Title
Perinatal and Genetic Influences on the Development of Cognitive Deficits and Subsequent ADHD

Author
Morgan, Julia Elizabeth

Publication Date
2019

Peer reviewed|Thesis/dissertation

UNIVERSITY OF CALIFORNIA

Los Angeles

Perinatal and Genetic Influences on the Development of Cognitive Deficits and Subsequent ADHD

A dissertation submitted in partial satisfaction of the requirements for the degree

Doctor of Philosophy in Psychology

by

Julia Elizabeth Morgan

2019

ABSTRACT OF THE DISSERTATION

Perinatal and Genetic Influences on the Development of Cognitive Deficits and Subsequent ADHD

by

Julia Elizabeth Morgan

Doctor of Philosophy in Psychology

University of California, Los Angeles, 2019

Professor Steve Sung-Yul Lee, Co-Chair

Professor Sandra Kan Loo, Co-Chair

Attention-deficit/hyperactivity disorder (ADHD) is a highly prevalent and costly mental health condition. Innovation in ADHD prevention requires elucidation of underlying causal processes to highlight precise targets for early interventions that promote resilience. However, although ADHD is sensitive to multiple risk factors, including considerable heritability as well as prenatal/perinatal influences (e.g., low birth weight, prenatal exposure to maternal metabolic conditions), the pathways mediating these associations are relatively unknown. This dissertation consists of three studies that address this important gap in knowledge directly.

Cognitive functioning domains including executive functioning (EF) and reasoning (e.g., cognitive flexibility, fluid reasoning) are biologically plausible pathways from genetic and prenatal/perinatal influences to individual differences in ADHD. However, to date, mediation has primarily been inferred rather than formally evaluated, and no study has concurrently tested

parallel or overlapping ADHD risk processes in the same sample. Thus, Study 1 employed multiple mediation to test diverse EF and reasoning dimensions as collective and unique mediators of ADHD symptoms from both birth weight and replicated candidate genes in a sample of youth from multiplex families with ADHD. Extending this novel integration of perinatal and genetic influences, Study 2 used a genome-wide association approach in a large population-based sample to estimate if correlations among birth weight, EF, reasoning, and ADHD symptoms were sensitive to shared genetic influences.

Although exposure to adverse maternal health factors during pregnancy (e.g., inflammation, hyperglycemia) reliably predict child EF deficits, it is unclear *which* factors most compromise child cognitive development and *when* exposure to these factors is most consequential. To improve traction specifically on the development of child EF deficits from prenatal/perinatal influences, Study 3 employed a prospective, longitudinal sample of maternal health and child development to evaluate multiple maternal metabolic and pro-inflammatory factors (i.e., C-reactive protein, glycated hemoglobin, blood pressure) simultaneously as predictors of offspring EF and compare their relative temporal influence prior to and across pregnancy.

Collectively, results of the three studies partially support that specific prenatal/perinatal influences uniquely predict particular domains of child cognitive development. Results are discussed in the context of implications for future research and for optimizing prevention strategies to reduce the significant public health burden of ADHD.

The dissertation of Julia Elizabeth Morgan is approved.

Christine Dunkel Schetter

Katherine H. Karlsgodt

Sandra Kan Loo, Committee Co-Chair

Steve Sung-Yul Lee, Committee Co-Chair

University of California, Los Angeles

2019

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Acknowledgements

This work was partially supported by a UCLA Graduate Division Dissertation Year Fellowship to Julia Morgan. Study 1 was supported by National Institute of Health (NIH) grants NS54124 to Dr. Sandra Loo and MH58277 to Dr. Susan Smalley. Study 2 used data from the Philadelphia Neurodevelopmental Cohort (PNC) obtained via dbGaP (Study Accession: phs000607.v2.p2) by authorized user Dr. Katherine Karlsgodt. Support for the PNC data collection was provided by NIH grants RC2MH089983 to Dr. Raquel Gur and RC2MH089924 to Dr. Hakon Hakonarson. All PNC subjects were recruited through the Center for Applied Genomics at the Children's Hospital in Philadelphia. Dr. Nicholas Mancuso of the UCLA QCB Collaboratory assisted with the genetic analyses for Study 2 and will be included as a co-author on any future publications originating from this work. Study 3 was supported by NIH grant HD072021 to Dr. Christine Dunkel Schetter. Study 3 is a version of Morgan, J. E., Lee, S. S., Mahrer, N. E., Guardino, C. M., Davis, E. P., Shalowitz, M. U., Ramey, S. L., & Dunkel Schetter, C. (under review). Maternal metabolic and pro-inflammatory factors prospectively predict child executive functioning: Time-sensitive effects before and across pregnancy. Co-author contributions are as follows: project directors (CDS, MUS, SLR), study design (JEM, SSL, CDL), statistical analyses (JEM), data management (JEM, CMG, NEM), manuscript writing (JEM), critical revisions to the manuscript (all authors). The author especially wishes to thank her research advisors and committee co-chairs, Drs. Steve Lee and Sandra Loo, and her committee members, Drs. Christine Dunkel Schetter and Katherine Karlsgodt, for their inspiration, encouragement, and support. The author also thanks Drs. Carrie Bearden, Christine Guardino, Nicole Mahrer, Loes Olde Loohuis, Roel Ophoff, and Dietsje Jolles, as well as her graduate student colleagues in the UCLA ADHD and Development Lab, for their support and consultation.

Vita

EDUCATION

2014	M.A.	University of California, Los Angeles; Major*:* Psychology
2010	B.A.	Emory University; Major: Psychology with Highest Honors, *summa cum laude*

HONORS, AWARDS, AND FELLOWSHIPS

2017 – 2018	Dissertation Year Research Fellowship, UCLA Graduate Division
2017	Honorable Mention, Society for Clinical Child and Adolescent Psychology (APA Division 53) Routh Research and Dissertation Award
2017	Wayne Levine Summer Research Fellowship, UCLA Psychology Department
2017	Charles Y. Nakamura Research Award, UCLA Psychology Department
2015	Graduate Summer Research Mentorship Award, UCLA Graduate Division
2014 – 2015	Graduate Research Mentorship Award, UCLA Graduate Division
2014	Honorable Mention, National Science Foundation Graduate Research Fellowship
2014	Graduate Summer Research Mentorship Award, UCLA Graduate Division
2013 – 2014	Distinguished University Fellowship, UCLA Graduate Division
2010	Highest Honors awarded to undergraduate thesis, Emory University
2010	Phi Beta Kappa Society, Emory University
2009	Psi Chi International Honor Society, Emory University
2006 – 2010	Dean's List, all undergraduate academic semesters

PUBLICATIONS

1. **Morgan, J. E.**, Lee, S. S., & Loo, S. K. (2019). Fluid reasoning mediates the association of birth weight with ADHD symptoms in youth from multiplex families with ADHD. *Journal of Attention Disorders,* 23(7), 682–691. doi: 10.1177/1087054716670006.
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1. **Morgan, J. E.**, Dvorsky, M. R., Meza, J. I., Jiang Y., & Pfiffner, L. J. (2019, June). Co-occurring psychopathology moderates social skills improvement in a randomized controlled trial of psychosocial intervention for children with ADHD. Poster presented at International Society for Research in Child and Adolescent Psychopathology, Los Angeles, CA.
2. Dvorsky, M. R., Ahmad, S., Friedman, L., **Morgan, J.**, & Pfiffner, L. (2019, June). Promotive predictors and trajectories of response to the Collaborative Life Skills (CLS) program for children with ADHD. Paper presented at International Society for Research in Child and Adolescent Psychopathology, Los Angeles, CA.
3. **Morgan, J. E.**, Lee, S. S., Guardino, C. M., Ramey, S. L., Shalowitz, M. U., & Dunkel Schetter, C. (2019, March). Higher maternal HbA_{1C} after the birth of one child prospectively predicts executive functioning deficits in subsequent offspring. In A. Cheadle & C. M. Guardino (Co-Chairs), *Stress and Resilience during the Postpartum Period: Implications for Maternal and Child Health across the Lifespan*. Symposium presented at American Psychosomatic Society, Vancouver, BC.
4. **Morgan, J. E.**, Lee, S. S., Loo, S. K., & Baker, B. L. (2017, June). Fluid reasoning mediates birth weight and ADHD symptoms in youth with intellectual disability. Poster presented at International Society for Research in Child and Adolescent Psychopathology, Amsterdam, Netherlands.
5. Yuhan, J. W., **Morgan, J. E.**, Wang, Z., & Lee, S. S. (2017, May). Parental ADHD symptoms interact with child ADHD and depression symptoms to predict negative parenting behavior. Poster presented at Association for Psychological Science, Boston, MA.
6. **Morgan, J. E.**, Baker, B. L., & Lee, S. S. (2016, August). Neurocognitive mediators of DAT1 x parenting behavior interactions for youth ADHD. In S. S. Lee (Chair), *Genetic and Temperamental Sensitivity to Parenting in Two High-Risk Longitudinal Samples*. Symposium presented at American Psychological Association, Denver, CO.
7. Rivera, V., **Morgan, J. E.**, De La Cerda, J. T., & Lee, S. S. (2016, May). Birth weight uniquely predicts ODD symptoms, but not internalizing symptoms, in youth with and without ADHD. Poster presented at Association for Psychological Science, Chicago, IL.
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10. **Morgan, J. E.**, & Lee, S. S. (2014, May). A multiple mediation model of serotonin transporter genotype and parenting behavior. Poster presented at Association for Psychological Science, San Francisco, CA.
11. Feder, A., Parides, M., aan het Rot, M., **Morgan, J. E.**, Ott, E., Saxena, S., Murrough, J., Perez, A., Iosifescu, D., & Charney, D. S. (2013, May). Intravenous ketamine: A potential novel therapeutic intervention for PTSD? Poster presented at Society of Biological Psychiatry, San Francisco, CA.
12. **Morgan, J. E.**, Calderon, S., Lebow, M., Iosifescu, D., Pietrzak, R. H., Charney, D. S., & Feder, A. (2012, September). Childhood trauma and comorbid mood and anxiety disorders in adult patients with post-traumatic stress disorder. Poster presented at International Society of Psychoneuroendocrinology, New York, NY.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is among the most prevalent and costly mental health conditions in the United States. Eleven percent of American youth aged 4 to 17 years are diagnosed with ADHD in their lifetime (Visser et al., 2014), incurring annuals costs between $143 to $266 billion (Doshi et al., 2012). Beyond its significant public health burden, there is also unmet clinical need given that even the most effective pharmacologic and behavioral interventions for ADHD have critical limitations (e.g., costly, time consuming, short-term gains; Sonuga-Barke & Halperin, 2010). Thus, development of ADHD prevention strategies must be prioritized. Innovation in ADHD prevention requires elucidation of underlying causal processes to highlight precise targets for early interventions that promote resilience (Sonuga-Barke & Halperin, 2010). However, although ADHD is sensitive to multiple risk factors, including considerable heritability as well as prenatal/perinatal influences (Halmøy, Klungsøyr, Skjærven, & Haavik, 2012; Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005; Thapar, Cooper, Eyre, & Langley, 2013), the pathways mediating these associations are relatively unknown. In addition to hindering prevention efforts, and because modern conceptualizations of validity advocate that validity in psychological science requires knowledge of causal mechanisms (Borsboom, Mellenbergh, & Van Heerden, 2004), poor understanding of processes underlying ADHD also limits its validity as a biological construct. My dissertation consists of three studies that addressed this important gap in knowledge directly.

Behavioral genetic, molecular genetic, and genome-wide studies converge around the significant heritability of ADHD (h^2 = .75-.90; Hawi et al., 2015; Thapar et al., 2013). Additionally, prenatal/perinatal factors including prenatal exposure to maternal metabolic conditions and inflammation reliably predict ADHD (Bhutta, Cleves, Casey, Cradock, & Anand,

2002; Instanes et al., 2015; Mina et al., 2016; Nomura et al., 2012). Birth weight has even been identified as a preliminary causal influence on the development of ADHD symptoms (Groen-Blokhuis, Middeldorp, van Beijsterveldt, & Boomsma, 2011; Pettersson et al., 2015). Evaluation of *biologically plausible* mediators is necessary to characterize causal processes and is therefore a priority. Executive function (EF) domains, which consist of separable but related higher-order cognitive processes involved in the control of goal-directed behavior (e.g., cognitive flexibility, working memory, response inhibition; Pennington & Ozonoff, 1996), are implicated in causal theories of ADHD (Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005) and share key risk factors with ADHD across genetic, prenatal/perinatal, cellular, and neural indicators. There is similar evidence for reasoning abilities, which consist of logical thinking and problem solving under novel circumstances, and are factorially separate from crystallized knowledge (Cattell, 1987). For example, there is considerable genetic overlap between ADHD, EF, and reasoning (Coolidge, Thede, & Young, 2000; Martin, Hamshere, Stergiakouli, O'Donovan, & Thapar, 2015), and these domains are similarly predicted from prenatal/perinatal factors (Aarnoudse-Moens, Weisglas-Kuperus, van Goudoever, & Oosterlaan, 2009; Bhutta et al., 2002; Morgan, Loo, & Lee, 2016). Additionally, EF and reasoning deficits are associated with neural abnormalities (i.e., hypoactivation in fronto-striato-parietal networks; reduced cortical surface area, thickness, and volume; Hart, Radua, Nakao, Mataix-Cols, & Rubia, 2013; Hobeika, Diard-Detoeuf, Garcin, Levy, & Volle, 2016; Skranes et al., 2013) that are (1) significantly heritable (Congdon, Poldrack, & Freimer, 2010), (2) sequelae of prenatal/perinatal factors (Griffiths et al., 2013; Martinussen et al., 2005; Skranes et al., 2013; Walhovd et al., 2012), and (3) implicated in ADHD etiology (Cortese et al., 2012; Narr et al., 2009; Shaw et al., 2012). Thus, EF and

reasoning dimensions are highly biologically plausible pathways from genetic and prenatal/perinatal influences to individual differences in ADHD.

Given that ADHD is sensitive to multiple causal influences (i.e., equifinality; Nigg et al., 2005), a strong design requires simultaneous evaluation of multiple cognitive mediators from various putative causal factors. However, to date, mediation has primarily been inferred rather than formally evaluated, and no study has concurrently tested parallel or overlapping ADHD risk processes in the same sample. Thus, Studies 1 and 2 of my dissertation integrated perinatal and genetic factors in prediction of EF, reasoning, and ADHD in two complementary, deeply phenotyped samples (i.e., with comprehensive data across genomic, neural, cognitive, and behavioral levels). In the UCLA ADHD Genetics Study, a multiplex family-based study of ADHD probands (n = 284), affected siblings (n = 255), and unaffected siblings (n = 107), Study 1 tested separable EF and reasoning dimensions as collective and unique mediators of ADHD symptoms from *both* birth weight and genetic risk *simultaneously* using multiple mediation. Study 2 expanded on Study 1 by examining common genetic variation shared among birth weight, ADHD symptoms, EF, and reasoning to determine if associations between these factors were sensitive to overlapping genetic influences. Study 2 was conducted in 7,774 subjects from the Philadelphia Neurodevelopmental Cohort (PNC), a population-based sample of youth.

Although prenatal/perinatal factors reliably predict EF facets (that, in turn, are involved in the development of ADHD), critical aspects of this prediction require clarification. First, because prenatal/perinatal risk factors for cognitive deficits are correlated, it is unclear *which* factors most compromise cognitive development. Second, because prior studies typically measured prenatal factors at a single time point (e.g., retrospective report of gestational diabetes instead of multiple blood glucose measurements across pregnancy), it is unknown *when* these

factors are most consequential. To improve traction specifically on the development of EF deficits from prenatal/perinatal influences, Study 3 of my dissertation evaluated diverse prenatal/perinatal factors simultaneously as predictors of offspring EF and compared their relative temporal influence prior to and across pregnancy in the Community Child Health Network (CCHN), an intensive multi-occasion prospective study of maternal and fetal health, and a follow-up study of offspring development to ages 4-6 years.

Collectively, my dissertation aimed to identify multiple biologically plausible risk processes underlying ADHD by refining EF predictions from prenatal/perinatal influences as well as formally evaluating diverse parallel or overlapping cognitive pathways to ADHD from well-defined genetic and perinatal risk factors. To date, interventions targeting aggregate cognitive deficits have shown limited efficacy in reducing youth ADHD symptoms (Cortese et al., 2015). However, if EF or reasoning dimensions uniquely mediate predictions of ADHD symptoms from prenatal/perinatal or genetic risk factors, follow-up studies testing early cognitive interventions *specifically* in youth with these risk factors and *prior* to the onset of symptoms would be indicated. Notably, there is growing evidence that various programs and activities (e.g., cognitive training, school-based curricula, exercise) improve cognitive development in youth aged 4-12, especially those exhibiting early EF deficits (Diamond, 2012; Diamond & Lee, 2011) and low birth weight preschoolers (Grunewaldt, Lohaugen, Austeng, Brubakk, & Skranes, 2013; Kristine Hermansen Grunewaldt, Skranes, Brubakk, & Lähaugen, 2015). Thus, early interventions targeting relevant cognitive domains in youth for whom these domains are most implicated (e.g., low birth weight children) may constitute a significant opportunity to reduce the incidence of ADHD and therefore its public health burden. Moreover, because cognitive deficits are central to multiple neurodevelopmental disorders (e.g., autism,

schizophrenia; McGrath et al., 2015), improved understanding of their etiology will facilitate broader innovations in prevention efforts across major forms of psychopathology.

