fluid reasoning may reflect a causal process underlying ADHD symptoms, but it requires further replication in diverse samples and has not been examined in youth with ID. To expand upon prior mediational investigations of birth weight and ADHD symptoms, the present study had two aims: (1) to test fluid reasoning, as measured by WISC Arithmetic, as a mediator of birth weight and multi-method/informant ADHD symptoms in a prospective longitudinal sample of ID and TD youth with temporally ordered constructs; and (2) to estimate whether this indirect effect extends to prediction of ADHD symptoms specifically in youth with ID by evaluating moderation of the indirect effect by ID vs. TD status as well as by IQ (i.e., moderated mediation).

Methods

Participants

Participants were 163 youth enrolled in the Collaborative Family Study, an ongoing prospective longitudinal study of children with or without developmental delays and their families conducted in California and Pennsylvania. The Collaborative Family Study was based at three universities: University of California, Los Angeles; University of California, Riverside; and Pennsylvania State University. Families of children with developmental delays were primarily recruited when children were age 3 years, with a small subset recruited when children were age 5 years, through agencies that provide assessment and intervention services for individuals with intellectual and developmental disabilities; families of children with typical cognitive development (TD) were recruited through preschools and daycare programs. At age 5, children were classified as either having intellectual disability (ID; n = 52) or TD (n = 111) based on full scale scores from the Stanford-Binet Intelligence Scale IV (SB-IV; Thorndike et al. 1986) and Vineland Adaptive Behavior Scales-II (VABS; Sparrow et al. 2005). Specifically, children with ID received a score of 40 to 84 on the SB-IV and a score below 85 on the VABS. TD children received a score of 85 or higher on the SB-IV and did not have a known developmental disability. Children with a diagnosis of autism were excluded from both the ID and TD groups at study entry. Among those meeting criteria for ID, 16 children had borderline ID (IQ = 71–84), 17 had mild ID (IQ = 55–70), and 19 had moderate ID (IQ = 36–54; American Psychiatric Association 2000). Children with borderline ID did not differ from children with mild or moderate ID with respect to sex ($\chi^2(1) = 0.79$, $p = 0.38$), race-ethnicity ($\chi^2(4) = 4.80$, $p = 0.31$), income ($Z = -0.81$, $p = 0.41$), birth weight ($Z = 1.71$, $p = 0.09$), or ADHD symptom measures ($Z < 1.29$ for all tests, $p > 0.19$ for all tests); thus, children in these three groups were combined and referred to as the ID group in the present study. Table 1 shows demographic and descriptive data for the sample.

Procedures

The Institutional Review Boards of all three collaborating universities approved all study procedures. Data for the current study were obtained from assessments conducted when youth were aged 5, 9, and 13. After parents and children gave consent and assent, respectively, parents completed multi-method measures of child psychopathology, while children completed neurocognitive and socioemotional assessments in a separate room. Rating scales were also mailed to teachers. Of the 236 children who completed the age 5 assessment, 163 also completed the age 9 assessment and had at least partially complete data on the key constructs for the present study (i.e., birth weight, fluid reasoning, ADHD symptoms). Missing age 9 data were non-randomly distributed by ID vs. TD status, with ID youth underrepresented at age 9 ($\chi^2(1) = 4.95$, $p = 0.02$), but unrelated to sex ($\chi^2(1) = 1.38$, $p = 0.24$), race-ethnicity ($\chi^2(4) = 7.37$, $p = 0.12$), or income ($Z = 0.17$, $p = 0.87$). We also used data from the age 13 assessment, at which 122 youth were retained. However, we employed Full Information Maximum Likelihood procedures (FIML; described below) so that analyses were conducted on the full age 9 sample of 163 youth.

Measures

ID Status and IQ IQ was assessed at age 5 using the Stanford-Binet Intelligence Scale IV (SB-IV; Thorndike et al. 1986). ID status was also assessed at age 5 using the SB-IV and the Vineland Scales of Adaptive Behavior-II (VABS; Sparrow et al. 2005). The SB-IV yields a score with a normed mean of 100 and standard deviation of 15. The VABS is a semi-structured parent interview that yields an Adaptive Behavior Composite score reflecting youth communication, daily living skills, and socialization; it also is normed with a mean of 100 and standard deviation of 15. Both the SB-IV and VABS are widely used assessment instruments for diagnosing ID, and have sound psychometric properties (Thorndike et al. 1986; Sparrow et al. 2005). For example, in a normative sample of individuals aged 5–23 years, internal consistencies for the SB-IV composite score ranged from 0.95–0.99 and concurrent validity was suggested by a median correlation of 0.80 between the SB-IV and other validated measures of intellectual functioning (e.g., WISC; Thorndike et al. 1986).

