

Antenatal active maternal asthma and other atopic disorders is associated with ADHD behaviors among school-aged children

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ABSTRACT

Background: Identifying modifiable risk factors for neuropsychological correlates of attention deficit hyperactivity disorder (ADHD) in early childhood can inform prevention strategies. Prenatal inflammatory states, such as maternal asthma and other atopic disorders, have been increasingly linked to enhanced risk for neurobehavioral disorders in children, with some studies suggesting sex-specific effects.

Objectives: To assess the association between maternal active asthma and/or atopy in the antenatal period and child symptoms of ADHD during mid-childhood and, given the male-bias in ADHD prevalence, to examine modifying effects of child sex.

Study design: The study sample includes 250 maternal-child pairs enrolled in the Boston-based Asthma Coalition on Community, Environment and Social Stress (ACCESS) pregnancy cohort. We defined antenatal active atopy based on maternal report of current asthma, allergic rhinitis or atopic dermatitis during and/or in the year before pregnancy. When children were approximately 6 years old, mothers completed a battery of standardized child behavior rating scales designed for evaluating symptoms of ADHD. We used multivariable quantile regression to assess the relations between maternal antenatal atopy and symptoms of ADHD among children.

Results: In adjusted models, maternal atopy was significantly associated with greater risk for ADHD behaviors, as indicated by scores on the Conners' Parent Rating Scale-Revised ADHD index ($\beta = 3.32$, 95% CI: 0.33, 6.32). In sex-stratified models this association was stronger among girls (5.96, 95% CI = 0.95, 10.96) compared to boys (-2.14 , 95% CI = -5.75 , 1.45, p -interaction = 0.01). Among girls, we observed a similar finding for the Behavior Assessment System for Children 2nd Edition Parent Rating Scale Attention Problems subscale ($\beta = 7.77$, 95% CI = 1.57, 13.97). Results from other outcome subscales were similar in magnitude and direction, however, associations did not reach statistical significance at the $p = 0.05$ level.

Conclusions: Maternal antenatal active atopy may be a risk factor for the development of ADHD-like symptoms, especially among girls.

1. Introduction

Attention-deficit hyperactivity disorder (ADHD) is one of the most common neurodevelopmental conditions, with nearly 10% of U.S. children receiving a diagnosis between 5 and 17 years of age, the majority of whom are boys (prevalence 12.3% versus 5.5% among girls) (American Psychiatric Association 2013; Willcutt, 2012). ADHD is characterized by symptoms of inattention, impulsive behavior and hyperactivity, and carries substantial lifelong consequences for both academic success and the development of healthy social relationships

(American Psychiatric Association, 2013; Biederman and Faraone, 2005; Fleming et al., 2017). Recent statistics indicate minority children receive less treatment, despite similar rates of ADHD symptoms across racial and ethnic groups, suggesting the disorder contributes to a growing disparity in children's neurobehavioral health (Coker et al., 2016; Cummings et al., 2017). While the etiology of ADHD and its neuropsychological correlates includes both genetic and environmental sources, modifiable risk factors contributing to development of the disorder have not been fully elucidated (Thapar et al., 2013); an improved understanding of these factors may help to detect higher-risk

Abbreviations: ACCESS, Asthma Coalition on Community Environment and Social Stress; ADHD, Attention Deficit Hyperactivity Disorder; BASC-2, Behavior Assessment System for Children, second edition; CPRS-R, Conners' Parent Rating Scale-Revised

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subgroups and inform prevention and intervention strategies.

Atopic disorders are the most prevalent chronic diseases in the developed world (Pawankar et al., 2012; Simpson et al., 2001), are more prevalent among ethnic minority and socioeconomically disadvantaged groups (Wright et al., 2004), and are especially problematic in urban environments, where triggers such as cockroach and mouse allergens, pollutants, and psychosocial stress are common (Matsui et al., 2008; Togias et al., 2010). While the etiology of these disorders, including asthma, atopic dermatitis and allergies, remains incompletely understood, they are collectively characterized by an exaggerated immune response to environmental triggers (Pawankar et al., 2012).

Prenatal inflammatory states have been increasingly linked to enhanced risk for early childhood neurobehavioral disorders, which may relate to altered fetal immune responses during central nervous system development (Bilbo and Schwarz, 2009; Boulanger-Bertolus et al., 2018; Estes and McAllister, 2016; Knuesel et al., 2014). For example, animal research has demonstrated experimentally-induced maternal immune activation during pregnancy can permanently alter neurodevelopmental trajectories and increase endophenotypes associated with neuropsychiatric disease and behavioral disorders (Meyer, 2014). In humans, inflammatory markers measured during pregnancy have been associated with altered patterns of structural and functional brain connectivity, as well as impaired impulse control and working memory in toddlers (Graham et al., 2018; Rasmussen et al., 2019; Rudolph et al., 2018; Spann et al., 2018). While maternal infection during pregnancy is associated with the pathogenesis of several neurodevelopmental and neuropsychiatric disorders (Knuesel et al., 2014; Bilbo and Schwarz, 2012), little research has investigated the role of common chronic diseases linked to immune activation in relation to behaviors characteristic of ADHD.