Study 1: Pathways from Birth Weight and Polygenic Risk to ADHD Symptoms in Youth from Multiplex Families with ADHD

Meta-analytic and prospective longitudinal evidence similarly suggest that birth weight inversely predicts individual differences in attention-deficit/hyperactivity disorder (ADHD; Aarnoudse-Moens et al., 2009; Bhutta et al., 2002; Halmøy et al., 2012; Martel, Lucia, Nigg, & Breslau, 2007; Momany, Kamradt, & Nikolas, 2017; Nigg & Breslau, 2007). There is also replicated evidence that birth weight predicts ADHD symptoms in co-twin control designs, providing quasi-experimental evidence that this association is independent of other well-characterized risk factors for ADHD (e.g., genetic influences, prematurity, prenatal teratogen exposure; Groen-Blokhuis, Middeldorp, van Beijsterveldt, & Boomsma, 2011; Pettersson et al., 2015). Thus, there is persuasive evidence that birth weight is an independent and potentially causal influence on the development of ADHD symptoms.

Although birth weight may causally influence ADHD, this does not contribute to knowledge about causal mechanisms that is needed to develop effective prevention strategies (Sonuga-Barke & Halperin, 2010). Evaluation of *biologically plausible* mediators is necessary to characterize causal processes and is therefore a priority. Birth weight positively predicts separable executive function (EF; e.g., working memory, response inhibition, cognitive flexibility) and reasoning dimensions (e.g., fluid reasoning; Aarnoudse-Moens et al., 2009; Bhutta et al., 2002; Burnett et al., 2015; Camerota, Willoughby, Cox, & Greenberg, 2015; Hutchinson et al., 2013; Wiggs et al., 2016) that in turn, are implicated in causal theories of ADHD (Nigg et al., 2005; Willcutt et al., 2005). EF and reasoning deficits are also associated with neural abnormalities (i.e., hypoactivation in fronto-striato-parietal networks; reduced cortical surface area, thickness, and volume; Hobeika, Diard-Detoeuf, Garcin, Levy, & Volle,

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 ADHD etiology (Cortese et al., 2012; Narr et al., 2009; Shaw et al., 2012). Thus, beyond statistical mediation, EF and reasoning facets are biologically plausible as causal mediators. To date, several studies have formally tested mediation from birth weight to ADHD through reasoning and other cognitive domains. For example, fluid reasoning mediated birth weight and ADHD symptoms in two independent prospective longitudinal studies (Morgan, Lee, Loo, Yuhan, & Baker, 2018; Morgan, Loo, et al., 2016) and in a cross-sectional study of youth from multiplex families with ADHD (Morgan, Lee, & Loo, 2016). Additionally, response variability mediated separate predictions of both inattention and hyperactivity/impulsivity symptoms from birth weight (Wiggs et al., 2016). Thus, based on their biological plausibility as mediators of birth weight and ADHD, coupled with replicated evidence of mediation by related cognitive functions, evaluation of mediated effects through diverse EF domains in addition to reasoning domains is warranted.

While there is evidence that EF and reasoning are potential pathways from birth weight to ADHD symptoms, ADHD is sensitive to multiple risk factors (i.e., equifinality) that include substantial heritability (~70-95%; Hawi et al., 2015; Thapar et al., 2013). Moreover, there is considerable variation in clinical presentation among youth with ADHD (e.g., inattention vs. hyperactivity/impulsivity, developmental trajectory), including variation in associated cognitive deficits (e.g., presenence or absence of EF deficits; Willcutt et al., 2005), neural abnormalities, and separable genetic and environmental influences (Nigg et al., 2005; Thapar et al., 2013). Thus, whereas particular EF or reasoning dimensions may mediate predictions of ADHD symptoms from birth weight, similar or other cognitive facets may mediate parallel or

overlapping pathways from genetic factors (Nigg et al., 2005). Like birth weight, genetic influences on ADHD are associated with EF and reasoning. Twin studies suggest considerable genetic overlap between ADHD, reasoning, and EF deficits (e.g., Coolidge et al., 2000) and meta-analytically implicated polymorphisms for ADHD as well as genome-wide polygenic ADHD risk scores also predict EF and IQ (Barnes, Dean, Nandam, O'Connell, & Bellgrove, 2011; Martin et al., 2015). Finally, multiple EF domains (e.g., working memory, response inhibition) are compelling ADHD endophenotypes, especially from dopaminergic genes (Gallo & Posner, 2016; Kamradt, Nigg, Friderici, & Nikolas, 2016; Loo et al., 2008; Nigg et al., 2018). Thus, a strong design would employ a multiple mediation framework to disentangle the cumulative and unique effects of EF/reasoning mediators from birth weight and *simultaneously* consider genetic influences in the same model.

Several methodological considerations will accelerate identification of biologically plausible mechanisms. First, continuous measures of birth weight and ADHD parallel pathophysiology and improve statistical power. Whereas most studies have dichotomized low birth weight vs. normal birth weight, birth weight is monotonically associated with ADHD symptoms (Groen-Blokhuis et al., 2011; Pettersson et al., 2015). Likewise, there is strong evidence that ADHD is best characterized continuously rather than dichotomously (Haslam, Holland, & Kuppens, 2012; Lubke et al., 2007). Second, other prenatal/perinatal risk factors, including prematurity as well as exposure to maternal metabolic and inflammatory conditions (e.g., gestational diabetes, hypertension) are correlated with birth weight (Valero De Bernabé et al., 2004), cognitive functioning (Adane et al., 2016; Tuovinen, Eriksson, Kajantie, & Räikkönen, 2014), and ADHD (Halmøy et al., 2012; Nomura et al., 2012), and therefore must be accounted for to adequately specify indirect effects from birth weight to ADHD. Third, because

the etiology of ADHD is highly polygenic (Middeldorp et al., 2016), polygenic risk scores (PRSs) are a preferred approach to estimate genetic influences in cognitive pathways underlying ADHD. In particular, multiple specific functional polymorphisms meta-analytically predicted ADHD, including the 48 base-pair (bp) variable number tandem repeat (VNTR) in exon 3 of the D4 receptor gene (DRD4), 40 bp VNTR in the 3' untranslated region of the dopamine transporter gene (DAT1), and 44 bp insertion/deletion in the promoter region of the serotonin transporter gene (5-HTTLPR; Gizer, Ficks, & Waldman, 2009; Hawi et al., 2015). Thus, to test indirect effects from both birth weight and genetic risk, the present study used PRSs calculated from these polymorphisms.

Aims

To review, although birth weight may causally influence ADHD symptoms, the mechanisms underlying this prediction are largely unknown, including overlapping or parallel pathways from genetic influences. To elucidate diverse indirect effects underlying youth ADHD symptoms, we tested separable biologically plausible EF and reasoning dimensions as collective and unique mediators of ADHD symptoms from *both* birth weight and genetic risk *simultaneously* in a sample of affected and unaffected siblings from multiplex families with ADHD (see Figure 1.1 for a conceptual model). We hypothesized that EF and reasoning would mediate predictions from birth weight and genetic risk but proposed no hypotheses about specific cognitive facets given their similar biological plausibility and the novelty of this mediation model.

Methods

Participants

Participants were 646 youth aged 5-19 years (M = 10.47, SD = 3.53; 40.87% 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 1.1. Families were recruited from the greater Los Angeles area via referrals from local psychiatry, pediatric, and community outlets (see Smalley et al., 2000 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 (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 = 107). 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 syndrome, generalized resistance to thyroid hormone).

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 ≥ 8 years of age). Additionally, mothers reported prenatal/perinatal data, youth completed a cognitive battery and provided a blood sample, and rating scales were mailed to teachers. All youth completed the cognitive 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 Smalley et al. (2000) for additional details regarding assessment procedures and reliability.

Measures

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) as well as informed by teacher ratings on the Teacher Report Form (TRF; Achenbach & Rescorla, 2001) and SNAP-IV (Swanson, 1992). The TRF is a normed rating scale yielding eight narrowband syndrome scales, including an Attention Problems scale with both inattention and hyperactivity/impulsivity items. The SNAP-IV rating scale is a widely used measure of youth ADHD. The K-SADS, TRF, and SNAP-IV have been extensively validated and demonstrate excellent psychometric properties (Achenbach & Rescorla, 2001; Kaufman et al., 1997; Swanson, 1992).

Prenatal/perinatal factors. Mothers retrospectively reported youth birth weights (*M* = 119.92 ounces, *SD* = 20.92, *range* = 26-202) as well as prematurity, gestational diabetes, and gestational hypertension (coded yes/no) on the Yale Neuropsychoeducational Assessment Scale

(Shaywitz, 1982). 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).

Genetic data. DNA was isolated from blood using the Puregene Kit (Gentra Systems, Minneapolis). Meta-analytically validated ADHD polymorphisms were genotyped according to standard procedures. Risk genotypes defined based on meta-analytic evidence included at least one copy of the DRD4 7-repeat allele, 5-HTTLPR long allele, and DAT1 10-repeat allele (Gizer et al., 2009). DAT1 genotype frequencies were distributed as follows: 10/10 (53.02%, $n = 246$), 9/10 (38.58%, $n = 179$), and 9/9 (8.41%, $n = 39$). Additionally, 5-HTTLPR genotype frequencies were distributed as follows: Long/Long (10.40%, $n = 47$), Short/Long (46.90%, $n = 212$), and Short/Short (42.70%, $n = 193$). These frequencies did not deviate from Hardy-Weinberg equilibrium ($p > .31$ for all tests). However, allele frequencies for DRD4 significantly deviated from Hardy-Weinberg equilibrium based on over-representation of the 7-repeat allele ($\chi^2(1) = 8.90$, $p < .01$): two copies of the 7-repeat allele (6.49%, $n = 29$), one copy of the 7-repeat allele (27.96%, $n = 125$), and no 7-repeat alleles (65.55%, $n = 293$). Similarly high rates of the 7-repeat allele have been reported in other oversampled ADHD studies (e.g., Trejo, Toscano-Flores, Matute, & de Ramírez-Dueñas, 2015). For the present analysis, we calculated a PRS from the three polymorphisms where 0 = no risk alleles and 6 = all risk alleles. Given the larger body of research on the role of dopaminergic genes in cognitive dysfunction and ADHD relative to 5-HTTLPR (e.g., Kamradt et al., 2016; Loo et al., 2008), we also calculated a second PRS from just DAT1 and DRD4, where 0 = no risk alleles and 4 = all risk alleles.

Cognitive functioning. Hypothesized EF mediators for the current study were selected from the cognitive battery based on meta-analytic evidence of their association with ADHD with at least moderate effect sizes (Homack & Riccio, 2004; Kofler et al., 2013; Willcutt et al., 2005); they included verbal working memory, visuospatial working memory, cognitive flexibility, interference control, response inhibition, and intraindividual response variability (i.e., reaction time variability). Fluid reasoning was also evaluated as mediator, given that it may be central to or even subsume EF facets (Cho et al., 2010; Conway, Cowan, Bunting, Therriault, & Minkoff, 2002), and because it reliably mediated birth weight and ADHD symptoms in prior studies (Morgan, Lee, et al., 2016; Morgan et al., 2018; Morgan, Loo, et al., 2016). All measures selected to assess cognitive functioning have been extensively validated and demonstrate excellent psychometric properties.

Verbal working memory was assessed using scaled scores from the Digit Span Backward subtest of the Wechsler Intelligence Scale for Children (WISC; Wechsler, 2003), during which subjects repeat back strings of numbers in the reverse order that they are presented. Visuospatial working memory was assessed via scaled scores from the Spatial Span Backward subtest of the WISC-Process Instrument (Kaplan, Fein, Kramer, Delis, & Moris, 1999). Spatial Span Backward is a visuospatial analogue of the Digit Span task. Next, we measured cognitive flexibility with the Trails B subtest from the Trail Making Test (Reitan, 1979), during which subjects draw lines to connect circles containing numbers and letters in an alternating sequential order. The overall score for this measure reflects the total time in seconds for the subject to complete the task. Fluid reasoning was assessed using scaled scores from the Arithmetic subtest of the WISC-III (Wechsler, 1991), which requires subjects to mentally solve orally presented math problems.

Interference control was estimated with the Interference Score from the Stroop Color-Word Test (Golden, 1978). The Stroop task consists of three different conditions. First, subjects must read as many color names as possible within the time limit (e.g., red, blue, green). Second, the letter X is displayed in different colors of ink (i.e., red, blue, green), and subjects must name as many ink colors as possible within the time limit. Third, color names are printed in different colors of ink such that the displayed word does not match the ink color (e.g., "red" printed in blue ink). Subjects must name the ink color and inhibit the automatic response of reading the word. An interference score, which measures interference control, was calculated by subtracting the total number of correct items on the second condition from the total number of correct items on the third condition such that higher interference scores represent better performance.

Finally, both response inhibition and response variability were calculated using data from the Stop Signal Task (SST; Logan, Schachar, & Tannock, 1997). The SST consists of four blocks comprised of "go" trials and "stop" trials. During the go trials, subjects press a button to indicate whether an X or O is displayed on the screen. However, on 25% of the stimuli presentations, an auditory tone is presented signaling the subject to inhibit the prepotent response of pressing the button (i.e., stop trial). The task was designed to adjust the presentation of the stop signal such that subjects successfully inhibit their responses on 50% of the stop trials. Response inhibition is typically estimated using the Stop Signal Reaction Time (SSRT), which was calculated for the current study by subtracting the mean delay after stop signals that were followed by successful inhibition from the mean reaction time across correct go trials for each block, and then averaging across all usable blocks. Response variability was calculated as the standard deviation of reaction times for correct go trials in each block, and then averaged across usable blocks. Usable blocks were determined using procedures recommended by Congdon et al.

(2012), whereby blocks were dropped from the final scores if they had less than 60% accuracy on go trials or the probability of stopping given the stop signal was outside the 25%-75% range. Although raw scores or scaled scores for the cognitive measures are presented in Table 1.1, they were converted to Z-scores for use in all analyses.

Statistical Analysis

Population Stratification. Unlike the current study, population stratification is primarily a concern when highly distinct strata (e.g., genetically distinct racial-ethnic groups) yield differences in allele frequencies that may threaten internal validity (Hutchison, Stallings, McGeary, & Bryan, 2004). Therefore, given that population stratification is contingent on race-ethnicity being associated with both genotype and outcome variable (Hutchison et al., 2004), and because the PRSs were non-randomly distributed by race-ethnicity in our sample ($F(5, 394) = 4.82$, $p < .01$ for the PRS calculated from all three candidate genes; $F(5, 420) = 9.76$, $p < .01$ for the PRS calculated from the two dopaminergic genes), race-ethnicity was controlled in all analyses.

Missing data. Approximately 34% of youth were missing data on at least one key study variable (e.g., birth weight, PRSs). 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 ($\chi^2(2823) = 2144.47$, $p > .99$).

Multiple mediation. Intraclass correlations (ICCs) indicated substantial between-family variation on key study variables: birth weight ($ICC = .48$), PRS (.56), verbal working memory

(*ICC* = .20), visuospatial working memory (*ICC* = .20), cognitive flexibility (*ICC* = .13), interference control (*ICC* = .12), response inhibition (*ICC* = .22), response variability (*ICC* = .28), fluid reasoning (*ICC* = .33), 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 the hypothesized cognitive domains as statistical mediators from birth weight and the candidate gene PRS (i.e., calculated from DRD4, DAT1, and 5-HTTLPR), we constructed an MSEM path analysis that simultaneously tested direct effects from birth weight and the PRS to all mediators (i.e., verbal working memory, visuospatial working memory, cognitive flexibility, interference control, response inhibition, response variability, fluid reasoning) and ADHD symptoms, and from all mediators to ADHD symptoms. Proposed covariates included demographic factors (i.e., age, sex, race-ethnicity, SES) and potential prenatal/perinatal confounds (i.e., prematurity; exposure to maternal gestational diabetes and hypertension). 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).

Given the modest to moderate correlations among most of the cognitive mediators (bivariate correlations ranged from r = .02-.71), we also evaluated separate single mediation models for each domain to increase power to detect indirect effects. Each single mediation model consisted of an MSEM path analysis that simultaneously tested direct effects from birth weight and the PRS to the respective cognitive mediator and ADHD symptoms, and from the cognitive mediator to ADHD symptoms.

Moderated mediation by polygenic risk. Based on preliminary evidence that dopaminergic genes may moderate the association between birth weight and ADHD rather than directly influence ADHD (e.g., Jackson & Beaver, 2015), we also evaluated moderation of indirect effects from birth weight to ADHD by the PRS (i.e., moderated mediation). Specifically, we added a PRS x birth weight interaction term to each of the single mediation models described above and calculated an index of moderated mediation for each model. These indices reflect the effect of the moderator (i.e., PRS) on the overall indirect effect from birth weight to ADHD symptoms through the cognitive mediator (Hayes, 2015).

Results

Indirect Effects from Birth Weight and Polygenic Risk to ADHD Symptoms through EF

We first evaluated the seven cognitive domains as statistical mediators of ADHD symptom from birth weight and the PRS simultaneously (see Figure 1.1 for conceptual model). Of note, the same pattern of results was observed when either of the PRSs were used to reflect

genetic risk (i.e., one calculated from DRD4, DAT1, and 5-HTTLPR vs. one calculated from only the two dopaminergic genes), and regardless of whether the proposed covariates were included in the model. Thus, for simplicity, only results for models using the dopaminergic candidate gene risk score and with select covariates (i.e., age, sex, race-ethnicity) are presented.