Birth Weight At the intake assessment, mothers retrospectively reported youth birth weights (M = 7.24 lb, SD = 1.50, *range* = 1.25–10.25). Maternal recall of offspring birth weight is highly correlated with medical record data (e.g., ICC = 0.99 in Yawn et al. 1998; also see Buka et al. 2004; Jaspers et al. 2010; O'Sullivan et al. 2000; Rice et al. 2007; Walton et al. 2000).

Fluid Reasoning Fluid reasoning was assessed at age 9 using scaled scores on the Arithmetic subtest of the Wechsler Intelligence Scale for Children–IV (WISC; Wechsler 2003), which requires subjects to mentally solve orally presented math problems. Arithmetic loads onto multiple cognitive domains in traditional four-factor WISC-IV models, but there is replicated evidence that it loads strongly and exclusively onto fluid reasoning in superior five-factor models (e.g., factor loading = 0.79; Keith et al. 2006; Weiss et al. 2013). Thus, while Arithmetic may be sensitive to working memory, verbal comprehension, and quantitative reasoning, it principally reflects fluid reasoning, which may subsume working memory and quantitative reasoning (Keith et al. 2006; Weiss et al. 2013). Of note, the distribution of Arithmetic scaled scores for ID youth varied considerably in this study (M = 4.10, SD = 2.68, *range* = 0–12), with only one youth receiving a score of 0; thus, there were no significant floor effects.

ADHD Symptoms *Diagnostic Interview Schedule for Children–IV* (Shaffer et al. 2000). At the age 9 and 13 assessments, ADHD symptom counts were determined with the Diagnostic Interview Schedule for Children–IV (DISC), a fully structured computer-assisted diagnostic interview that was conducted with mothers and is keyed to Diagnostic and

Table 1 Sample demographics and descriptive statistics

	ID (n = 52)	TD (n = 111)	*Z or* χ^2 (*df*)
Female, *% of sample*	45.45	44.14	0.02 (1)
Race-ethnicity	–	–	9.44 (4)
White, *% of sample*	50.00	63.96	–
African American, *% of sample*	4.55	6.31	–
Asian, *% of sample*	2.27	1.80	–
Latino/Hispanic, *% of sample*	29.55	9.91	–
Other, *% of sample*	13.64	18.02	–
Family income, *M (SD)*	4.46 (1.87)	5.25 (1.80)	2.58*
Stanford-Binet IV IQ (age 5), *M (SD)*	59.52 (14.75)	103.71 (11.98)	10.28**
Vineland Composite (age 5), *M (SD)*	62.08 (10.93)	104.76 (16.60)	9.82**
Birth weight in pounds, *M (SD)*	6.97 (1.79)	7.35 (1.37)	1.35
WISC Arithmetic (age 9), *M (SD)*	4.10 (2.68)	11.30 (2.97)	9.13**
DISC ADHD symptoms (age 9), *M (SD)*	5.89 (5.44)	3.01 (4.26)	−3.36**
DISC ADHD symptoms (age 13), *M (SD)*	6.48 (4.45)	2.99 (3.82)	−4.33**
CBCL/TRF Attention Problems (age 9), *M (SD)*	62.19 (8.34)	54.64 (6.67)	−6.00**
CBCL/TRF Attention Problems (age 13), *M (SD)*	60.92 (7.32)	54.60 (5.30)	−4.97**

ID intellectual disability; *TD* typically developing; *ADHD* attention-deficit/hyperactivity disorder; *WISC* Wechsler Intelligence Scale for Children; *DISC* Diagnostic Interview Schedule for Children; *CBCL/TRF* mean composite of parent and teacher *T* scores on the Child Behavior Checklist and Teacher Report Form; family income assessed on a scale of 1 = "$0–$15,000" to 7 = ">$95,001" annually; *Z* values from Wilcoxon-Mann-Whitney tests of the difference between ID vs. TD groups are provided for continuous variables; χ^2 values (with degrees of freedom in parentheses) testing the difference between ID vs. TD groups are provided for categorical variables

*$p < 0.01$ **$p < 0.001$

Statistical Manual of Mental Disorders–IV criteria (DSM: American Psychiatric Association 2000). The DISC has been extensively validated and demonstrates excellent psychometric properties, including high test–retest reliability (r = 0.79 after 1 year) and internal consistency (ICC = 0.84) in a large community sample (Shaffer et al. 2000).