We extend this research by investigating prospective associations between active maternal asthma and other atopic disorders during the antenatal period and symptoms of ADHD among school aged children. We hypothesize children born to mothers with active atopy during the antenatal period will exhibit more problem behaviors associated with ADHD.

2. Methods

2.1. Study sample

The study sample is comprised of English- and Spanish-speaking maternal-child pairs enrolled in the Asthma Coalition on Community, Environment and Social Stress (ACCESS) birth cohort, which recruited pregnant women and their unborn children from prenatal clinics in Boston, MA between 2002 and 2010 (Wright et al., 2008). This analysis was restricted to 295 children who completed neurodevelopmental testing, which was conducted on a subsample of participants at approximately 6 years of age. We additionally excluded participants with missing maternal atopy ($n = 33$) or covariate ($n = 1$) data and 11 siblings, resulting in a final analytic sample of 250 mother-child pairs. Study procedures were approved by the human studies committees at the Brigham & Women's Hospital and Boston Medical Center. Written consent was obtained from mothers and assent was additionally obtained for children ≥ 7 years old.

2.2. Maternal atopy in the antenatal period

Women completed a structured, in-person interview during pregnancy (93% at mean $\pm$ standard deviation (sd): 27.0 ± 8.3 weeks gestation) or within approximately 4 months of delivery (7% at 18.7 ± 14.8 weeks following birth). During this interview information was ascertained on lifetime history of asthma and other atopic disorders, as well as recent symptoms of or medication use for these disorders, supporting active disease during or proximate to pregnancy (hereafter denoted antenatal). Specifically, we defined active maternal

asthma in the year before the prenatal interview based on maternal self-report of an asthma diagnosis by a health care professional and 1) symptoms of asthma (wheezing, shortness of breath, cough, chest tightness, waking up at night with asthma) at least once per month in the previous year, or 2) use of medication for asthma within the previous year. We created a composite indicator of maternal active atopy in the antenatal period defined as: 1) active asthma as described above, and/or 2) self-reported atopic dermatitis (eczema) with ongoing symptoms during pregnancy, and/or 3) self-reported doctor-diagnosed allergic rhinitis (hay fever) with ongoing symptoms during pregnancy.

2.3. Child behavioral evaluation

When children were 6.5 ± 1.0 years old, mothers completed two widely-used standardized measures for evaluating symptom correlates of ADHD and related problem behaviors: the Connors' Parent Rating Scales-Revised (CPRS-R) and the Behavior Assessment System for Children, Second Edition Parent Rating Scale (BASC-2) (Conners' et al., 1997; Reynolds and Kamphaus, 2004). The CPRS-R is comprised of 80 items that cluster into 13 scales, including an ADHD index, DSM-IV Inattentive subscale, DSM-IV Hyperactive-Impulsive subscale, and DSM-IV Total subscale, which were used in these analyses. The ADHD index provides the best overall indicator of children at risk for an ADHD diagnosis, whereas the two symptom subscales help differentiate between the predominant subtypes of ADHD (inattentive versus hyperactive-impulsive). The DSM-IV Total score reflects symptoms of combined inattention and hyperactive-impulsive type ADHD and is aligned with the DSM-IV diagnostic criteria for ADHD. The CPRS-R scales are validated for use in Spanish-speaking populations and have acceptable internal consistency ($\alpha = 0.83$ – 0.96) and test-retest reliability ($r = 0.67$ – 0.85) (Conners' et al., 1997).

The 160-item BASC-2 is a comprehensive measure for evaluating adaptive and problem behaviors in community and home settings (Reynolds and Kamphaus, 2004). The parent report version yields scores on 14 primary scales, including Attention Problems and Hyperactivity scales, which measure the core symptoms of ADHD and reflect a child's ability to sustain attention, capacity for self-control and frequency of impulsive behaviors. Like the CPRS-R, these scales are validated for use by Spanish speakers and demonstrate acceptable internal consistency ($\alpha = 0.85$), test-retest reliability ($r = 0.85$ – 0.86) and inter-rater reliability between different parents or caregivers ($r = 0.73$ – 0.75) (Reynolds and Kamphaus, 2004).

In order to compare across subscales, we calculated t-scores by standardizing raw scores by age (BASC-2) or age and sex (CPRS-R) against normative samples of children from a range of socioeconomic, racial and geographic backgrounds as outlined in the administrative manuals (Conners' et al., 1997; Reynolds and Kamphaus, 2004). T-scores derived from each instrument are designed to have a mean of 50 and standard deviation of 10, with higher scores indicating more problem behaviors across subtests.