At the within level (i.e., individual youth within families), no significant direct effects were observed from birth weight or the PRS to the mediators (i.e., *a* paths), although both birth weight and the PRS marginally predicted fluid reasoning (Table 1.2). The effects of the mediators on ADHD symptoms (i.e., *b* paths) were significant for fluid reasoning and cognitive flexibility, and marginally significant for visuospatial working memory, but not for the remaining mediators (Table 1.3). Neither the total effect of birth weight nor its corresponding direct effect (i.e., controlling for the mediators and the PRS) was significantly related to ADHD symptoms (respectively, B = -0.008, SE = 0.017, p = .64; B = -0.005, SE = 0.017, p = .79). Likewise, both the total effect of the PRS and its corresponding direct effect (i.e., controlling for the mediators and birth weight) were unrelated to ADHD symptoms (respectively, B = -0.063, SE = 0.561, p = .91; B = 0.120, SE = 0.576, p = .83). Finally, no significant within-level indirect effects of birth weight on ADHD symptoms through the mediators were observed, or of the PRS on ADHD symptoms through the mediators (i.e., the Monte Carlo confidence interval included zero for all indirect effects); however, there was a marginal indirect effect of birth weight on ADHD symptoms through fluid reasoning (B = -.004, SE = .003, *95% CI* = -.011, .001). Results were unchanged when the above models were repeated in prediction of separate inattention and hyperactivity/impulsivity symptom domains.

Next, to increase power to detect indirect effects, we evaluated separate single mediation models in prediction of ADHD symptoms for each mediator. Although birth weight predicted

fluid reasoning, and fluid reasoning, visuospatial working memory, and cognitive flexibility predicted ADHD symptoms, no other direct effects were observed. Additionally, no significant indirect effects from birth weight or the PRS to ADHD symptoms through the mediators were observed, although the indirect effect of birth weight on ADHD symptoms through fluid reasoning was again marginal (*B* = -.004, *SE* = .003, *95% CI* = -.011, < .001). Thus, results from the single mediation models were consistent with the multiple mediation model. Finally, no between-level direct or indirect effects among birth weight, PRS, cognitive mediators, and ADHD symptoms were observed in any model, suggesting that indirect effects were also not observed across families.

Moderation of Indirect Effects from Birth Weight by Polygenic Risk

We also evaluated moderation of indirect effects from birth weight to ADHD symptoms through the cognitive mediators by the PRS, for which the index of moderated mediation reflected the effect of the PRS on the indirect effect. For all within-level indirect effects through the mediators, the index of moderated mediation did not differ from zero: verbal working memory (*B* = -0.002, *SE* = 0.002, *p* = .27), visuospatial working memory (*B* = -0.004, *SE* = 0.003, *p* = .16), cognitive flexibility (*B* = 0.004, *SE* = 0.003, *p* = .14), interference control (*B* = -0.002, *SE* = 0.002, *p* = .36), response inhibition (*B* = -0.001, *SE* = 0.002, *p* = .61), response variability (*B* = -0.005, *SE* = 0.004, *p* = .18), and fluid reasoning (*B* = -0.001, *SE* = 0.002, *p* = .78). Thus, polygenic risk for ADHD did not moderate the indirect effect of birth weight on ADHD symptoms through cognitive functioning across all domains assessed. Indices of moderated mediation were also not significant at the between level, suggesting that moderated mediation was similarly not observed across families.

Discussion

We evaluated biologically plausible EF and reasoning dimensions as collective and unique mediators of ADHD symptoms from both birth weight and genetic risk simultaneously in a sample of youth from multiplex families with ADHD. None of the proposed EF domains (i.e., verbal working memory, visuospatial working memory, cognitive flexibility, interference control, response inhibition, response variability) significantly mediated predictions from either birth weight or a PRS calculated from meta-analytically validated candidate genes, and there was a marginal indirect effect of birth weight on ADHD symptoms through fluid reasoning. Although hypotheses were generally disconfirmed, the findings underscore the need for more focused studies on ADHD risk processes to inform prevention efforts. In particular, whereas this study was the first to concurrently test diverse pathways from both perinatal risk and genetic risk in the same sample, future research should similarly statistically model equifinality (i.e., multiple underlying pathways) by evaluating additional biologically plausible mechanisms in ADHD etiology.

Unlike previous evidence of independent birth weight-EF associations (e.g., Burnett et al., 2015; Camerota et al., 2015) and EF-ADHD associations (Willcutt et al., 2005), EF did not mediate predictions of ADHD symptoms from birth weight in the present study. These null findings are consistent with the few prior studies that directly tested mediation, albeit with different measures of the featured EF domains. In a sample of 498 youth aged 6-17 years, response variability, but neither working memory nor response inhibition, mediated separate predictions of inattention and hyperactivity/impulsivity symptoms from birth weight (Wiggs et al., 2016). Other prior direct tests of mediation focused on non-EF domains. In particular, fluid reasoning mediated birth weight and ADHD symptoms in several diverse studies (Morgan et al.,

2018; Morgan, Loo, et al., 2016), including in a prior study from the present sample of youth from multiplex families with ADHD (i.e., Morgan, Lee, et al., 2016). Thus, the marginal indirect effect of birth weight on ADHD symptoms through fluid reasoning observed in the present multiple mediation model converges with these prior findings. Although fluid reasoning may be central to or even subsume EF facets, it is nonetheless a distinct construct and is not included in traditional models of EF (Cho et al., 2010; Conway et al., 2002; Miyake et al., 2000). Thus, to date, no studies have identified significant mediated effects through the EF constructs examined herein, with the exception of response variability. Interestingly, response variability has been conceptualized as a cognitive attribute that accounts for a substantial proportion of the variance in EF performance, rather than as an actual component of EF per se (Russell et al., 2006).

That EF domains did not statistically mediate predictions of ADHD from birth weight may reflect several factors. First, because there are numerous approaches to assessing and modeling individual EF constructs (e.g., laboratory-based vs. ecological measures, raw scores on individual tests vs. empirically derived latent constructs), we cannot rule out that the null findings for EF mediators were not affected by the specific measures selected for this study. Thus, the observed findings must be replicated using other measures of the same EF constructs. Second, non-EF facets (i.e., fluid reasoning) may be more salient to ADHD predictions from birth weight or perinatal factors specifically, whereas EF may influence ADHD through orthogonal pathways. For example, response inhibition and interference control mediated the association between having a family history of ADHD and ADHD symptoms in preschool-aged children, but there were no significant indirect effects from a composite prenatal risk factor that included birth weight (Pauli-Pott, Dalir, Mingebach, Roller, & Becker, 2013). Third, whereas the majority of mediational studies have used case-control or population-based samples, the present

study consisted of youth with high genetic load for ADHD and elevated ADHD symptoms. It is plausible, therefore, that indirect EF pathways from birth weight to ADHD may differentiate youth with vs. without ADHD rather than heterogeneity *within* ADHD youth. Thus, in addition to a continued focus on identifying non-EF mediators of birth weight and ADHD, future studies should examine complex mediation models that reflect the diverse pathways underlying ADHD but in diverse samples (e.g., population-based).

That the PRS calculated from several candidate genes did not predict indirect effects on ADHD in this study converges with accumulating research on the replicability of candidate gene approaches in psychopathology. While there is meta-analytic evidence for the hypothesized polymorphisms as susceptibility variants for ADHD (i.e., DRD4, DAT1, 5-HTTLPR), these findings are infrequently replicated (Duncan & Keller, 2011). Moreover, recent results from the Psychiatric Genomics Consortium (PGC) ADHD Subgroup identified 12 independent loci that reached genome-wide significance for ADHD among ~20,000 cases and 34,000 controls (Demontis et al., 2018), none of which included DRD4, DAT1, or 5-HTTLPR. To address these concerns, we plan to further test indirect effects from polygenic risk to ADHD symptoms through EF and reasoning in the present sample, but using a PRS calculated from genome-wide significant single nucleotide polymorphisms (SNPs). ADHD youth in the current sample (n = 539) were genotyped on the Infinium PsychArray BeadChip (PsychChip) platform, a high-density Illumina microarray that provides ~550,000 tag SNP markers and is enriched for common SNPs, small copy number variations, and rare variants in psychiatrically relevant regions. Thus, risk alleles and odds ratios identified for the 12 genome-wide significant loci in the PGC ADHD genome-wide association study (GWAS) will be used to calculate a PRS in the present sample. Specifically, the number of observed risk alleles at each genome-wide significant

locus (i.e., 0, 1, or 2) will be multiplied by its respective odds ratio observed in the PGC GWAS and summed across the set of genome-wide significant SNPs. These analyses will be underway shortly, after the completion of this dissertation.

Several additional limitations of the present study should be noted. First, whereas this study was cross-sectional, temporally ordered predictors, mediators, and outcomes are necessary to infer causal mediation (Kraemer, Stice, Kazdin, Offord, & Kupfer, 2001). Second, birth weight was assessed via maternal recall, which although highly correlated with medical record data (e.g., Yawn et al., 1998), is less accurate. Therefore, we cannot rule out the possibility that retrospective measurement limited the ability to detect indirect effects from birth weight in the present study. Third, despite the relatively large sample ($N = 646$), 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 test the complex models examined herein (e.g., moderated mediation, mediation with many correlated mediators). Thus, further evaluation of these hypotheses in larger prospective longitudinal samples is warranted.

Whereas there is an emerging literature on mechanisms underlying youth ADHD symptoms, this study is the first to simultaneously explore indirect effects from multiple risk factors in the same model. We specifically found that verbal working memory, visuospatial working memory, cognitive flexibility, interference control, response inhibition, and response variability did not mediate the associations of birth weight or polygenic risk with ADHD symptoms, although fluid reasoning marginally mediated birth weight and ADHD. Efforts to identify complex, parallel or intersecting ADHD risk processes through biologically plausible mediators, such as the mediation models tested in the current study, are necessary to develop

prevention strategies that will reduce the burden associated with this prevalent and costly condition (Sonuga-Barke & Halperin, 2010). Thus, continued examination of pathways from birth weight and genetic influences to ADHD symptoms ultimately has potential to elucidate alterable processes in the etiology of ADHD.

Table 1.1. Sample demographics and descriptive statistics ($N = 646$)

	% of sample		*M (SD), range*
Sex (female)	40.87	Age, years	10.48 (3.53), 5-19
Ethnicity:		Full Scale IQ	108.87 (15.65), 71-152
Caucasian	71.47	SES	2.63 (0.91), 1-5
African American/Black	4.81	Birth weight, ounces	119.92 (20.92), 26-202
Hispanic/Latino	8.53	Polygenic Risk Score	2.51 (1.11), 0-6
Asian	2.17	Dopaminergic Risk Score	1.86 (0.89), 0-4
Mixed	10.23	Total ADHD symptoms	11.17 (5.00), 0-18
Other	2.79	Digit Span Backwards	10.10 (3.19), 2-18
ADHD diagnosis	83.44	Spatial Span Backwards	10.55 (2.93), 1-19
Premature birth	14.99	Trails B	50.54 (26.73), 11-180.28
Gestational diabetes	2.90	Stroop Interference Score	0.65 (6.30), -.23.75-33.95
Gestational hypertension	6.98	Stop Signal Reaction Time	421.06 (163.38), 135-1253
		Reaction Time Variability	221.84 (70.72), 62.5-448
		Fluid reasoning	10.94 (3.42), 1-19

Note: ADHD = attention-deficit/hyperactivity disorder; SES = socioeconomic status assessed with the Hollingshead scale on an ordinal scale from 1 = highest to 5 = lowest; Polygenic Risk Score = score calculated from DAT1, DRD4, and 5-HTTLPR; Dopaminergic Risk Score = score calculated from DAT1 and DRD4 only

Table 1.2. Within-level direct effects from birth weight and the polygenic risk score to all mediators (i.e., *a* paths)

	Birth Weight			Polygenic Risk Score		
Mediator	*B*	*SE*	*p*	*B*	*SE*	*p*
Verbal WM	.005	.004	.17	.057	.101	.58
Visuospatial WM	.005	.004	.15	-.053	.104	.61
Cognitive flexibility	-.002	.004	.54	.067	.103	.51
Interference control	< .001	.004	.93	.107	.106	.31
Response inhibition	- .001	.003	.85	.136	.099	.17
Reaction time variability	.003	.003	.34	-.018	.094	.85
Fluid reasoning	.006	.003	.07^{+}	.153	.088	.08^{+}

$^{+}$p < .10 *p < .05

Note: WM = working memory

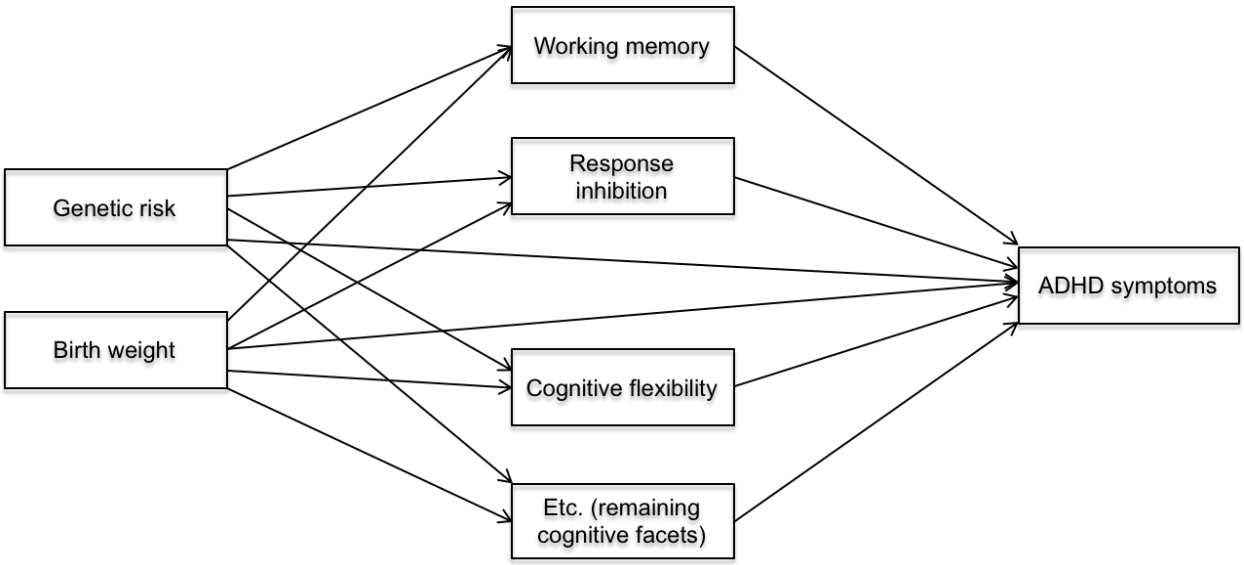
Table 1.3. Within-level direct effects from all mediators to ADHD symptoms (i.e., *b* paths)

	ADHD symptoms		
Mediator	*B*	*SE*	*p*
Verbal WM	-.079	.295	.79
Visuospatial WM	-.473	.272	.08^{+}
Cognitive flexibility	-.673	.280	.02*
Interference control	-.163	.273	.55
Response inhibition	-.200	.446	.67
Reaction time variability	.620	.470	.19
Fluid reasoning	-.672	.322	.04*

$^{+}$p < .10 *p < .05

Note: WM = working memory

Figure 1.1. Conceptual model for the study



Study 2: The Association of Polygenic Risk for Birth Weight with Cognitive Functioning and ADHD symptoms in the Philadelphia Neurodevelopmental Cohort

Meta-analytic and prospective longitudinal evidence similarly suggest that birth weight inversely predicts individual differences in attention-deficit/hyperactivity disorder (ADHD; Aarnoudse-Moens et al., 2009; Bhutta et al., 2002; Franz et al., 2018; Halmøy et al., 2012; Martel et al., 2007; Momany et al., 2017; Nigg & Breslau, 2007). In fact, low birth weight and/or premature birth confer a nearly 3-fold increase in risk for being diagnosed with ADHD (Franz et al., 2018). Birth weight is therefore among the strongest known risk factors for ADHD (Nigg & Song, 2018). Low birth weight predicts multiple neural abnormalities (i.e., hypoactivation in fronto-striato-parietal networks; reduced cortical surface area, thickness, and volume; Griffiths et al., 2013; Martinussen et al., 2005; Skranes et al., 2013; Walhovd et al., 2012) that are implicated in ADHD etiology (Cortese et al., 2012; Narr et al., 2009; Shaw et al., 2012). Thus, the association of birth weight with ADHD symptoms is not only reliable but also biologically plausible. Finally, and perhaps most importantly, 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 other well-characterized ADHD risk factors (e.g., prematurity; Groen-Blokhuis, Middeldorp, van Beijsterveldt, & Boomsma, 2011; Pettersson et al., 2015). Collectively, therefore, there is persuasive evidence that birth weight reflects a considerable causal influence in the development of ADHD symptoms.