Child Behavior Checklist/Teacher Report Form (Achenbach and Rescorla 2001). At the age 9 and 13 assessments, mothers also completed the Child Behavior Checklist (CBCL), a normed 113-item rating scale yielding eight narrowband syndrome scales, broadband internalizing and externalizing scales, and a total score. Each item is rated from 0 = "not true" to 2 = "very true/often true." Additionally, teachers completed the Teacher Report Form (TRF), yielding parallel scales to the CBCL. Although the CBCL and TRF are not diagnostic measures of ADHD, they are (1) highly correlated with DSM-based symptom measures, (2) extensively validated with excellent reliability and validity (e.g., test-retest reliability of 0.92 and 0.95 for the CBCL and TRF Attention Problems scale in a normative sample, ability to discriminate between referred and non-referred youth), and (3) can be easily combined as a single multi-informant measure to conservatively reduce the number of tests (Achenbach and Rescorla 2001). Thus, similar to prior studies on mediation of birth weight and ADHD symptoms (Morgan et al. 2016b), we used a mean composite of parent and teacher reported *T* scores from the Attention Problems scale (age 9 $r_s = 0.65$, $p < 0.001$; age 13 $r_s = 0.45$, $p < 0.001$), which includes inattention and hyperactivity/impulsivity items. Parent ratings were used exclusively when teacher data were missing (age 9 n = 38; age 13 n = 52), given that youth with teacher data were similar to youth without teacher data with respect to demographic factors, ID status, birth weight, fluid reasoning, and ADHD symptoms ($\chi^2 < 7.76$ for all tests with categorical variables, $Z < 1.42$ for all tests with continuous variables, $p > 0.10$ for all tests with either continuous or categorical variables, suggesting that teacher data were missing at random).

Statistical Analysis

Mediation Approximately 30% of the 163 youth were missing data on at least one key study variable (e.g., age 13 ADHD symptoms). Thus, we used FIML estimation for all analyses. FIML optimally remediates missing data when as much as 50% of data are missing at random or missing completely at random (MCAR; Schlomer et al. 2010). Evaluation of missing data patterns via Little's MCAR Test (Little 1988) suggested that data were MCAR in this sample ($\chi^2(60) = 64.75$, $p = 0.32$).

We evaluated age 9 Arithmetic as a mediator of birth weight and age 13 ADHD symptoms via two mediation models in Mplus 7.0 (Muthén and Muthén 1998–2015) that *separately* predicted DISC ADHD symptom counts and

CBCL/TRF Attention Problems *T* scores. Each model simultaneously calculated regression-based path coefficients as well as point estimates and 95% bias-corrected confidence intervals (CIs) for the indirect effect through Arithmetic using 5000 bootstrap simulations; statistical significance is assumed when the interval excludes zero. Bootstrapped CIs for indirect effects are statistically more powerful than traditional mediation techniques (Zhao et al. 2010) and robust to non-normal data (Preacher and Hayes 2008). Race-ethnicity, family income, and measure-consistent age 9 ADHD symptoms were included as covariates in both models. Sex was also controlled in prediction of DISC ADHD symptoms, but not in prediction of CBCL/TRF Attention Problems given that the *T* scores are already adjusted for sex and age. Per Preacher and Kelley (2011), effect sizes were calculated using the *completely standardized indirect effect*, which can be interpreted on a scale of 0.01 = small, 0.09 = medium, and 0.25 = large.

To assess specificity of the observed indirect effects through Arithmetic, we also conducted *multiple* mediation analysis that simultaneously tested indirect effects through age 9 Arithmetic with indirect effects through two other age 9 WISC subtests: (1) Matrix Reasoning, another measure of fluid reasoning that also taps visuospatial domains, and (2) Vocabulary, a measure of verbal comprehension (Keith et al. 2006; Wechsler 2003; Weiss et al. 2013). To preserve power, and because multiple mediation stringently controls for intercorrelations among these three highly correlated WISC subtests ($r = 0.68–0.80$, $p < 0.001$), covariates were not included in the multiple mediation analysis.

Moderated Mediation Next, to more precisely estimate whether indirect effects from birth weight through Arithmetic extend to prediction of ADHD symptoms specifically in youth with ID, we evaluated moderation of the observed indirect effects by ID vs. TD status and by continuously measured IQ. First, we added dummy codes for ID status and an ID status x birth weight interaction term to the single mediation models predicting age 13 DISC ADHD symptoms and CBCL/TRF Attention Problems described above (such that the moderated mediation models were identically adjusted for the multiple covariates), and calculated an index of moderated mediation for each model. Because the moderator was dichotomous, these indices reflect the difference between separate conditional indirect effects (i.e., an indirect effect conditioned on a particular value of the moderator) for youth with ID (n = 52) and for TD youth (n = 111; Hayes 2015). Second, we fit additional moderated mediation models where a continuous IQ variable and an IQ x birth weight interaction term were added to the single mediation models predicting age 13 DISC ADHD symptoms and CBCL/TRF Attention Problems, and calculated an index of moderated mediation for each model. Because the moderator was continuous, these indices reflect the effect of the moderator (i.e., IQ) on the overall indirect effect (Hayes 2015). Statistical significance of moderated mediation was determined via bootstrapped 95% bias-corrected CIs for the indices of moderated mediation, again using 5000 bootstrap simulations.

Results

Mediation of Birth Weight and ADHD Symptoms by WISC Arithmetic

Bivariate correlations among the key study variables are presented in Table 2. As expected, birth weight was positively correlated with age 9 Arithmetic ($r_s = 0.19$, $p = 0.02$), which in turn, negatively correlated with age 13 DISC ADHD symptoms ($r_s = -0.37$, $p < 0.001$) and CBCL/TRF Attention Problems *T* scores ($r_s = -0.54$, $p < 0.001$).

As mentioned previously, FIML estimation was employed in all mediation analyses such that all results described below were derived from the full sample of 163 youth. We first tested mediation of birth weight and age 13 DISC ADHD symptoms by age 9 Arithmetic in the entire sample of ID and TD youth, controlling for age 9 DISC ADHD symptoms, sex, race-ethnicity, and family income. Regression-based path coefficients generated by this model are presented in Fig. 1. There was a significant indirect effect of birth weight on age 13 DISC ADHD symptoms through age 9 Arithmetic ($B = -0.129$, $SE = 0.081$, *95% CI* = −0.341, −0.010), whereby birth weight positively predicted Arithmetic, which in turn negatively predicted DISC ADHD symptoms. The effect size for this indirect effect (i.e., the *completely standardized indirect effect*) was −0.05, indicating a small to medium effect.

We also tested mediation of birth weight and age 13 CBCL/TRF Attention Problems *T* scores by age 9 Arithmetic, controlling for age 9 CBCL/TRF Attention Problems, race-ethnicity, and family income (*T* scores are also adjusted for sex). Regression-based path coefficients generated by this model are presented in Fig. 2. There was a significant indirect effect of birth weight on age 13 CBCL/TRF Attention Problems through age 9 Arithmetic ($B = -0.187$, $SE = 0.110$, *95% CI* = −0.493, −0.026), whereby birth weight positively predicted Arithmetic, which in turn negatively predicted CBCL/TRF Attention Problems. The effect size for this indirect effect was −0.04, indicating a small to medium effect. Thus, Arithmetic mediated birth weight and ADHD symptoms across all methods and informants.[1]

[1] When ADHD symptom dimensions were examined separately, age 9 Arithmetic significantly mediated birth weight and age 13 DISC hyperactivity/impulsivity symptoms ($B = -0.070$, $SE = 0.042$, *95% CI* = −0.184, −0.012, *completely standardized indirect effect* = −0.04), whereas the indirect effect predicting age 13 DISC inattention symptoms was marginal but directionally consistent ($B = -0.060$, $SE = 0.052$, *95% CI* = −0.201, 0.016, *completely standardized indirect effect* = −0.03).