Birth weight also reliably predicts multiple cognitive functions that are often impaired in ADHD, including facets of executive function (EF; i.e., working memory, cognitive flexibility, vigilance) and reasoning (i.e., nonverbal, verbal, and spatial reasoning; Aarnoudse-Moens et al., 2009; Bhutta et al., 2002; Burnett et al., 2015; Camerota et al., 2015; Hutchinson et al., 2013;

Lahat, Van Lieshout, Saigal, Boyle, & Schmidt, 2014; Skranes et al., 2013). In turn, deficits in EF and reasoning are implicated in ADHD etiology (Biederman et al., 2009; Doyle, Biederman, Seidman, Reske-Nielsen, & Faraone, 2005; Morgan et al., 2018; Nigg et al., 2005; Tamm & Juranek, 2012; Willcutt et al., 2005). Given that EF and reasoning deficits share the same neural abnormalities that are secondary to low birth weight and ADHD (Griffiths et al., 2013; Hobeika et al., 2016; Martinussen et al., 2005; Skranes et al., 2013; Walhovd et al., 2012), these domains have been formally evaluated as mediators of birth weight and ADHD. For example, fluid reasoning mediated predictions of ADHD symptoms from birth weight in two independent prospective longitudinal studies of children and adolescents (Morgan et al., 2018; Morgan, Loo, et al., 2016) and in a cross-sectional study of youth from multiplex families with ADHD (Morgan, Lee, et al., 2016). Thus, birth weight is a biologically plausible predictor of individual differences in EF and reasoning, and these associations may underlie the subsequent development of ADHD symptoms.

Individual differences in birth weight, reasoning, EF, and ADHD symptoms are substantially heritable (Friedman et al., 2008; Hawi et al., 2015; Jacobs, van Os, Derom, & Thiery, 2007; Lunde, Melve, Gjessing, Skjærven, & Irgens, 2007). They are also polygenic, with significant variation in each phenotype captured by additive influences of common single nucleotide polymorphisms (SNPs) across the genome. The most recent genome-wide association study (GWAS) meta-analysis of birth weight estimated a modest but statistically significant SNP-based heritability of approximately 15% (Horikoshi et al., 2016). Similarly, the most recent corresponding study for ADHD estimated a SNP-based heritability of 22% (Demontis et al., 2018). Finally, genome-wide complex trait analysis has highlighted a strong additive influence of common SNPs on reasoning and EF (h^2_{SNP} = .46 for a latent EF/reasoning factor; Robinson et al.,

2015). Because ADHD symptoms, reasoning, and EF are reliably intercorrelated and sensitive to variation in common SNPs (albeit to varying degrees), it is unsurprising that there is now growing evidence for their overlapping genetic origins in studies employing polygenic risk scores (PRSs). A PRS is calculated in a target sample by multiplying the number of risk alleles at a particular locus by its observed effect on the phenotype in a relevant discovery sample and summing across all SNPs below a certain significance threshold (Wray et al., 2014). To date, PRSs for ADHD predicted cognitive phenotypes related to EF and reasoning, including IQ, working memory, and vigilance/attention (Martin et al., 2015; Nigg et al., 2018), suggesting that associations among ADHD symptoms, EF, and reasoning likely reflect shared genetic influences. Here, we propose that consideration of polygenic risk for *birth weight* in the development of EF, reasoning, and ADHD symptoms is warranted given that birth weight (1) reliably and biologically plausibly predicts multiple EF and reasoning domains, (2) putatively causally predicts ADHD symptoms, and (3) like ADHD, EF, and reasoning, is influenced by variation in common SNPs.

Although co-twin control studies suggested that the total effect of birth weight on ADHD symptoms may be independent of genetic confounds (Groen-Blokhuis et al., 2011; Pettersson et al., 2015), this does not preclude genetic confounding of *indirect* effects from birth weight to ADHD symptoms through cognitive functioning. 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, shared genetic influences on EF, reasoning, and ADHD may confound indirect effects from birth weight to ADHD symptoms (e.g., Morgan, Loo, et al., 2016). The present study was based on the hypothesis that polygenic risk for birth weight constitutes some of the shared genetic variance underlying EF, reasoning, and ADHD.

Crucially, if a birth weight PRS directly or indirectly predicted ADHD symptoms, the corresponding effects observed from the birth weight phenotype to date may reflect shared genetic influences. This distinction has key clinical implications for prevention and intervention efforts targeting lower birth weight children, given that primarily environmentally-based vs. genetically driven pathologies may vary in their response to different clinical approaches (Moffitt, Caspi, & Rutter, 2006).

Aims

To review, although birth weight reliably predicts multiple EF and reasoning domains and is likely a causal influence on ADHD symptoms, it is unclear whether the observed predictions from birth weight reflect overlapping genetic influences. We calculated a birth weight PRS in a target sample of 7,774 youth from the Philadelphia Neurodevelopmental Cohort (PNC), a population-based deep phenotyping study of children and adolescents, using published GWAS findings from a separate discovery sample of 143,677 individuals (Horikoshi et al., 2016). To expand upon prior mediational studies of birth weight and ADHD symptoms, the present study had two aims: (1) to test the association of polygenic risk for birth weight with individual differences in EF, reasoning, and ADHD, and (2) to evaluate separable EF and reasoning domains as mediators of the birth weight PRS and ADHD symptoms. Because the PRS was calculated where higher scores directly predicted higher birth weights (measured continuously), we hypothesized that polygenic risk for birth weight would positively predict separable EF and reasoning domains and inversely predict ADHD symptoms.

Methods

Participants

The target sample consisted of 7,774 youth aged 8-22 years (*M* age = 13.80, *SD* = 3.68; 50.99% female) from the PNC, a large-scale community cohort study of clinical and neurobehavioral phenotypes conducted jointly through the Center for Applied Genomics (CAG) at Children's Hospital of Philadelphia (CHOP) and the Brain Behavior Laboratory at the University of Pennsylvania. Approximately 50,000 youth were initially recruited through CAG while receiving medical care in non-psychiatric pediatric clinics within the CHOP network; they presented with diverse medical concerns ranging from well-child visits and minor problems to chronic and potentially life-threatening health problems.

After providing written informed consent/assent at the time of their CHOP medical appointment, participants provided a blood sample and access to their Electronic Medical Records (EMRs) and agreed to be re-contacted for future studies. Of these, EMRs stratified by age, gender, and ethnicity were randomly selected for screening to obtain a quasi-epidemiologic sample of youth that are representative of the greater Philadelphia area. Participants were required to be proficient in English, ambulatory, in stable health, and capable of completing study procedures that included a cognitive battery. Exclusion criteria consisted of severe developmental delay, significant hearing loss, or limited mobility. Approximately 19,000 youth met these criteria and were invited to participate in the PNC, of which ~9,500 have completed study procedures to date and have individual-level data available through dbGaP. See Satterthwaite et al. (2016) for additional details regarding participants and recruitment. The target sample for the present study consisted of 7,774 youth from the PNC with usable genotype data following data quality control procedures (described below). Complete demographic data and descriptive statistics for the target sample are presented in Table 2.1.

Procedures

All PNC study procedures were approved by the CHOP and University of Pennsylvania Institutional Review Boards. Genotype and EMR data were already available for all youth at the start of the study. Assessments were conducted either at the University of Pennsylvania or in participants' homes. Specifically, youth and/or their parents completed a computerized structured interview (GO-ASSESS) with intensively trained Bachelor's or Master's degree-level assessors, and youth additionally completed a Computerized Neurocognitive Battery (CNB; Gur et al., 2012; Gur et al., 2010). The GO-ASSESS interview included demographic factors and an abbreviated psychiatric interview based on the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS; Kaufman et al., 1997). Prior to completing the CNB, each youth was also administered a brief standardized reading assessment from the Wide Range Achievement Test 4 (WRAT; Wilkinson & Robertson, 2006), which was used to determine ability to complete the battery and to provide an overall estimate of verbal cognitive ability. See Calkins et al. (2015), Merikangas et al. (2015), and Satterthwaite et al. (2016) for additional details. For the current study, genotype data were downloaded through dbGaP (Study Accession: phs000607.v1.p1). Phenotype data were also downloaded from dbGaP (Study Accession: phs000607.v2.p2), but from a later data release that included demographic variables not previously available in the first release.

Measures

ADHD symptoms. There is strong evidence that ADHD exists on a continuum, with ADHD cases reflecting the extreme end of this continuum (Haslam et al., 2012; Lubke et al., 2007). Supporting this, PRSs derived from ADHD cases predicted dimensional measures of ADHD in the general population (Groen-Blokhuis et al., 2014). Moreover, measured continuously, birth weight is monotonically associated with ADHD symptoms (Groen-Blokhuis

et al., 2011; Pettersson et al., 2014). Thus, ADHD symptom counts were used exclusively in the present study. ADHD symptoms were assessed with the GO-ASSESS interview developed from a modified K-SADS (Kaufman et al., 1997). The K-SADS is a semi-structured interview keyed to Diagnostic and Statistical Manual of Mental Disorders–IV (DSM-IV) criteria (American Psychiatric Association, 1994) that has been extensively validated and demonstrates excellent psychometric properties (Calkins et al., 2015; Kaufman et al., 1997). Interviews were conducted either only with the parent (for youth aged 8-10 years), separately with both parent and youth (11-17 years), or only with the youth (18-21 years). For the present study, we used parent-reported ADHD data for youth aged 8-17 and participant-reported data for youth aged 18-22.

The ADHD module of the GO-ASSESS interview specifically included six items corresponding to symptoms of inattention and three items corresponding to symptoms of hyperactivity/impulsivity, with some of the items querying more than one discrete ADHD symptom. Thus, we used a total count calculated across these nine items to reflect ADHD symptoms ($\alpha = .91$). This symptom count did not directly correspond to all 18 possible DSM-IV ADHD symptoms and was significantly zero-inflated (i.e., ~44% of youth did not exhibit any ADHD symptoms), which is an important study limitation. However, given that youth with values of 1-9 on the ADHD symptom count comprised 56% of the sample and because each discrete value was endorsed by at least ~5% of the sample (e.g., 6.40% of youth exhibited all nine ADHD symptoms), more variation in ADHD was captured relative to diagnostic status alone ($M = 2.64$, $SE = 3.08$, *range* = 0-9); see Calkins et al. (2015) for additional details regarding assessment of ADHD.

EF and reasoning. The CNB assesses a range of cognitive facets across several domains and is comprised of tasks used to examine specific brain systems during functional neuroimaging

(Gur et al., 2012; Gur et al., 2010). All tasks are extensively validated with excellent psychometric properties (Gur et al., 2012; Gur et al., 2010; Moore et al., 2015). Three separable EF domains were assessed as part of the CNB: (1) abstraction and cognitive flexibility, (2) vigilance and visual attention, and (3) working memory. Likewise, three reasoning domains were assessed: (1) nonverbal reasoning, (2) verbal reasoning, and (3) spatial reasoning. Separate measures of accuracy and speed were calculated for each of the six EF or reasoning domains. Correlations among the accuracy measures ranged from r_s = .27-.57 ($p < .001$ for all tests) and all accuracy measures were modestly and negatively correlated with ADHD symptoms (r_s = -.10-.19; $p < .001$ for all tests). Correlations among the speed measures ranged from r_s = .05-.43 ($p < .001$ for all tests), except that nonverbal reasoning speed was unrelated to vigilance/visual attention speed (r_s = .01, p = .45). Of the speed measures, only working memory speed and verbal reasoning speed were correlated with ADHD symptoms (respectively, r_s = .03, p = .01; r_s = .11, $p < .001$). To reduce the number of statistical tests in the present study, we used only the six accuracy measures as the primary cognitive outcomes due to their stronger correlations with ADHD symptoms and based on prior genetic analysis of the CNB tasks in this sample (i.e., Robinson et al., 2015). Table 2.2 presents descriptions of the specific tasks and scoring procedures for each accuracy phenotype. Also in line with prior genetic analysis of the CNB tasks in this sample (i.e., Robinson et al., 2015), youth with scores greater than four standard deviations from the mean of any EF or reasoning variable were designated as missing. Although raw scores for the EF and reasoning measures are presented in Table 2.1, their Z-scores were used in all analyses.

Additional phenotypes. Several demographic factors were also gathered as part of the GO-ASSESS interview, including youth age and sex as well as maternal education level. As

mentioned previously, a brief reading assessment from the WRAT 4 (Wilkinson & Robertson, 2006) was administered to each youth to estimate verbal cognitive ability (Calkins et al., 2015; R.C. Gur et al., 2012). As described in Merikangas et al. (2015), data on 42 medical conditions spanning 14 different organ systems and medical specialties were obtained from electronic searches of EMRs (i.e., allergy and immunology; cardiology; ear, nose, and throat; endocrine and metabolism; gastroenterology; hematology; nephrology; neurology; oncology; orthopedics; pediatrics; pulmonology and airways; surgery; urology). When adequate diagnostic information could not be obtained from electronic searches, EMRs were manually reviewed for International Classification of Diseases–Ninth Revision codes by nurses and other qualified medical staff. Discrepant information was then reconciled by physician review for approximately 5% of participants. Next, an index of the overall severity of any medical conditions was calculated for each youth: 0 = "no medical problems," 1 = "minor, no CNS impact," 2 = "moderate," 3 = "significant," and 4 = "major." Notably, youth age, sex, verbal cognitive ability, and medical condition severity as well as maternal education were all significantly correlated with ADHD symptoms and/or at least half of the proposed cognitive phenotypes. For example, maternal education was negatively correlated with ADHD symptoms and positively correlated with each of the six cognitive phenotypes (respectively, r_s = -.11, $p < .001$; r_s = .09-.26, $p < .001$ for all tests).

Genetic data. Genotype data were distributed across four Illumina arrays: HumanHap610-Quad v1, HumanHap550 v1, HumanHap550 v3, and HumanOmniExpress-12 v1. Quality control (QC) and imputation were performed offsite at the Broad Institute using the Ricopili pipeline developed by the Psychiatric Genomics Consortium (https://github.com/Nealelab/ricopili/wiki). Subjects and SNPs were included in pre-imputation

data sets based on the following QC criteria: SNP call rate > .95 (before subject removal), subject call rate > .98, autosomal heterozygosity deviation (| Fhet | < 0.2), SNP call rate > .98 (after subject removal), difference in SNP missingness between cases and controls < .02, and SNP Hardy-Weinberg equilibrium ($p < 10{-}6$ in controls or $p < 10{-}10$ in cases). After these filters were applied, genotype data for 7,774 youth were retained for imputation. Data sets were merged before imputation, with the exception of the OmniExpress data due to its significant differences from the other chips. Therefore, imputation was conducted separately in two batches. Unobserved genotypes from each batch were imputed using the IMPUTE2 package and the reference haplotypes in Phase 3 of the 1000 Genomes Project. Following imputation, 2,297,260 SNPs were available for youth who had been genotyped on HumanHap platforms (n = 6,122) and 3,889,715 SNPs were available for youth who had been genotyped on the OmniExpress platform (n = 1,652). Population stratification was assessed using principal component analysis (PCA) of a set of high-quality markers (i.e., HapMap3 SNPs, minor allele frequency > 0.05, no extreme Hardy-Weinberg deviation) that were pruned for linkage disequilibrium. Ten genotype principal components (PCs) were computed for each of the two imputation batches and used as covariates in all analyses to account for population structure.

Statistical Analysis

Birth weight PRS calculation. The most recent published GWAS meta-analysis of birth weight (Horikoshi et al., 2016; n = 143,677 individuals of European ancestry) was used as the discovery data set for computation of birth weight PRSs in the target sample. The discovery sample included only individuals of European ancestry because they comprised the vast majority of the overall trans-ancestry study (n = 143,677 out of a total 153,781 subjects) and because ancestry-specific summary statistics were not available for the other populations. The birth

weight PRS was calculated in the target sample using PRSice 2.1.2 (Euesden, Lewis, & O'Reilly, 2015) where the number of risk alleles for each SNP (0, 1, 2) was multiplied by its respective effect on birth weight in the discovery data set (β) and averaged across all SNPs below a significance threshold of $p < .005$. Birth weight was measured continuously in the discovery sample, and β values for each SNP were aligned to the birth weight raising allele (Horikoshi et al., 2016). Thus, higher scores on the birth weight PRS in the target sample corresponded to higher values of birth weight in the discovery sample. Birth weight PRSs were calculated separately for target sample youth from the two genotype imputation batches.

Hypothesis testing. We constructed regression models independently evaluating the effect of the birth weight PRS on each of the seven phenotypes (i.e., ADHD symptoms, abstraction/cognitive flexibility, vigilance/visual attention, working memory, nonverbal reasoning, verbal reasoning, and spatial reasoning). Given their zero-inflated overdispersion, we fit a general linear model specifying a zero-inflated negative binomial distribution in prediction of ADHD symptoms. Linear regression was used to predict the six cognitive phenotypes, which were transformed using a rank-based inverse normal transformation to approximate a normal distribution. All models employed standard errors calculated from 100 bootstrap simulations, which are robust to non-normal data, and controlled for child age, sex, verbal cognitive abilities, severity of co-occurring medical conditions, and maternal education level (as a proxy for child SES). Additionally, to account for population structure/ancestry, all models further controlled for the 10 genotype PCs described above. Regressions models were conducted separately for youth from the two genotype imputation batches and then meta-analyzed to determine an overall effect of the birth weight PRS on each phenotype for the entire sample of 7,774 youth. Meta-analyses employed either an inverse-weighted fixed effects model or, if significant heterogeneity was

detected, an inverse-weighted random effects model. Significance values for the meta-analyses were corrected for the number of outcomes examined. Mediation tests of the cognitive phenotypes were planned only if direct effects from the birth weight PRS had corrected $p < .05$.