Table 2 Bivariate associations among the key constructs

	1.	2.	3.	4.	5.	6.	7.	8.
1. Sex	–							
2. Income	−0.01	–						
3. IQ	−0.01	−0.30**	–					
4. Birth weight	0.03	0.03	0.10	–				
5. WISC Arithmetic	0.03	0.30**	0.81**	0.19*	–			
6. DISC ADHD symptoms (age 9)	0.22*	−0.05	−0.34**	0.04	−0.38**	–		
7. DISC ADHD symptoms (age 13)	0.26*	−0.15	−0.38**	−0.15	−0.37**	0.46**	–	
8. CBCL/TRF Attention Problems (age 9)	0.07	−0.23*	−0.54**	−0.04	−0.53**	0.63**	0.56**	–
9. CBCL/TRF Attention Problems (age 13)	0.18	−0.31**	−0.48**	−0.20*	−0.54**	0.51**	0.66**	0.77**

ADHD attention-deficit/hyperactivity disorder; *WISC* Wechsler Intelligence Scale for Children; *DISC* Diagnostic Interview Schedule for Children; *CBCL/TRF* mean composite of parent and teacher *T* scores on the Child Behavior Checklist and Teacher Report Form; family income assessed on a scale of 1 = "$0–$15,000" to 7 = ">$95,001" annually

*$p < 0.05$ **$p < 0.001$

Additionally, to assess specificity of the observed indirect effect through Arithmetic, we conducted *multiple* mediation analyses that simultaneously tested indirect effects through age 9 Arithmetic, Vocabulary, and Matrix Reasoning. In prediction of age 13 DISC ADHD symptoms, there was a specific indirect effect of birth weight through age 9 Arithmetic ($B = -0.139$, $SE = 0.099$, *95% CI* = −0.423, −0.002, *completely standardized indirect effect* = −0.04), but not through Vocabulary or Matrix Reasoning (respectively, $B = -0.036$, $SE = 0.072$, *95% CI* = −0.287, 0.052, *completely standardized indirect effect* = −0.01; $B = 0.003$, $SE = 0.079$, *95% CI* = −0.139, 0.185, *completely standardized indirect effect* < 0.01). Similarly, in prediction of age 13 CBCL/TRF Attention Problems, there was a specific indirect effect of birth weight through age 9 Arithmetic ($B = -0.444$, $SE = 0.216$, *95% CI* = −0.978, −0.111, *completely standardized indirect effect* = −0.09), but not through Vocabulary or Matrix Reasoning (respectively, $B = -0.023$, $SE = 0.068$, *95% CI* = −0.264, 0.054, *completely standardized indirect effect* > −0.01; $B = -0.001$, $SE = 0.113$, *95% CI* = −0.259, 0.207, *completely standardized indirect effect* > −0.01). Thus, these multiple mediation models were consistent with the single mediator models, suggesting that indirect effects from birth weight to multi-method/informant ADHD symptoms were specific to fluid reasoning assessed with Arithmetic rather than to other WISC neurocognitive domains.

Moderation of the Indirect Effect through WISC Arithmetic by ID Status and IQ

Next, we evaluated moderation of the observed indirect effect from birth weight to age 13 ADHD symptoms through age 9 Arithmetic by ID vs. TD status using the index of moderated mediation (i.e., the difference between separate conditional indirect effects for ID and TD youth; Hayes 2015). For predictions of both DISC ADHD symptoms and CBCL/TRF Attention Problems, the index of moderated mediation was not significant (respectively, $B = 0.032$, $SE = 0.084$, *95% CI* = −0.078, 0.279; $B = 0.035$, $SE = 0.113$, *95% CI* = −0.149, 0.331). Thus, ID vs. TD status did not moderate