Results

We first evaluated the association of the birth weight PRS with the six cognitive phenotypes, controlling for youth age, sex, medical condition severity, and verbal cognitive abilities as well as maternal education level and the 10 PCs from the genotype PCA. Results from the separate regression models for youth from the two imputation subsamples are presented in Table 2.3. Based on meta-analysis of the main effects observed in the two imputation subsamples, which provided an estimate of the overall effect in the entire target sample of 7,774 youth, the birth weight PRS positively predicted abstraction/cognitive flexibility ($B = 0.001$, $SE < 0.001$, $p < .01$). However, this effect was attenuated to marginal significance after correction for the number of outcomes examined ($p = .05$). The birth weight PRS was unrelated to the remaining cognitive phenotypes (Table 2.4).

Next, we evaluated the association of the birth weight PRS with ADHD symptoms, controlling for youth age, sex, medical condition severity, and verbal cognitive abilities as well as maternal education level and the 10 PCs from the genotype PCA. Results from the separate regression models for youth from the two imputation subsamples are again presented in Table 2.3. In the meta-analysis estimating an overall effect in the entire target sample, the birth weight PRS was unrelated to ADHD symptoms ($B < 0.001$, $SE = 0.001$, $p = .73$; Table 2.4).

Discussion

We calculated a birth weight PRS based on published GWAS findings and evaluated its association with individual differences in EF, reasoning, and ADHD in a population-based

sample of 7,774 youth from the PNC. Controlling for youth demographic and clinical factors (i.e., age, sex, medical condition severity, verbal cognitive ability, maternal education level) as well as population structure, the birth weight PRS was unrelated to all proposed phenotypes after correction for multiple tests. Although potentially underpowered and therefore preliminary, these findings suggest that common genetic variation associated with birth weight may be unrelated to EF, reasoning, and ADHD symptoms. If replicated in a sample with phenotypic birth weight data (so that the association of birth weight with cognitive functioning and ADHD symptoms can be confirmed in the same sample), these results would (1) converge with previous behavioral genetic research to suggest that predictions of ADHD symptoms from birth weight may not reflect shared genetic influences, and (2) provide evidence that phenotypic correlations of birth weight with EF and reasoning are not confounded by common genetic risk for birth weight.

Although this could not be directly tested given that phenotypic data for birth weight were unavailable in the PNC, findings from the current study are consistent with behavioral genetic evidence that birth weight predictions of ADHD symptoms are independent of genetic confounds (e.g., Groen-Blokhuis et al., 2011; Pettersson et al., 2015). For example, in a sample of over 29,000 twins, Groen-Blokhuis et al. (2011) found that lower birth weight predicted higher ADHD symptoms similarly across birth weight discordant monozygotic, dizygotic, and unrelated pairs. That is, because the lower birth weight individuals from both unrelated and monozygotic twin pairs (who are genetically identical) consistently exhibited increased ADHD symptoms compared to their higher birth weight counterparts, observed effects of birth weight on ADHD symptoms did not reflect shared genetic factors. In the present study, the birth weight PRS was unrelated to ADHD symptoms, which provides additional preliminary evidence that these two phenotypes are genetically independent and extends findings to singleton births from

the general population (although findings are limited to common genetic variation underlying birth weight and not alternative forms of genetic variation such as rare variants). Furthermore, the birth weight PRS was unrelated to all proposed EF and reasoning domains after correction for multiple tests, suggesting that potential mediation of birth weight and ADHD symptoms by these cognitive domains may not be influenced by shared genetic factors. Importantly, however, these preliminary null findings require further testing, especially in larger samples with available birth weight data.

Because there was a marginal, albeit not statistically significant, association of the birth weight PRS with abstraction/cognitive flexibility (corrected $p = .05$), it is important to note that the present analyses may have been underpowered to detect significant effects. Thus, although we interpret the birth weight PRS as being unrelated to abstraction/cognitive flexibility, given the critical need to minimize Type I error in genetic epidemiology, further testing of this association is warranted. In particular, several factors may have adversely impacted power in the present analyses. First, there was poor overlap between SNPs genotyped in the discovery and target samples, even after imputation of unobserved genotypes in the target sample. Specifically, the calculated birth weight PRS was based on only ~60% of genotypes available in the discovery data set. Second, the birth weight PRS included SNPs that were correlated with birth weight at $p < .005$ in the discovery sample, which is a stringent threshold compared to other PRS studies that employed thresholds up to $p < .50$. Although there is currently no consensus regarding the optimal significance threshold for inclusion of loci in PRSs, there is evidence that more conservative thresholds maximize predictive ability in the target sample as discovery sample sizes increase; this is because true positives become more enriched in lower *p*-value SNPs in these larger samples (Ripke et al., 2014; Wray et al., 2014). Thus, while a conservative

significance threshold was appropriate in the current study, sensitivity analyses evaluating if our observed results are consistent across PRSs calculated with a range of lower and higher *p*-value thresholds are needed to determine the optimal threshold in this specific sample (e.g., < .005, .005, .01, .05). Third, alternative approaches to account for population structure, such as limiting analyses to individuals of European ancestry, should be explored; this may be especially helpful given that the birth weight PRS was calculated using a European ancestry discovery sample. Finally, although tests of mediation were not performed in the current study given the lack of significant direct effects from the birth weight PRS to the proposed mediators, indirect effects may still emerge once power is improved.

To address these concerns, we plan to further examine associations among polygenic risk for birth weight, EF, reasoning, and ADHD symptoms in the present sample by (1) re-imputing the genetic data to increase overlap with the birth weight GWAS summary statistics, (2) incorporating PRSs calculated using multiple significance thesholds, and (3) further exploring the effect of population stratification on the association tests. These analyses are currently underway and will be completed prior to submission of this study for publication. Given that larger discovery samples are more important than larger target samples to sufficiently power PRS association analysis (Dudbridge, 2013), and because PRS associations with ADHD and cognitive functioning were observed in smaller samples than the current target sample of 7,774 youth (i.e., N = 656-6,832; Martin et al., 2015; Nigg et al., 2018), we believe power issues were primarily attributable to the factors described above rather than the size of the current target sample.

Another important limitation of the present study was that phenotypic data on birth weight were unavailable. Notably, a benefit of using a PRS approach is the ability to use a large

discovery sample to estimate genetic risk for one phenotype (e.g., birth weight) and test for association with a second phenotype (e.g., ADHD) in an independent and more deeply phenotyped sample. Although it is not a requirement that both samples have data on both phenotypes (Dudbridge, 2013; Wray et al., 2014), stronger conclusions could be drawn if the birth weight PRS was validated in the present target sample by significantly predicting birth weight. Additionally, because the present study aimed to determine if polygenic risk for birth weight confounds *indirect* effects from birth weight to ADHD symptoms, it will be helpful to confirm that birth weight indeed indirectly predicts ADHD symptoms in this sample (unfortunately, birth weight data for the PNC is not currently publicly available). Importantly, the present discovery sample was very large (N = 143,677), suggesting that estimates of the beta weights used to calculate the birth weight PRS were likely stable and accurate (Dudbridge, 2013). Nonetheless, the present study would be more informative if an additional replication sample were included to validate the calculated birth weight PRS. In addition to the follow-up analyses described above, therefore, we will also attempt to replicate the present findings from the PNC target sample in an independent replication sample with phenotypic birth weight data (e.g., the UCLA ADHD Genetics Study sample used in Study 1 or a sample ascertained by one of our collaborators).

We found that a birth weight PRS based on published GWAS findings was unrelated to EF, reasoning, and ADHD symptoms in a population-based sample of youth. Findings tentatively align with prior research suggesting that predictions of ADHD symptoms from birth weight are not attributable to shared genetic influences. Moreover, to our knowledge, this study was the first to employ a genome-wide molecular genetic approach to examine possible genetic influences on putative phenotypic correlations between birth weight and the proposed EF and

reasoning domains. If birth weight predictions of ADHD symptoms and EF/reasoning are independent of genetic confounds in both the proposed follow-up analyses and in replication studies, it will be important to characterize the mechanisms underlying lower birth weight that eventually lead to suboptimal neurodevelopment. For example, experimental evidence in non-human animals suggest that disparities in birth weight among monozygotic twins may arise from differential in utero nourishment (for review see Groen-Blokhuis et al., 2011) or even epigenetic changes that occur during gestation (Gordon et al., 2011). However, these hypotheses have not been directly tested in humans, and it is unknown if influences on birth weight in twins are similar to those for singleton births. Ultimately, identification of biologically plausible mechanisms underlying the development of cognitive dysfunction and ADHD, such as those from birth weight, will be critical to informing prevention and intervention efforts for neurodevelopmental disorders.

Table 2.1. Sample demographics and descriptive statistics (N = 7,774)

	% of sample		*M (SD), range*
Sex (female)	50.99	Medical condition severity	1.63 (1.15), 0-4
Reported Race:		Verbal cognitive ability	102.71 (16.23), 55-145
European American	60.81	Abstraction/cognitive flexibility	1.93 (0.72) 0.02-3.60
African American/Black	25.78	Vigilance/attention	87.26 (8.76), 35.56-100
Multiracial/Other	12.41	Working memory	92.64 (7.76), 33.33-100
Not reported/missing	1.00	Verbal reasoning	72.41 (20.01), 0-100
	M (SD), range	Nonverbal reasoning	50.89 (19.57), 0-100
Age, years	13.80 (3.68), 8-22	Spatial reasoning	39.52 (18.46), 0-100
Maternal education, years	14.58 (2.44), 2-20	ADHD symptoms	2.64 (3.08) 0-9

Note: Verbal cognitive ability reflects standard scores; all EF and reasoning domain values reflect percent accuracy, with the exception of abstraction/cognitive flexibility which reflects the proportion of correct responses multiplied by the number of learned rules with 1 added to the number of rules; ADHD = attention-deficit/hyperactivity disorder

Table 2.2. Measure descriptions for executive function (EF) and reasoning phenotypes

Phenotype	Measure	Measure Description	Score Calculation
Abstraction and cognitive flexibility	The Penn Conditional Exclusion Test	Subjects decide which of four objects does not belong with the other three objects based on multiple sorting rules that change across the duration of the task	Proportion of correct responses multiplied by the number of learned rules, with 1 added to the number of rules to accommodate participants who did not learn any rule
Vigilance and visual attention	Penn Continuous Performance Test	Horizontal lines in 7-segment displays appear on the screen and subjects press a button when the displays form a digit or letter	Percent accuracy calculated as the percentage of true positives and true negatives out of the total number of response opportunities across both letter and number trials
Working memory	Penn Letter N-Back Test	Subjects attend to a sequence of letters and press a button according to rules that differ across three conditions: when the letter is an "X" (i.e., 0-back), when the letter is the same as the previous letter (i.e., 1-back), and when the letter is the same as the letter before the previous letter (i.e., 2-back)	Percent accuracy from the 2-back condition, calculated as the percentage of true positives and true negatives out of the total number of response opportunities from this condition
Verbal reasoning	Penn Verbal Reasoning Test	Subjects solve a series of verbal analogy problems	Percent accuracy calculated the percentage of correct responses out of all possible items
Nonverbal reasoning	Penn Matrix Reasoning Task	Subjects solve matrix reasoning problems similar to those from the Matrix Reasoning subscale of the Wechsler Intelligence Scale for Children (Wechsler, 1991)	Percent accuracy calculated the percentage of correct responses out of all possible items
Spatial reasoning	Penn Line Orientation Test	Subjects click a button to rotate a line until it has the same angle as another line	Percent accuracy calculated the percentage of correct responses out of all possible items

Table 2.3. Birth weight coefficients from separate regressions predicting cognitive phenotypes and ADHD symptoms in each subsample

	Sample 1 birth weight PRS (n = 6,122)			Sample 2 birth weight PRS (n = 1,652)		
Phenotype	*B*	*SE*	*p*	*B*	*SE*	*p*
Abstraction/cognitive flexibility	.0011	.0004	< .01**	.0002	.0008	.77
Vigilance/visual attention	.0004	.0003	.30	.0003	.0006	.66
Working memory	.0005	.0003	.08	.0002	.0008	.83
Nonverbal reasoning	.0003	.0003	.45	.0007	.0007	.35
Verbal reasoning	-.0004	.0003	.90	.0010	.0006	.09
Spatial reasoning	-.0005	.0004	.12	.0009	.0006	.15
ADHD symptoms	-.0006	.0003	.11	.0002	.0007	.05*

*uncorrected $p < .05$ **corrected $p < .05$

Note: PRS = polygenic risk score; ADHD = attention-deficit/hyperactivity disorder

Table 2.4. Overall effects of the birth weight PRS on cognitive phenotypes and ADHD symptoms estimated via meta-analysis

	Birth weight PRS		
Phenotype	*B*	*SE*	*p*
Abstraction/cognitive flexibility	.0010	.0004	< .01*
Vigilance/visual attention	.0003	.0003	.27
Working memory	.0005	.0003	.08
Nonverbal reasoning	.0003	.0003	.28
Verbal reasoning	.0002	.0008	.81
Spatial reasoning	.0001	.0007	.89
ADHD symptoms	.0004	.0010	.73

*uncorrected $p < .05$ (corrected $p > .05$)

Note: PRS = polygenic risk score; ADHD = attention-deficit/hyperactivity disorder

Study 3: Maternal Metabolic and Pro-inflammatory Factors Prospectively Predict Child Executive Functioning: Time-Sensitive Effects Before and Across Pregnancy

Executive functioning (EF) domains are separable but related higher-order cognitive processes involved in the control of goal-directed behavior (Pennington & Ozonoff, 1996) and regulated by fronto-striato-parietal networks (e.g., Hart, Radua, Nakao, Mataix-Cols, & Rubia, 2013). Major domains of EF, which include cognitive flexibility and response inhibition (Miyake et al., 2000), reliably predict individual differences in child socioemotional, behavioral, and academic development (e.g., Clark, Prior, & Kinsella, 2002; Diamantopoulou, Rydell, Thorell, & Bohlin, 2007). Moreover, EF deficits are implicated in the etiology of multiple neurodevelopmental disorders including attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder, and schizophrenia (McGrath et al., 2015; Willcutt et al., 2005). Given the broad role of EF in child outcomes, EF may be a critical target for prevention studies to promote healthy child development. Additionally, various programs and activities (e.g., cognitive training, school-based curricula, exercise) may improve EF development in young children who are already exhibiting early deficits (Diamond, 2012; Diamond & Lee, 2011), suggesting that EF may be a modifiable risk factor. Thus, improved understanding of well-defined predictors of individual differences in EF would critically inform prevention efforts across major domains of psychopathology and psychosocial functioning.

Maternal physical health during pregnancy is crucial to offspring neurodevelopment. In particular, prenatal exposure to adverse maternal metabolic conditions is associated with broad cognitive deficits in children (e.g., lower IQ; e.g., Adane et al., 2016; Krakowiak et al., 2012; Tuovinen, Eriksson, Kajantie, & Räikkönen, 2014), including preliminary evidence that maternal gestational diabetes and hypertension specifically predict child EF (Bolanos, Matute, Ramirez-

Duenas Mde, & Zarabozo, 2015; Wade & Jenkins, 2016). For example, in a community sample of mothers and offspring recruited immediately after the birth of the child, retrospectively reported prenatal hypertension negatively predicted EF in preschool-aged children (Wade & Jenkins, 2016). Although the mechanisms underlying these associations are not fully understood, potential indirect effects though maternal hyperglycemia and inflammation or fetal hypoxia and oxidative stress, among other factors, are plausible (Adane et al., 2016; Ornoy, Reece, Pavlinkova, Kappen, & Miller, 2015; Tuovinen et al., 2014). Thus, maternal diabetes and hypertension during pregnancy are potential precursors to individual differences in child EF.

Prenatal exposure to maternal inflammation also predicts broad cognitive impairments (Jonakait, 2007; van der Burg et al., 2016) and neurodevelopmental disorders that are characterized by EF deficits such as autism and schizophrenia (Brown et al., 2014; Brown et al., 2009; Canetta et al., 2014; van der Burg et al., 2016); this includes exposure to both acute inflammation (e.g., maternal infections) and chronic, low-grade inflammation such as persistently elevated pro-inflammatory cytokine and C-reactive protein (CRP) levels associated with maternal obesity. Although maternal infections during pregnancy specifically predicted EF domains in non-human animals (see Meyer, Feldon, & Dammann, 2011 for review) and human adult offspring (Brown et al., 2009), to our knowledge, associations between maternal inflammation and EF in younger children have not yet been examined. This is surprising given the strong relation of childhood EF with both psychosocial and neurodevelopmental outcomes. Experimental evidence suggests that causal effects of prenatal inflammation on child EF are biologically plausible. For example, in non-human primates, in utero exposure to maternal pro-inflammatory response induced postnatal structural abnormalities in brain regions that modulate EF (i.e., prefrontal cortex; Short et al., 2010). Thus, given that prenatal exposure to maternal

inflammation is broadly associated with child neurodevelopment, coupled with preliminary evidence for biologically plausible associations with EF specifically, investigation of pro-inflammatory predictors of EF in children is strongly indicated.