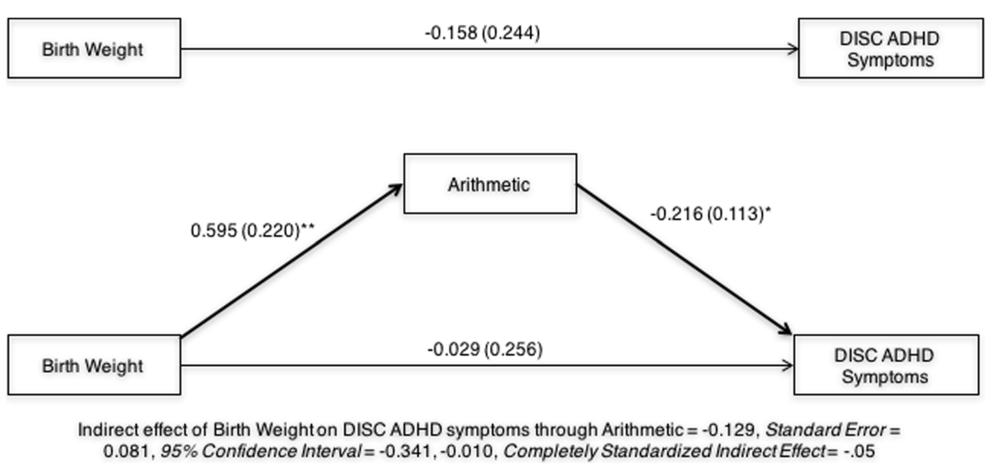

Fig. 1 Mediation of birth weight and age 13 DISC ADHD symptoms by age 9 fluid reasoning (i.e., WISC Arithmetic), controlling for age 9 DISC ADHD symptoms, sex, race-ethnicity, and family income ($n = 163$). *Note:* Numbers shown reflect unstandardized beta coefficients (and standard errors). *$p < 0.05$ **$p < 0.01$

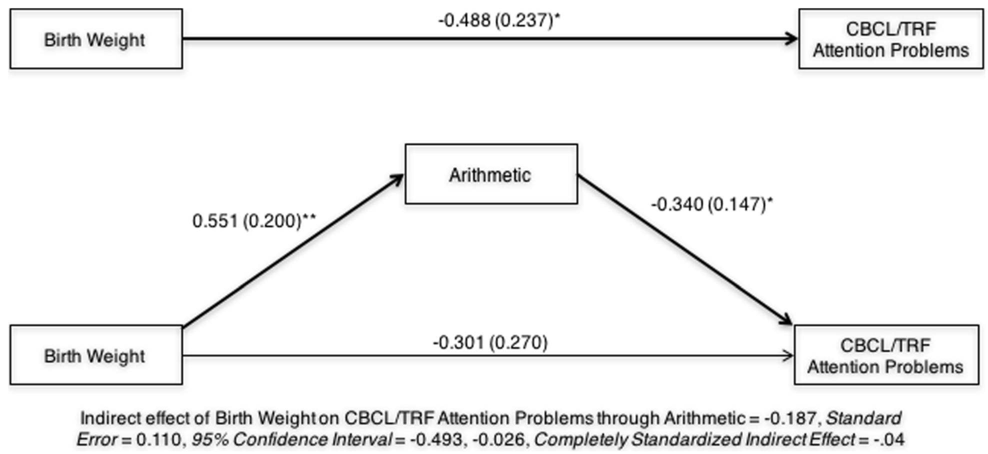

Fig. 2 Mediation of birth weight and age 13 CBCL/TRF Attention Problems *T* scores by age 9 fluid reasoning (i.e., WISC Arithmetic), controlling for age 9 CBCL/TRF Attention Problems, race-ethnicity, and family income (*T* scores are also adjusted for sex; $n = 163$). *Note:* Numbers shown reflect unstandardized beta coefficients (and standard errors). *$^*p < 0.05$ $^{**}p < 0.01$*

the indirect effect of birth weight on ADHD symptoms through Arithmetic across all methods and informants (i.e., the indirect effect did not differ between youth with ID and TD youth).

We also evaluated moderation of the observed indirect effect from birth weight to age 13 ADHD symptoms through age 9 Arithmetic by youth IQ, for which the index of moderated mediation reflected the effect of IQ on the indirect effect. For predictions of both DISC ADHD symptoms and CBCL/TRF Attention Problems, the index of moderated mediation was not different from zero (respectively, $B < 0.001$, $SE = 0.001$, *95% CI* $= -0.004, 0.002$; $B < 0.001$, $SE = 0.002$, *95% CI* $= -0.005, 0.005$). Thus, IQ did not moderate the indirect effect of birth weight on ADHD symptoms through Arithmetic across all methods and informants (i.e., the indirect effect did not differ based on IQ).