Despite growing evidence for prenatal metabolic conditions and inflammation as precursors to child cognitive development (including EF), critical aspects of these associations require clarification. First, because gestational diabetes, hypertension, and inflammation may be intercorrelated (e.g., Hedderson & Ferrara, 2008; Qiu, Sorensen, Luthy, & Williams, 2004; Smith et al., 2005), it is unclear *which* maternal physiological factors most affect child neurodevelopment. It is also unclear if these maternal factors predict child cognitive deficits specifically or are sensitive to child cognitive deficits via shared variance with potential confounds including pre-pregnancy maternal obesity (Adane, Mishra, & Tooth, 2016; Christian & Porter, 2014; Mina et al., 2016; van der Burg et al., 2016), prenatal maternal depression (e.g., Deave, Heron, Evans, & Emond, 2008; Kozhimannil, Pereira, & Harlow, 2014), preterm birth (e.g., Aarnoudse-Moens, Weisglas-Kuperus, van Goudoever, & Oosterlaan, 2009; Sibai et al., 2000), low birth weight (e.g., Burnett et al., 2015; Camerota et al., 2015; Valero De Bernabé et al., 2004), and birth and neonatal complications (e.g., emergency cesarean sections; Scholl, Sowers, Chen, & Lenders, 2001; Wiggs et al., 2016). Second, rather than employing multiple assays of metabolic or pro-inflammatory biomarkers across pregnancy, prior studies typically relied on retrospective report or medical record review of specific maternal diagnoses, which obscures inferences about *when* during pregnancy particular fetal exposures are most detrimental. Moreover, pre-pregnancy maternal health is also associated with offspring cognitive outcomes (e.g., preconception diabetes; Adane et al., 2016; Adane et al., 2016), yet no studies have directly compared preconception vs. prenatal maternal health factors in prediction of child

cognitive functioning. Identifying potential "sensitive periods" could critically inform the timing of interventions to promote maternal health directly and indirectly improve child neurodevelopment. Thus, to meaningfully clarify the specificity of maternal metabolic conditions and inflammation to child neurodevelopment, predictive models must evaluate multiple maternal biomarkers simultaneously with stringent control of related prenatal/perinatal risk factors, and directly compare the relative influence of maternal biomarkers from preconception and across pregnancy.

Aims

To review, whereas exposure to maternal metabolic conditions and inflammation are biologically plausible risk factors for child EF deficits, their unique associations with child EF are unknown. Moreover, it is also unclear if the timing of these risk factors (i.e., before, early, or later in pregnancy) differentially affect offspring development. The current study combined intensive prospective measurement of maternal health before and during pregnancy as well as longitudinal follow-up of offspring from birth through early childhood. Metabolic and pro-inflammatory indicators were assayed before and during pregnancy, including maternal glycated hemoglobin (HbA_{1C}), CRP, and blood pressure (BP), while child EF was assessed at ages 4-6 years. To improve knowledge on the development of EF deficits from maternal metabolic conditions and inflammation, we evaluated multiple metabolic and pro-inflammatory indicators (i.e., HbA_{1C}, CRP, BP) in prediction of major domains of child EF with rigorous control of potential confounds. We also compared these factors prior to pregnancy and across multiple prenatal time points to ascertain if their associations with EF were temporally specific.

Methods

Participants

Participants were 89 children aged 4 to 6 years (*M* age = 4.67, *SD* = 0.65; 60.67% female; 48.31% Latino or Hispanic White, 29.21% non-Hispanic White, 20.22% African-American/Black, and 2.25% Multiracial) whose mothers were followed prospectively before and during pregnancy as part of the Community Child Health Network (CCHN). The CCHN is a multi-site research network funded by the Eunice Kennedy Shriver National Institutes of Child Health and Human Development to investigate disparities in maternal and child health and improve the health of families (Ramey et al., 2015). Recruitment procedures and criteria as well as maternal demographics are described in detail elsewhere (Dunkel Schetter et al., 2013; Ramey et al., 2015). Briefly, mothers were recruited across five study sites with predominantly low-income recruitment areas in Washington, DC, Baltimore, MD, Los Angeles County, CA, Lake County, IL, and eastern North Carolina immediately after the birth of an index child (i.e., the older siblings of the children included in the present study).

CCHN mothers completed up to five study visits between 6 months and 2 years after the birth of the index child (n = 2,089). At three of the study sites (i.e., North Carolina, Washington, DC, and Lake County, IL), mothers who reported they were pregnant with a subsequent child during this 2-year follow-up period (n = 416) were invited to participate in additional study visits. Three hundred and forty-three mothers consented to continued follow-up and completed at least one study visit during or shortly after the subsequent pregnancy. Next, these mothers were invited to participate with their subsequent child in a longitudinal child development study. One hundred and twenty-five children were enrolled and completed a study visit at ages 3-5 years. Of these, 89 children completed a second study visit at ages 4-6 years that included evaluation of EF (89 children have completed the second study visit as of the present analyses; data collection is ongoing). Complete demographic data and descriptive statistics for the current sample of 89

children are presented in Table 3.1. Notably, this sample differed demographically from many other studies of prenatal health and/or child development that have typically employed samples that are predominantly non-Hispanic White, highly educated, and less likely to be poor. The Institutional Review Boards of all collaborating study sites approved all study procedures.

Procedures

All study visits were conducted in participants' homes, with attempts to match interviewer ethnicity to that of the participant. The present study used maternal health data collected during three CCHN study visits: (1) prior to maternal pregnancy with the study child (i.e., preconception), (2) during approximately the second trimester of prenatal development, and (3) during approximately the third trimester of prenatal development. Perinatal data were extracted from neonatal records, and child EF data were collected at the age 4-6 year study visit. See Figure 3.1 for an outline of the data collection time points used in the present study and the key variables assessed at each of these visits.

Because mothers became pregnant with the study children at different times during the 2-year CCHN follow-up phase, each individual mother's most recent CCHN visit prior to conception of the study child was designated as the preconception visit for the current study. The mean length of time in months between the identified preconception visit and the date of study child conception was 4.82 months (*SD* = 4.44, *range* = 0-21.59). The first prenatal study visit occurred primarily during the second trimester (*M* weeks gestation = 20.17, *SD* = 4.60, *range* = 6.71- 26.57), although due to participant availability, study visits occurred during weeks 6-13 of the pregnancy for a small number of mothers (*n* = 3). The second prenatal study visit occurred largely during the third trimester (*M* weeks gestation = 32.79, *SD* = 3.35, *range* = 26.71-40.28), with three mothers completing the second prenatal study visit during weeks 26-27. Importantly,

the results of the current analyses were unchanged when data collected outside of strict, non-overlapping trimester cutoffs were excluded (results available upon request). Thus, all analyses described hereafter used all available data from the first and second prenatal visits, and the respective results are interpreted as reflecting the second and third trimesters.

Measures

Maternal metabolic and pro-inflammatory factors. Biomarkers of maternal metabolic conditions and inflammation were collected during the preconception, second trimester, and third trimester visits, and included: (1) HbA_{1C} (%) with a clinical cutoff of 5.7% reflecting pre-diabetes (American Diabetes Association, 2017); (2) high-sensitivity CRP (hsCRP, referred to hereafter as CRP; mg/L), with a pro-inflammatory state defined as > 3.0 mg/L (Pearson et al., 2003); and (3) systolic and diastolic BP (mmHg), with clinical cutoffs of 120 for systolic BP and 80 for diastolic BP reflecting prehypertension (WHO criteria; three blood pressure readings were taken during each home visit, and a mean score was calculated). HbA1c is a diagnostic indictor of diabetes that reflects long-term glucose concentrations over the prior 60-90 days, and is therefore a highly reliable marker of glycemic control (Goldstein et al., 2003). CRP is a well-characterized marker of inflammation in the body, and is the only pro-inflammatory marker with established clinical cutoffs (Pearson et al., 2003); its production in the liver is stimulated by pro-inflammatory cytokines (i.e., tumor necrosis factor, interleukin-1, interleukin-6) in response to infection, tissue damage, and other harmful stimuli. Blood pressure is a diagnostic indicator of hypertension. Although cutoffs are provided above to aide interpretation, maternal biomarkers were evaluated as continuous variables in all analyses for the current study. Maternal biomarkers were modestly to moderately correlated across the preconception, second trimester, and third trimester visits: HbA_{1C} (r_s = .37-51, $p < .01$), CRP (r_s = .34-55, $p < .05$), and BP (r_s = .45-62, $p <$

.01). Pre-pregnancy maternal body mass index (BMI) was also extracted from the preconception visit data and used as covariate in the present analyses. BMI was calculated as weight (kg) divided by height squared (meters), with BMI of 30.0 or greater reflecting obesity.

Epidemiological studies of systemic inflammation in non-pregnant individuals have typically excluded those with CRP values greater than 10 mg/L because higher values may reflect acute inflammation secondary to infection or injury (Ridker, 2003). However, based on the substantial evidence for the negative impact of both chronic low-grade and acute maternal inflammation on child neurodevelopment (e.g., Brown et al., 2014; Brown et al., 2009; Meyer et al., 2011; van der Burg et al., 2016), and because CRP levels may increase during pregnancy (Hwang, Kwon, Kim, Park, & Kim, 2007), excluding participants with CRP values greater than 10 mg/L would likely diminish meaningful variance in prediction of child EF. Therefore, we used sample-specific criteria to classify and exclude outliers, whereby CRP values greater than three standard deviations from the sample mean were excluded. This resulted in exclusion of second trimester CRP data for only one mother with a value of 24.4 mg/L, whereas all CRP values from the preconception and third trimester time points were within three standard deviations of the mean for those time points.

Maternal depression. Maternal depression was assessed at the preconception, second trimester, and third trimester visits and included as a covariate in tests of the biomarkers from each of the respective time points. Preconception maternal depression was measured with the Edinburgh Postnatal Depression Scale (Cox, Holden, & Sagovsky, 1987), a 10-item measure of depression symptomatology). Mothers rated the severity of their symptoms experienced in the past 7 days on a 4-point scale, and a total score was summed ($\alpha = .83$). At the two prenatal visits, maternal depression was assessed with the short form of the Center for Epidemiological Studies

Depression Inventory (CES-D; Santor & Coyne, 1997), a 9-item measure of depression with excellent psychometric properties. While commonly used in the general population, the CES-D has also been validated specifically in pregnant women (Marcus, Flynn, Blow, & Barry, 2005). Mothers rated the severity of their symptoms in terms of days per week on a 4-point scale, and a total score was summed (second trimester $\alpha = .80$; third trimester $\alpha = .76$).

Perinatal factors. Factors relevant to child cognitive functioning were extracted from medical records and included as covariates in analyses: birth weight (grams), gestational age (weeks), and birth or neonatal health complications (combined into a single variable coded yes/no). Examples of birth/neonatal health complications in the current sample included emergency cesarean section, jaundice, respiratory problems, and hypoplastic left heart syndrome.

Child EF. Child EF domains were assessed with the Early Childhood version of the NIH Toolbox Cognition Battery (NIHTB-CB; Gershon et al., 2013). The NIHTB-CB was developed through a large multi-site initiative to design state-of-the-art, standardized, and easily-administrated measures of cognitive functioning across the lifespan, in addition to other health domains, with funding from the NIH Blueprint for Neuroscience Research (Gershon et al., 2013). The Early Childhood version of the NIHTB-CB was specifically designed for young children aged 3-6 years, and included age-appropriate computerized measures of cognitive flexibility and inhibitory control (Zelazo et al., 2013). Cognitive flexibility, which refers to the ability to switch fluidly between two separate tasks or mental sets (Miyake et al., 2000), was assessed using the Dimensional Change Card Sort Task (DCCS). The DCCS required children to sort a series of test cards according to one dimension (e.g., color) and then according to another dimension (e.g., shape). Response inhibition, or the ability to inhibit inappropriate or automatic responses (Miyake et al., 2000), was assessed via the Flanker Inhibitory Control and Attention

Test. For the Flanker, children indicated the orientation of a centrally presented stimulus while inhibiting their attention to other stimuli that surround it (i.e., the flankers). The Early Childhood NIHTB-CB has English- and Spanish-Language versions, both of which are extensively validated and demonstrate excellent psychometric properties (Akshoomoff et al., 2014; Casaletto et al., 2015, 2016; Mungas et al., 2013; Zelazo et al., 2013).

The NIHTB-CB was administered to the study children in their primary language, English (n = 73, 82.02%) or Spanish (n = 16; 17.98%). Because DCCS and Flanker scores did not differ between English- and Spanish-speaking children in the current sample (respectively, $t(84) = -0.24$, $p = .81$; $t(84) = -0.57$, $p = .57$), EF data were collapsed across languages. As recommended by the NIHTB-CB developers, we used T-scores for each EF domain that were adjusted for child age, sex, race-ethnicity, and maternal education level (Casaletto et al., 2015, 2016). Children with DCCS and Flanker T-scores more than three standard deviations from the mean (n = 1 for both measures) were designated missing. DCCS and Flanker T-scores were moderately correlated ($r = .30$, $p < .01$).

Statistical Analysis

Missing data. All 89 children had maternal biomarker data available from at least one of the three time points (i.e., preconception, second trimester, third trimester), 66 (74%) had biomarker data at two time points, and 32 (34%) had biomarker data at all three time points. The number of children with available maternal biomarker data at each time point was as follows: preconception (n = 64; 72%), second trimester (n = 49; 57%), third trimester (n = 66; 74%). Additionally, 86 children (96%) had usable data for both of the EF domains (i.e., cognitive flexibility, response inhibition). Given the missing data associated with intensive, longitudinal follow-up, we used full information maximum likelihood (FIML) estimation to maximize sample

size for all analyses. FIML optimally remediates missing data when the amount of missingness per variable is up to 50% and data are missing at random or missing completely at random (MCAR; Schlomer, Bauman, & Card, 2010). Little's MCAR Test (Little, 1988) indicated that data were indeed MCAR in this sample ($\chi^2(359) = 364.52$, $p = .41$). Thus, all analyses described below were conducted on the full sample of 89 children using FIML estimation.

Hypothesis testing. We first constructed separate regression models predicting child cognitive flexibility (i.e., DCCS *T*-scores) as follows: (1) simultaneously evaluating preconception maternal HbA_{1C}, CRP, and BP; (2) simultaneously evaluating second trimester maternal HbA_{1C}, CRP, and BP; and (3) simultaneously evaluating third trimester maternal HbA_{1C}, CRP, and BP. Each model employed robust standard errors, which are robust to non-normal data, and controlled for the study site at which the child was assessed and the language in which the cognitive battery was administered; these variables were selected as initial covariates because data from both English- and Spanish-language versions of the DCCS were included in analyses and because DCCS scores from the Washington, DC study site were higher than those from Lake County, IL ($t(83) = -2.13$, $p = .04$). The DCCS *T*-scores were also already adjusted for child age, sex, race-ethnicity, and maternal education level. To rigorously control for potential prenatal/perinatal confounds found to associate with maternal metabolic and pro-inflammatory factors or child cognitive functioning outcomes in prior studies, the following covariates were then added to each model in a second step: maternal depression from the respective measurement time point, maternal preconception BMI, child birth weight, child gestational age, and child birth/neonatal complications. Next, for any biomarker that predicted child cognitive flexibility, we conducted further analyses to determine if the association was temporally specific. That is, we constructed an additional model that simultaneously evaluated multiple measures of that

biomarker from preconception, second trimester, and third trimester as predictors of child cognitive flexibility. The same analytic strategy was then repeated but in prediction of child response inhibition (i.e., Flanker *T*-scores).

Results

Prediction of Child Cognitive Flexibility from Maternal Biomarkers

Bivariate correlations among key study variables are presented in Table 3.2. We first evaluated whether *preconception* (i.e., $M = 4.82$ months prior to the date of conception) maternal HbA_{1C}, CRP, and BP uniquely predicted child cognitive flexibility (i.e., DCCS *T*-scores). To facilitate interpretation, standardized regression coefficient values (β) are reported after the unstandardized regression parameters values (*B* and *SE*) in this section. Covarying for study site and cognitive battery language (*T*-scores were also adjusted for child age, sex, race-ethnicity, and maternal education level), preconception maternal HbA_{1C} inversely predicted child cognitive flexibility ($B = -4.75$, $SE = 2.37$, $p = .04$, $\beta = -0.24$); neither preconception maternal CRP ($B = -0.16$, $SE = 0.35$, $p = .65$, $\beta = -0.06$) nor preconception maternal BP ($B = -0.37$, $SE = 9.25$, $p = .97$, $\beta = -0.01$) was associated with child cognitive flexibility. When the prenatal/perinatal covariates were added to the model (i.e., preconception maternal depression, preconception maternal BMI, child birth weight, child gestational age, and child birth/neonatal complications), the association between preconception maternal HbA_{1C} and child cognitive flexibility was attenuated to trend-level significance; however, the size and direction of the effect remained unchanged ($B = -4.75$, $SE = 2.68$, $p = .08$, $\beta = -0.23$; standardized regression coefficients for the fully saturated model are presented in Table 3.3). Thus, higher maternal HbA_{1C} *prior to pregnancy* uniquely predicted poorer child cognitive flexibility at ages 4-6 years, but the effect was attenuated with inclusion of all covariates. Of note, although $p > .05$ for the effect of

preconception maternal HbA_{1C} on child cognitive flexibility after rigorously controlling for all covariates, this was likely a power issue given the modest sample size ($N = 89$) and because the size and direction of the effect were almost identical to the significant effect in the model controlling for preconception CRP, BP, and demographic factors.