Discussion

We evaluated mediation of birth weight and ADHD symptoms by WISC Arithmetic, a measure of fluid reasoning, in a prospective longitudinal sample of youth with ID and their TD peers. Age 9 Arithmetic uniquely mediated the association of birth weight with age 13 multi-method/informant ADHD symptoms, controlling for age 9 ADHD symptoms and relevant demographic factors. Additionally, neither ID vs. TD status nor IQ moderated the observed mediated effects, indicating that the indirect effect through Arithmetic did not differ between ID and TD youth or across youth IQs. These findings are consistent with previous research suggesting that individual differences in fluid reasoning, separate from other neurocognitive factors, may constitute a causal pathway from birth weight to ADHD symptoms in TD youth, and provide preliminary evidence that this mediating pathway operates similarly in youth with ID.

That Arithmetic mediated the development of ADHD symptoms from birth weight in the present study converges with prior evidence of fluid reasoning deficits in low birth weight children (e.g., Lahat et al. 2014), and fluid reasoning deficits as well as hypoactivation in brain regions that modulate fluid reasoning in youth with ADHD (Tamm and Juranek 2012), albeit using different measures of fluid reasoning. Moreover, the observed indirect effect through Arithmetic replicates evidence from separate case-control and sibling studies of ADHD, including similar effect sizes for the indirect effect; this is especially notable given important differences across all studies. Specifically, two previous studies discovered an indirect pathway from birth weight to dimensional measures of ADHD symptoms through Arithmetic, but in ADHD-oriented samples of youth with cognitive development in the typical range: (1) a case-control ADHD study (youth ages 5–10 at baseline and 7–13 at follow-up) that statistically controlled for co-occurring internalizing and externalizing symptoms (Morgan et al. 2016b), and (2) a study of siblings from a broad age range with high genetic load for ADHD that controlled for youth IQ (Morgan et al. 2016a). Importantly, the present study extended hypotheses to a prospective longitudinal sample of youth with or without ID, suggesting that ADHD symptoms have similar etiologies from birth weight in youth with ID and youth with typical cognitive abilities. Similarly, Neece et al. (2013b) found that other reliable ADHD risk factors (i.e., youth DRD4 genotype and set-shifting abilities, parental ADHD symptoms) predicted ADHD symptoms in ID and TD youth regardless of cognitive status. However, we know of no other studies that have examined biologically plausible risk processes underlying ADHD symptoms in youth with ID. Thus, the etiology of ADHD in youth with ID is a novel focus of the present study and a critical priority for future research.

Although interventions targeting aggregate neurocognitive deficits (e.g., cognitive training) have shown limited efficacy in reducing youth ADHD symptoms (Cortese et al. 2015), fluid reasoning is responsive to intervention, including in children with ID as well as TD children with ADHD (e.g., Bergman Nutley et al. 2011; Ferrer et al. 2009; Jaeggi et al.

2008; Perrig et al. 2009; Tamm et al. 2010). Given replicated evidence from this and other studies that fluid reasoning, as measured by Arithmetic, mediates specific predictions of ADHD symptoms from birth weight in TD youth, follow-up studies testing early fluid reasoning interventions *specifically* in TD youth with lower birth weights and *prior* to the onset of ADHD symptoms is indicated. Moreover, because our findings suggest that this pathway also extends to youth with ID, early interventions targeting fluid reasoning in low birth weight youth with ID may significantly reduce the increased burden of ADHD in this population.

Several key limitations should be noted. First, birth weight was assessed via maternal recall, which although highly correlated with medical record data (e.g., Yawn et al. 1998), is less accurate. Second, although there is replicated evidence that Arithmetic primarily reflects fluid reasoning (e.g., Keith et al. 2006; Weiss et al. 2013), weaker fluid reasoning factor loadings have been reported elsewhere (e.g., Benson et al. 2013). Additionally, Arithmetic may recruit other neurocognitive functions in addition to fluid reasoning (e.g., working memory), and some studies have conceptualized it as a broad measure of multiple neurocognitive constructs rather than fluid reasoning (e.g., Doyle et al. 2005). Therefore, we cannot rule out that other constructs underlying Arithmetic affected the observed findings. For example, an alternative explanation is that deficits in multiple domains including working memory, attention, and/or quantitative reasoning account for the indirect effect of birth weight on ADHD symptoms through Arithmetic. Thus, we await studies that disentangle the separable components underlying Arithmetic to further refine pathways from birth weight to ADHD.