Second, we evaluated whether *second trimester* maternal HbA_{1C}, CRP, and BP uniquely predicted child cognitive flexibility. Covarying for study site and cognitive battery language (*T*-scores were also adjusted for child age, sex, race-ethnicity, and maternal education level), none of the second trimester biomarkers predicted child cognitive flexibility: CRP ($B = -0.09$, $SE = 0.35$, $p = .80$; $\beta = -0.04$), HbA_{1C} ($B = -4.40$, $SE = 3.33$, $p = .19$, $\beta = -0.24$), BP ($B = 0.70$, $SE = 7.92$, $p = .93$, $\beta = 0.01$). Thus, no further second trimester analyses were conducted in prediction of child cognitive flexibility.

Third, we evaluated whether *third trimester* maternal HbA_{1C}, CRP, and BP uniquely predicted child cognitive flexibility. Controlling for study site and cognitive battery language (*T*-scores were also adjusted for child age, sex, race-ethnicity, and maternal education level), third trimester maternal CRP inversely predicted child cognitive flexibility ($B = -0.67$, $SE = 0.29$, $p = .02$; $\beta = -0.29$); neither third trimester maternal HbA_{1C} ($B = -0.16$, $SE = 1.47$, $p = .91$, $\beta = -0.01$) nor third trimester maternal BP ($B = -3.51$, $SE = 6.99$, $p = .62$, $\beta = -0.06$) was associated with child cognitive flexibility. When the prenatal/perinatal covariates were added to the model (i.e., third trimester maternal depression, preconception maternal BMI, child birth weight, child gestational age, and child birth/neonatal complications), third trimester maternal CRP continued to predict child cognitive flexibility ($B = -0.70$, $SE = 0.31$, $p = .02$, $\beta = -0.31$; standardized regression coefficients for the fully saturated model are presented in Table 3.4). Thus, higher

maternal CRP during the *third trimester* of pregnancy uniquely and robustly predicted poorer child cognitive flexibility at ages 4-6 years.

Temporal Specificity of Maternal HbA_{1C} and CRP to Child Cognitive Flexibility

To further clarify that the observed association between maternal HbA_{1C} and child cognitive flexibility was temporally specific (i.e., specific to *preconception* levels of maternal HbA_{1C} only), we simultaneously evaluated preconception, second trimester, and third trimester maternal HbA_{1C} in prediction of child cognitive flexibility. Consistent with the model comparing all preconception biomarkers above, preconception maternal HbA_{1C} also inversely predicted child cognitive flexibility over and above second and third trimester maternal HbA_{1C} (B = -5.87, SE = 2.58, p = .02; β = -0.30). Consistent with the prior models testing all second trimester and third trimester biomarkers, neither second trimester HbA_{1C} (B = -2.50, SE = 4.48, p = .58, β = -0.13) nor third trimester HbA_{1C} (B = 2.04, SE = 2.51, p = .42, β = 0.14) was associated with child cognitive flexibility over and above the effect of preconception HbA_{1C}. Thus, higher maternal HbA_{1C} specifically at *preconception* predicted poorer child cognitive flexibility at ages 4-6 years.

To further clarify that the observed association between maternal CRP and child cognitive flexibility was specific to exposure during the *third trimester* only, we simultaneously evaluated preconception, second trimester, and third trimester maternal CRP in prediction of child cognitive flexibility. Consistent with the model comparing all biomarkers from the third trimester above, third trimester maternal CRP also inversely predicted child cognitive flexibility over and above preconception and second trimester maternal CRP (B = -1.24, SE = 0.47, p = .01; β = -0.56). Consistent with the prior models testing all preconception and second trimester biomarkers, neither preconception CRP (B = 0.34, SE = 0.31, p = .27, β = 0.13) nor second trimester CRP (B = 0.45, SE = 0.58, p = .44, β = 0.20) was associated with child cognitive

flexibility over and above third trimester CRP. Thus, higher maternal CRP specifically during the *third trimester* predicted poorer child cognitive flexibility at ages 4-6 years.

Prediction of Child Response Inhibition from Maternal Biomarkers

We then repeated the regression models for each time point (i.e., maternal biomarkers from preconception, second trimester, and third trimester) but in prediction of child *response inhibition* (i.e., Flanker *T*-scores). Covarying for study site and cognitive battery language (*T*-scores are also adjusted for child age, sex, and race-ethnicity, and maternal education level), maternal HbA_{1C}, CRP, and BP from all time points were unrelated to child response inhibition. Thus, no further analyses were conducted in prediction of child response inhibition.

Post Hoc Analyses

Given the specific pattern of results observed where *both* preconception maternal HbA_{1C} and third trimester maternal CRP independently predicted child cognitive flexibility, we conducted exploratory follow-up analyses to test their potential interactive effect. Controlling for study site and cognitive battery language (*T*-scores were also adjusted for child age, sex, race-ethnicity, and maternal education level), a preconception maternal HbA_{1C} x third trimester maternal CRP interaction was unrelated to child cognitive flexibility (B = -0.20, SE = 0.68, p = .77, β = -0.04).

Based on the timing of the observed associations, it is also worth considering whether preconception maternal HbA_{1C} predicts child EF indirectly through third trimester maternal CRP, especially given accumulating evidence for the role of inflammation in hyperglycemia (e.g., Qiu et al., 2004). However, the present sample (N = 89) was smaller than that required to adequately power tests of mediation using resampling methods for path coefficients of even small effect size (i.e., N = 148; Fritz & Mackinnon, 2007; Mackinnon, Lockwood, & Williams, 2004). Notably,

however, preconception HbA_{1C} and third trimester CRP were unrelated in the present study (r_s = -.24, p = .10), which is inconsistent with mediated effects.

Discussion

We evaluated multiple maternal metabolic and pro-inflammatory factors (i.e., HbA_{1C}, CRP, and BP) as unique predictors of child EF (i.e., cognitive flexibility, response inhibition) in an intensive, prospective longitudinal study of prenatal health and child development. Multiple maternal biomarkers were assayed at preconception, second trimester, and third trimester time points, allowing for temporally specific comparisons in prediction of child EF. Higher maternal HbA_{1C} at preconception, but not preconception CRP or BP, uniquely predicted poorer child cognitive flexibility at ages 4-6 years, even with stringent control of relevant demographic factors and concurrent preconception maternal CRP and BP. Effects from maternal HbA_{1C} were specific to the preconception period only, and preconception HbA_{1C} robustly predicted child cognitive flexibility over and above maternal HbA_{1C} from the second and third trimesters. Higher maternal CRP during the third trimester of pregnancy, but not third trimester HbA_{1C} and BP, also uniquely predicted poorer child cognitive flexibility, even with stringent control of demographic covariates, concurrent third trimester maternal HbA_{1C} and BP, and multiple prenatal/perinatal confounds (i.e., preconception maternal BMI, third trimester maternal depression, child birth weight, child gestational age, and child birth/neonatal complications). Effects from maternal CRP were specific to the third trimester only, and third trimester CRP robustly predicted child cognitive flexibility over and above preconception and second trimester CRP. None of the second trimester maternal biomarkers predicted child cognitive flexibility, and child response inhibition was unrelated to maternal biomarkers from all time points. These findings reflect prospective evidence that (1) exposure to maternal hyperglycemia and inflammation uniquely

predict the development of cognitive flexibility deficits in children, and (2) that these associations are dependent on the timing of the exposure before or during pregnancy.

That preconception maternal HbA_{1C}, a marker of hyperglycemia secondary to Type I or Type II diabetes, predicted child cognitive flexibility is consistent with prior evidence that preconception maternal diabetes broadly predicts offspring cognitive functioning (see Adane et al., 2016 for review). However, to our knowledge, this is the first study to observe an effect of preconception HbA_{1C} on child EF. Preconception maternal HbA_{1C} may influence embryonic neurodevelopment (and presumably, indirectly affect later EF development) via multiple biologically plausible pathways that include oxidative stress, hypoxia, apoptosis, and epigenetic modifications (see Ornoy et al., 2015 for review). For example, there is replicated evidence in non-human animals that maternal hyperglycemia alters embryonic gene expression implicated in the formation of the central nervous system and in the fetus's response to oxidative stress and hypoxia (Ornoy et al., 2015; Pavlinkova, Michael, & Kappen, 2009). Preconception maternal hyperglycemia also impedes the formation of the placenta, which provides the developing embryo and fetus with oxygen and nutrients (Leach, 2011). In turn, prenatal oxidative stress, hypoxia, and malnutrition are associated with suboptimal neurodevelopment ranging from severe brain damage to more mild cognitive impairments in both human and non-human animals (Georgieff, 2007; Golan, Lev, Hallak, Sorokin, & Huleihel, 2005; Graf, Kekatpure, & Kosofsky, 2013), and with neurodevelopmental disorders in humans (e.g., Smith, Schmidt-Kastner, McGeary, Kaczorowski, & Knopik, 2016). However, further research is needed to formally evaluate mechanisms that mediate preconception maternal HbA_{1C} and child cognitive flexibility specifically.

Although 28% of children in this sample were born to mothers who met clinical HbA1C cutoffs for prediabetes prior to pregnancy (> 5.7%), none of the mothers exceeded the clinical threshold for a diabetes diagnosis at that time (> 6.5%; American Diabetes Association, 2017). Thus, these findings suggest that even subclinical elevations in preconception HbA_{1C} may adversely affect offspring EF development. To date, meta-analytic evidence from observational studies suggests that preconception care for women with Type I or II diabetes significantly decreases maternal HbA_{1C} by the first trimester and reduces the risk of preterm delivery, congenital malformations, and offspring mortality (Wahabi, Alzeidan, Bawazeer, Alansari, & Esmaeil, 2010). If replicated, these findings suggest that efforts to expand screening and targeted delivery of interventions to women with subclinical HbA_{1C} may reduce the substantial public health burden of child EF deficits and associated neurodevelopmental conditions. Importantly, there are currently insufficient data from randomized controlled trials to fully ascertain the efficacy of preconception care for maternal diabetes with respect to mother and infant health outcomes (Tieu, Middleton, Crowther, & Shepherd, 2017). Thus, research on preconception interventions for women with diabetes remains a critical priority and may benefit from incorporation of women with subclinical HbA_{1C}.

In contrast to preconception diabetes, gestational diabetes first occurs during the second or third trimester of pregnancy and often resolves quickly after birth (American Diabetes Association, 2017). Notably, neither maternal HbA_{1C} from the second nor third trimester predicted child EF in the current study, which is consistent with one prior study in which gestational diabetes predicted child working memory, but not cognitive flexibility (Bolanos et al., 2015). However, second and third trimester HbA_{1C} in the present study likely reflected both continuations of pre-existing hyperglycemia and the emergence of hyperglycemia not previously

present, limiting comparisons with research focusing exclusively on gestational diabetes diagnoses. Comparisons with prior studies are also limited by their reliance on cross-sectional measures. Whereas we directly measured HbA_{1C} and other maternal biomarkers before and during pregnancy, a considerable strength of the current study, prior research on maternal diabetes and child cognitive functioning assessed diabetes at a single time point via retrospective maternal report or medical record confirmation of a diagnosis (Adane et al., 2016). Thus, whereas our findings suggested that preconception maternal HbA_{1C} was more salient to child EF than prenatal HbA_{1C}, larger prospective longitudinal studies are needed to prosecute predictions of child EF from gestational diabetes and HbA_{1C}.

We also found that maternal CRP specifically from the third trimester uniquely and robustly predicted child cognitive flexibility. This finding converges with a large literature implicating maternal inflammation in offspring neurodevelopment (Jonakait, 2007; van der Burg et al., 2016). However, to our knowledge, this is the first study to observe an association of maternal CRP with child EF. Based on reliable associations between maternal CRP, maternal metabolic conditions (i.e., diabetes, hypertension, obesity), and adverse birth outcomes (e.g., prematurity and delivery complications; e.g., Christian & Porter, 2014; Elovitz et al., 2011; Qiu et al., 2004; Smith et al., 2005), child EF predictions from CRP may either mediate or be mediated by these correlated factors. Notably, however, in the present study, third trimester maternal CRP *uniquely* predicted child cognitive flexibility, even with control of concurrent HbA_{1C} and BP as well as other prenatal/perinatal confounds (e.g., preconception maternal BMI, child gestational age, birth/neonatal complications). Moreover, none of these covariates significantly predicted child EF over and above third trimester CRP. Although this does not rule out mediated effects of maternal CRP from metabolic conditions or through perinatal

complications per se, if replicated, these findings may be consistent with experimental evidence in non-human animals that maternal inflammation is highly proximal to offspring neurodevelopment. Maternal pro-inflammatory factors not only alter the functioning of the placenta but also transfer to amniotic fluid and enter fetal circulation (Urakubo, Jarskog, Lieberman, & Gilmore, 2001). In turn, this can trigger a pro-inflammatory response in the fetus that is capable of permeating the blood–brain barrier (Meyer et al., 2006). Thus, maternal inflammation may rapidly influence fetal brain development through various biologically plausible mechanisms, such as inhibition of fetal neurotrophic factors (Golan et al., 2005) and neurotransmitter levels (Vuillermot, Weber, Feldon, & Meyer, 2010).

Because child cognitive flexibility was predicted specifically from third trimester maternal CRP, and not preconception or second trimester CRP, it is important to note that the prefrontal cortex continues to develop during the third trimester (Monk, Webb, & Nelson, 2001); it therefore remains susceptible to adverse prenatal environments like maternal pro-inflammatory state. For example, in rhesus monkeys, maternal infection during the third trimester elicited postnatal structural abnormalities in offspring prefrontal cortex and other brain regions relevant to EF (Short et al., 2010). The third trimester may in fact distinctively reflect a time of particular neurodevelopmental susceptibility to maternal inflammation, as exposure to maternal infection during late pregnancy, but not mid-pregnancy, induced elevations in cytokine gene expression in fetal mouse brain (Meyer et al., 2006). Collectively, therefore, the non-human animal literature suggests that the association of third trimester maternal inflammation (as reflected by elevated maternal CRP) with child cognitive flexibility observed in the present study might reflect a causal chain of events that hinders healthy development of brain regions regulating EF. However, similar to predictions from preconception maternal HbA_{1C}, further research is needed

to identify proximal mechanisms that mediate third trimester maternal inflammation and child cognitive flexibility specifically. If the third trimester further proves to be a sensitive period for maternal inflammation and offspring EF, this would inform the timing of prenatal interventions and preventive strategies to promote maternal and fetal health.

Notably, there is growing evidence for inflammation as a potential precursor to hyperglycemia (e.g., Qiu et al., 2004), although we are unaware of research suggesting effects in the opposite direction where preconception hyperglycemia predicts inflammation later in pregnancy. Although the present study did not evaluate mediation, results were inconsistent with mediated effects of preconception HbA_{1C} on child cognitive flexibility via third trimester maternal CRP. Additionally, preconception HbA_{1C} and third trimester CRP did not interact to predict child cognitive flexibility, suggesting that the effects of these risk factors are not mutually dependent. Collectively, therefore, the independent and specific predictions of child cognitive flexibility from preconception HbA_{1C} and third trimester CRP suggest possible equifinality, in which multiple distinct pathways eventuate in the same outcome. Thus, further research including formal tests of mediation is needed to clarify if pathways from preconception HbA_{1C} and third trimester CRP are convergent or independent.

Several key limitations should be noted. First, despite the use of reliable measures and an intensive, prospective longitudinal research design to maximize statistical power, the analyses were limited by the modest sample size (e.g., underpowered to perform mediation tests). Second, although response inhibition and cognitive flexibility begin to develop early in life and are definitely present at ages 4-6 years, they advance substantially across middle childhood (e.g., Best & Miller, 2010). Thus, it will be important to replicate the present findings not only in larger samples but also in prospective longitudinal studies of youth across development. For

example, predictions of child response inhibition from maternal biomarkers, although not observed in the present study, may be evident in older children once response inhibition is more fully developed. Similarly, although maternal BP at preconception and prenatally was unrelated to child cognitive flexibility here, these factors may predict later child EF outcomes. Another logical extension of the present findings is to clarify if the observed effects of maternal HbA_{1C} and CRP on child cognitive flexibility also extend to neurodevelopmental disorders that are associated with poor cognitive flexibility (e.g., ADHD).

We observed individual differences in preconception maternal HbA_{1C} and third trimester maternal CRP as both temporally-specific and unique predictors of child cognitive flexibility. To our knowledge, this study was the first to employ multiple assays of maternal metabolic and pro-inflammatory factors over time, directly compare preconception and prenatal exposures, and control for numerous potential confounds in prediction of child EF. Future studies must aim to characterize the proximal mechanisms that mediate preconception maternal HbA_{1C}, third trimester maternal CRP, and child cognitive flexibility. Identification of biologically plausible mechanisms underlying EF development will be critical to informing prevention and intervention efforts across major domains of child psychopathology and psychosocial functioning.