Third, although the present sample (n = 163) exceeds that required to adequately power tests of mediation using resampling methods for path coefficients of even small effect (i.e., n = 148; Fritz and Mackinnon 2007; Mackinnon et al. 2004), larger samples may be preferable to test the moderated mediation models examined herein. Due to the relatively low number of youth meeting criteria for ID (n = 52) compared to TD youth (n = 111), the analysis to detect a difference between these groups on the indirect effect may have been underpowered. Relatedly, although there was a significant total effect predicting CBCL/TRF Attention Problems (i.e., the association of birth weight with CBCL/TRF Attention Problems unadjusted for Arithmetic), the total effect predicting DISC ADHD symptoms was not significant. A significant total effect is not required for the presence of indirect effects (Loeys et al. 2015), and indirect effects in the absence of a total effect were also observed in previous mediational studies of birth weight and ADHD (e.g., Morgan et al. 2016a; Wiggs et al. 2016). However, the lack of a significant total effect underlying DISC ADHD symptoms, which may be attributable to higher power to detect indirect effects relative to the total effect (Loeys et al. 2015), is contrary to the larger literature on birth weight and ADHD. Thus, further evaluation of these hypotheses in larger prospective longitudinal samples of youth with ID is warranted.

Fourth, although the distribution of Arithmetic scaled scores for ID youth varied considerably in this sample, this measure may evidence floor effects in the general population of youth with ID. Fifth, because we focused on prediction of ADHD symptoms at age 13, we were unable to address whether indirect effects through Arithmetic predicted ADHD onset or severity earlier in development. Control of age 9 ADHD symptoms in the featured mediation models suggested that the observed relation between birth weight and age 9 Arithmetic (i.e., the a path of the indirect effect) was independent of concurrent ADHD symptoms on Arithmetic performance, and that age 9 Arithmetic predicted age 13 ADHD symptoms (i.e., the b path) over and above the effect of age 9 ADHD symptoms. Thus, the onset of fluid reasoning deficits may worsen pre-existing ADHD symptoms by age 13 *or* result in the emergence of ADHD symptoms not previously present at age 9; however, clarifying this effect is not possible in the present sample given that Arithmetic was not assessed earlier in development and because temporally ordered constructs, which are a critical strength of the present study, are necessary to infer causal mediation (Kraemer et al. 2001).

Finally, while Arithmetic significantly mediated birth weight and ADHD symptoms, the size of the effect was small. ADHD is sensitive to multiple etiologies (i.e., equifinality; Nigg et al. 2005) and additional neurocognitive functions (e.g., executive functions) may mediate parallel pathways from birth weight (Wiggs et al. 2016) or other risk factors (e.g., genetic) in both ID and TD youth. For example, working memory is a potential endophenotype for ADHD (Loo et al. 2008), but this pathway has not been examined in ID youth. Thus, evaluation of diverse biologically plausible mediators underlying ADHD symptoms must be a continued priority, especially in youth with ID.

Consistent with prior research in TD youth, we found that individual differences in fluid reasoning, as measured by Arithmetic, mediated birth weight and age 13 ADHD symptoms in a prospective longitudinal sample, and that this indirect effect was similar for ID and TD youth as well as across youth IQs. Although, based on the current study and prior studies, mediation by fluid reasoning is putatively causal, it likely reflects a single component of a multilevel neurodevelopmental pathway from birth weight to ADHD. For example, potential mechanisms underlying neurodevelopmental impairments that trigger fluid reasoning deficits and ADHD include deficient in utero nourishment preceding birth weight or even postnatal complications arising from birth weight (e.g., neonatal malnutrition; De Curtis and Rigo 2004; Georgieff 2007; Groen-Blokhuis et al. 2011). Thus, future research must aim to characterize pathways from birth weight to fluid reasoning and from fluid reasoning to

ADHD symptoms. Moreover, given the frequent co-occurrence and increased burden of ADHD symptoms in youth with ID, it will be important to replicate the present findings in other samples that include youth with IQs below the typically developing range. Ultimately, identification of biologically plausible mechanisms underlying the development of ADHD symptoms in youth with ID will be critical to informing prevention and intervention efforts to reduce the augmented burden of these co-occurring conditions.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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