Table 3.1. Sample demographics and descriptive statistics ($N = 89$)

	% of sample		*M (SD), range*
Child sex (female)	60.67	Maternal education, years	12.93, (3.39), 6-20
Child race-ethnicity:		Preconception maternal BMI	30.11 (7.47), 17.65-56.22
African-American/Black	20.22	Preconception HbA_{1C}, %	5.32 (0.50), 4.10-6.10
Non-Hispanic White	29.21	2nd trimester HbA_{1C}, %	4.86 (0.54), 3.80-6.50
Latino or Hispanic White	48.31	3rd trimester HbA_{1C}, %	5.09 (0.69), 3.60-6.60
Multiracial	2.25	Preconception CRP, mg/L	4.41 (3.97), 0.20-14.70
Child language (Spanish)	17.98	2nd trimester CRP, mg/L	8.14 (4.89), 0.70-24.40
Study Site:		3rd trimester CRP, mg/L	7.08 (4.33), 0.10-20.10
North Carolina	8.99	Preconception systolic BP, mmHg	110.35 (9.60), 79-142
Washington, DC	19.10	2nd trimester systolic BP, mmHg	107.28 (10.28), 87-135
Lake County, IL	71.91	3rd trimester systolic BP, mmHg	110.96 (10.07), 89-133
Birth/neonatal complications	17.81	Preconception diastolic BP, mmHg	69.74 (8.31), 52-86
	M (SD), range	2nd trimester diastolic BP, mmHg	65.29 (8.09), 48-83
Child age, years	4.67 (0.65), 4-6	3rd trimester diastolic BP, mmHg	66.63 (8.38), 49-87
Household income, $	67,128 (63,799), 265-350,000	Preconception maternal EPDS	4.71 (4.41), 0-18

Child birth weight, grams	3262.43 (532.37), 1247-4564	2nd trimester maternal CESD	16.25 (3.97), 10-24
Child gestational age, weeks	38.83 (1.91), 28-42	3rd trimester maternal CESD	16.81 (5.44), 10-35
Cognitive Flexibility T-score	49.61 (10.70), 15-71		
Response Inhibition T-score	51.35 (9.95), 14-74		

Note: Median household income = $43,300; BMI = body mass index; HbA_{1C} = glycated hemoglobin; CRP = C-reactive protein, BP = blood pressure; EPDS = total score on the Edinburgh Postnatal Depression Scale; CESD = total score on the Center for Epidemiological Studies Depression Inventory

Table 3.2. Bivariate associations of independent variables with child executive functions

	Cognitive Flexibility	Response Inhibition
Preconception HbA_{1C}	-.12	.07
2nd trimester HbA_{1C}	-.24	-.13
3rd trimester HbA_{1C}	-.04	.10
Preconception CRP	-.05	.13
2nd trimester CRP	-.15	-.01
3rd trimester CRP	-.30**	.10
Preconception systolic BP	-.05	-.06
2nd trimester systolic BP	-.14	.02
3rd trimester systolic BP	-.17	.06
Preconception maternal EPDS	-.08	-.08
2nd trimester maternal CESD	.02	.03
3rd trimester maternal CESD	.14	-.03
Preconception maternal BMI	< .01	.08
Child birth weight	< .01	-.17
Child gestational age	.26*	-.13
Birth/neonatal complications	-.04	-.09

*$p < .05$ **$p < .01$

Note: HbA_{1C} = glycated hemoglobin; CRP = C-reactive protein, BP = blood pressure; EPDS = total score on the Edinburgh Postnatal Depression Scale; CESD = total score on the Center for Epidemiological Studies Depression Inventory; BMI = body mass index

Table 3.3. Regression model predicting child cognitive flexibility from preconception maternal HbA_{1C}, CRP, and BP

	Child Cognitive Flexibility			
Independent Variables	β	*SE*	*p*	*95% CI*
Cognitive battery language (Spanish)	.18	.12	.13	–
Study Site (North Carolina)	.11	.10	.26	–
Study Site (Washington, DC)	.35	.12	< .01**	.13, .58
Child birth weight	-.08	.16	.60	–
Child gestational age at birth	.23	.14	.09^{+}	-.04, .50
Child birth or neonatal complications	-.15	.11	.18	–
Preconception maternal BMI	.05	.20	.80	–
Preconception maternal depression	.01	.10	.95	–
Preconception maternal HbA_{1C}	-.23	.13	.08^{+}	-.49, .02
Preconception maternal BP	-.01	.16	.94	–
Preconception maternal CRP	-.01	.21	.97	–

$^{+}p < .10$ $^{*}p < .05$ $^{**}p < .01$

Note: β = standardized coefficient; reference group for Study Site = "Lake County, IL"; BMI = body mass index; HbA_{1C} = glycated hemoglobin; BP = blood pressure (systolic/diastolic); CRP = C-reactive protein

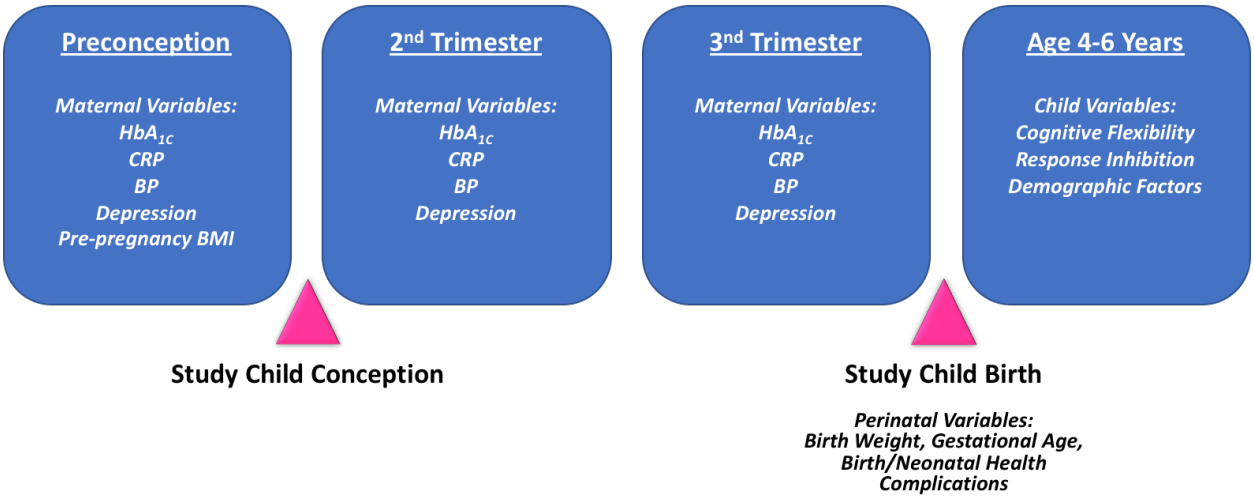
Table 3.4. Regression model predicting child cognitive flexibility from third trimester maternal HbA_{1C}, CRP, and BP

	Child Cognitive Flexibility			
Independent Variables	β	*SE*	*p*	*95% CI*
Cognitive battery language (Spanish)	.07	.11	.52	–
Study Site (North Carolina)	.11	.13	.39	–
Study Site (Washington, DC)	.35	.11	< .01**	.12, .57
Child birth weight	-.03	.13	.83	–
Child gestational age at birth	.18	.11	.10	–
Child birth or neonatal complications	-.21	.11	.05+	-.43, < .01
Preconception maternal BMI	.08	.12	.50	–
Third trimester maternal depression	.04	.11	.72	–
Third trimester maternal HbA_{1C}	-.02	.11	.88	–
Third trimester maternal BP	-.01	.12	.99	–
Third trimester maternal CRP	-.31	.13	.02*	-.56, -.05

+$p < .10$ *$p < .05$ **$p < .01$

Note: β = standardized coefficient; reference group for Study Site = "Lake Country, IL"; BMI = body mass index; HbA_{1C} = glycated hemoglobin; BP = blood pressure (systolic/diastolic); CRP = C-reactive protein

Figure 3.1. Outline of key study variables and data collection time points



Note: HbA_{1C} = glycated hemoglobin; BP = blood pressure; CRP = C-reactive protein; BMI = body mass index

Conclusions

Although the development of ADHD is sensitive to diverse genetic and prenatal/perinatal risk factors, little is known about the pathways that mediate these associations. Several cognitive domains are biologically plausible mediators, but mediation has primarily been inferred rather than formally evaluated and no study has concurrently tested multiple parallel or overlapping effects from both prenatal/perinatal and genetic influences. Relatedly, it is unclear which pregnancy factors (e.g., inflammation, blood glucose) most compromise child neurodevelopment and whether the timing of these indicators differentially affects offspring cognitive development. Thus, employing three unique yet complementary samples, this dissertation aimed to improve traction on biologically plausible risk processes underlying ADHD by refining EF predictions from prenatal influences as well as evaluating multiple EF and reasoning pathways to ADHD from well-defined genetic and prenatal/perinatal risk factors.

To review, Study 1 employed multiple mediation to test diverse EF and reasoning dimensions as collective and unique mediators of predictions of ADHD symptoms from both birth weight and replicated candidate genes in a sample of youth from multiplex families with ADHD. Extending this novel integration of birth weight and genetic influences, Study 2 used a genome-wide association approach in a large population-based sample to conduct preliminary estimations of whether birth weight, EF, reasoning, and ADHD symptoms are sensitive to shared genetic influences. Finally, Study 3 employed a prospective, longitudinal sample of prenatal health and child development to evaluate several maternal metabolic and pro-inflammatory factors simultaneously as predictors of offspring EF and compare their relative temporal influence prior to and across pregnancy. Reviewed below, several key findings emerged across studies and I consider their clinical implications as well as implications for future research.

Collectively, these studies partially support that specific prenatal/perinatal influences are unique risk factors for particular domains of child cognitive development. Whereas individual differences in preconception maternal HbA_{1C} and third trimester maternal CRP specifically and uniquely predicted child cognitive flexibility in Study 3, measures of cognitive flexibility and other EF domains (e.g., response inhibition, working memory) were unrelated to birth weight in Studies 1 and 3 as well as unrelated to a birth weight PRS calculated in Study 2 (although it is unknown if EF domains were unrelated to birth weight in Study 2). Collectively, this pattern of results suggests that birth weight may not predict ADHD through EF. Supporting this, whereas birth weight and ADHD symptoms were not significantly mediated by EF domains including working memory (Morgan, Lee, et al., 2016; Morgan, Loo, et al., 2016; Wiggs et al., 2016) and response inhibition (Wiggs et al., 2016) in several prior studies, some of these studies have shown that non-EF facets including fluid reasoning reliably mediate the association of birth weight and ADHD symptoms. Thus, future research on birth weight predictions of ADHD may benefit from an increased focus on non-EF domains.

Although these conclusions cannot be drawn from the current results, it is plausible that the future analyses planned for Studies 1 and 2 may ultimately further support fluid reasoning as a mediator of birth weight and ADHD symptoms over EF domains. To date, in Study 1, we found that fluid reasoning, and not EF domains, marginally mediated birth weight and ADHD symptoms. Next, in Study 2, polygenic risk for higher birth weight was marginally correlated with increased accuracy on the Penn Conditional Exclusion Test (PCET), a measure of abstraction and cognitive flexibility. Notably, abstraction is closely related to fluid reasoning, and these terms are sometimes even used interchangeably (e.g., Packwood, Hodgetts, & Tremblay, 2011). The PCET task consists of multiple trials that require subjects to determine

which of four displayed objects does not belong with the other three objects based on several sorting rules that change across the duration of the task. Participants are not directly informed of the sorting rules, but instead receive feedback on their responses to each trial to aide their rule learning. Interestingly, recent factor analysis of the PCET revealed that cognitive flexibility is reflected only in the amount of perseverative errors (i.e., categorizing items using the same incorrect sorting concept on consecutive trials despite negative feedback), whereas the number of correctly identified sorting rules indicates abstraction abilities (Thomas et al., 2015). Moreover, although the PCET is a highly reliable measure of abstraction, its reliable assessment of cognitive flexibility is limited to the impaired ability range (e.g., as observed in individuals with schizophrenia) because perseverative errors are rare among typically developing individuals (Thomas et al., 2015). Given that abstraction/cognitive flexibility was calculated using the proportion of correct responses on the PCET multiplied by the number of learned rules in Study 2, this phenotype likely reflected abstraction more so than cognitive flexibility. Specifically, the number of perseverative errors was indistinguishable from the overall PCET accuracy score that was available in the PNC, and this score was a direct function of the number of learned rules. Additionally, the PNC was a population-based sample consisting primarily of typically developing youth, an important consideration given that the PCET precisely measures abstraction across all ability levels (and especially among individuals with average to mildly impaired abilities) whereas it only reliably measures cognitive flexibility at the highly impaired end of the spectrum (Thomas et al., 2015). Therefore, given the overlap of abstraction with fluid reasoning, if the birth weight PRS is validated and if the marginal association of polygenic risk for birth weight with PCET performance observed in Study 2 is revealed to be significant in our planned follow-up analyses, this would further suggest the specificity of birth weight to fluid

reasoning over EF domains; it would also provide preliminary evidence of possible genetic confounding of indirect effects from birth weight to ADHD symptoms through fluid reasoning (although association analysis with the birth weight phenotype in the PNC would be necessary to substantiate these conclusions). Supporting this possibility, PCET accuracy positively predicted ADHD symptoms over and above child age, sex, verbal cognitive ability, medical condition severity, and maternal education in the Study 2 target sample (B = -.11, SE = .01, $p < .001$).

Whereas it is plausible that reasoning facets are more salient to birth weight, orthogonal risk factors or processes may similarly predict EF development. For example, Study 3 suggested that particular maternal metabolic and pro-inflammatory factors from specific time points in fetal development (i.e., preconception maternal HbA_{1C} and third trimester maternal CRP) may be especially salient to child cognitive flexibility deficits. Moreover, in light of increasing evidence that EF domains, and particularly working memory, are strong ADHD endophenotypes (Kamradt et al., 2016; Loo et al., 2008; Martin et al., 2015; Nigg et al., 2018), genetic factors likely play a key role in the development of EF deficits and subsequent ADHD. Studies employing a PRS approach to birth weight are poised to clarify if variation in common SNPs underlying particular EF domains (i.e., working memory, vigilance) and ADHD are distinct from SNP variation underlying birth weight. Thus, by highlighting particular maternal health factors for child EF and conducting preliminary work on polygenic predictors of EF, the results from this dissertation may contribute to increasingly focused studies on risk processes underlying EF and ADHD.

Beyond the additional genome-wide analyses that are currently underway for Studies 1 and 2, there are numerous points of departure from the findings outlined in this dissertation. First, although EF did not mediate predictions of ADHD symptoms in Studies 1 and 2, EF deficits are known endophenotypes for ADHD. Therefore, continued efforts to characterize

genetic variation underlying both EF and ADHD are needed, especially using multiple measures of these EF constructs to limit measurement error. These efforts should prioritize genome-wide methods over candidate gene approaches and may benefit from investigating common genetic variation underlying shared predictors of EF and ADHD beyond birth weight. Second, given that Study 3 provided the first evidence for preconception HbA_{1C} and third trimester CRP as predictors of child cognitive flexibility, future studies are needed to replicate and refine these novel associations. Replication in larger prospective longitudinal samples will be especially helpful in determining if preconception HbA_{1C} and third trimester CRP are indeed more harmful to child neurodevelopment than exposure to these factors at other time points or exposure to other prenatal/perinatal risk factors; this is because larger samples will minimize the possibility that the results observed here were impacted by insufficient power to detect associations with the other independent variables. The specificity of our findings will also be further enhanced by studies that include longitudinal follow-up of child EF later in development (i.e., late childhood and even adolescence). Moreover, randomized controlled trials of interventions to reduce maternal CRP or HbA_{1C} (e.g., behavioral and pharmacological treatments) could provide critical experimental evidence for causal effects on offspring outcomes. Third, because we only examined cognitive flexibility and response inhibition in Study 3, similar models to those employed should be examined in prediction of other cognitive domains that are relevant to neurodevelopmental disorders, including EF (e.g., working memory) and non-EF domains (e.g., fluid reasoning). Fourth, if the findings from Study 3 are replicated, future studies should aim to identify proximal mechanisms that mediate associations of preconception HbA_{1C} and third trimester CRP with child cognitive flexibility. Because there is limited evidence for these mechanisms in humans, studies that employ intensive ascertainment across multiple levels of

analysis (e.g., genetic, cellular, neural, behavioral) will be especially helpful in this regard. Finally, although evaluation of ADHD symptoms was beyond the scope of Study 3, similar analysis in this sample predicting ADHD symptoms is warranted and would complement the observed results for cognitive flexibility. In fact, we have already proposed a follow-up study in this sample examining similar models to those in Study 3 but in prediction of *T*-scores from the ADHD subscale of the CBCL.

Collectively, findings in this dissertation reinforce the importance of prioritizing prevention strategies rather than interventions attempting to remediate cognitive deficits that may underlie the onset of neurodevelopmental disorders. That maternal HbA_{1C} and CRP predicted child EF deficits underscores the need for policymakers and healthcare providers to consider the far-reaching effects of maternal health conditions, even prior to pregnancy, on offspring neurodevelopment. These findings also suggest that children exposed to maternal hyperglycemia and inflammation are critical targets for interventions to promote healthy neurodevelopment prior to the onset of cognitive deficits. Furthermore, follow-up analyses for Studies 1 and 2 may reinforce lower birth weight children as additional targets for neurodevelopmental prevention strategies. For example, given growing evidence that various programs improve cognitive development in lower birth weight preschoolers (e.g., cognitive training; Grunewaldt et al., 2013; Grunewaldt et al., 2015), indirect effects of these interventions on the subsequent development of ADHD symptoms could be investigated. Ultimately, the studies in this dissertation emphasize that to understand the development of complex behavioral outcomes such as cognitive functioning and ADHD, we must consider a full range of individual and environmental pathways that may be both discrete and intersecting. Future studies that consider different sources of prenatal/perinatal and genetic risk simultaneously across multiple levels of analysis and

developmental periods are needed to characterize the complex mechanisms underlying child neurodevelopment and inform prevention efforts.

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