2.4. Covariates

Information about mother-child sociodemographics (race/ethnicity, maternal education, maternal and child age, child sex), and life-style factors (cigarette smoking and second hand smoke exposure, negative life events) was collected using structured questionnaires. Children's early life wheeze and asthma status was ascertained by asking mothers whether her child experienced "wheezing or whistling in the chest" or had been diagnosed with asthma by a healthcare professional; these questions were asked approximately every three months between delivery and 24 months and every 6 months between 24 months and 36 months (Chiu et al., 2014). We classified mothers as prenatal smokers if they self-reported ever smoking during pregnancy, as indicated by responses to questionnaires administered at enrollment and during the third trimester. We defined exposure to second hand

smoke based on maternal report of exposure to tobacco smoke for one hour or more per week during pregnancy. Prenatal stress was assessed using the Crisis in Family Systems-Revised survey (CRISYS-R), which asks mothers to endorse life events experienced during the previous six months across 11 domains (e.g. financial hardship, violence, discrimination) as positive, negative or neutral (Shalowitz et al., 1998). The CRISYS-R was administered in mid- to late pregnancy and has been validated for use among Spanish speakers (Berry et al., 2006). We created a negative life event (NLE) domain score by summing the number of domains for which the mother endorsed at least one life event as negative, resulting in a possible score from 0 to 11 with higher values indicating greater stress.

2.5. Statistical analyses

We used multivariable quantile regression to evaluate associations between antenatal active maternal atopy and children's behavior. Quantile regression relaxes the assumptions of ordinary least square regression (e.g. normality of residuals), reduces the influence of outlying points, and is appropriate for outcomes that follow a skewed distribution (Beyerlein, 2014; Koenker and Bassett, 1978). We analyzed t-scores from four CPRS-R subscales (ADHD index, Inattention, Hyperactivity, Total) and two BASC-2 subscales (Attention Problems, Hyperactivity) in separate models. We modeled behavioral data at the 50th percentile, which roughly corresponds to linear regression at the mean.

We *a priori* adjusted models for several sociodemographic variables, including child exact age at neurobehavioral testing, maternal age at delivery, race/ethnicity, and maternal education. We additionally controlled for maternal prenatal NLEs domain score, which was significantly associated with both maternal antenatal atopy (odds ratio (OR): 1.21, 95% CI: 1.02, 1.45) and child behavior (e.g. CPRS-R ADHD index: β from quantile regression at 50th percentile: 1.0, 95%: 0.18, 1.82) in bivariate models and changed effect estimates between maternal atopy and behavior by > 10% when included as a covariate. While it is plausible that mothers with asthma or another atopic disorder would be less likely to smoke due to their symptoms, in our sample mothers with these diagnoses were more likely to smoke during pregnancy (any atopy OR: 3.10, 95% CI: 1.31, 7.28; asthma OR: 2.47, 95% CI: 1.00, 7.33), suggesting smoking may be an ancestor of atopic disorder rather than a consequence of it (i.e. abstinence due to symptom exacerbation from smoking). Based on this finding, in addition to results from several large studies indicating an association between smoking and asthma (Enriquez et al., 2007; Kurinczuk et al., 1999; Tata et al., 2007), we treated prenatal exposure to cigarette smoke as a confounder rather than a mediator. In contrast, we conceptualized preterm birth, birthweight adjusted for gestational age, and child early-life asthma as potential mediators based on published research demonstrating these factors are both consequences of maternal atopic disease (Mendola et al., 2013; Murphy et al., 2011; Vaezi et al., 2017) and risk factors for child ADHD (Coghill et al., 2011; Grizenko et al., 2015; Halmoy et al., 2012; Henriksen et al., 2015; Silva et al., 2014; Yuksel et al., 2008). Because we are interested in the total effect of maternal atopic disease on child ADHD symptoms we did not adjust for these variables. Given the sex-bias associated with ADHD we investigated potential effect modification by child sex using interaction terms and stratified analyses.

In secondary analyses, we used multivariable logistic regression to evaluate associations between active antenatal maternal atopy and behavioral rating scale scores dichotomized at the threshold for clinically significant risk, as defined by the CPRS-R (t-scores > 65) and BASC-2 (t-score > 70) administrative manuals.

3. Results

Table 1 presents characteristics of the study sample.

Table 1

Characteristics of ACCESS maternal-child pairs included in analyses (n = 250).

	Mean $\pm$ SD or N (%)
Race/ethnicity	
White	20 (8)
African American	72 (29)
Latino/Hispanic	148 (59)
Other	10 (4)
High school education or less	171 (68)
Age at delivery (years)	27.4 $\pm$ 5.6
Negative life events (NLEs) domain score ^a	2.5 $\pm$ 2.0
Exposure to cigarette smoke during pregnancy ^b	73 (29)
Child sex: boy	139 (56)
Maternal antenatal asthma and/or atopy ^c	52 (21)
Allergic rhinitis	9 (4)
Atopic dermatitis	20 (8)
Asthma	36 (14)
Child age at neurobehavioral testing	6.5 $\pm$ 1.0
CPRS-R t-scores ^d (median $\pm$ IQR)	
ADHD index	49.0 $\pm$ 13.0
DSM-IV Inattentive	48.0 $\pm$ 10.0
DSM-IV Hyperactive-Impulsive	51.0 $\pm$ 12.0
DSM-IV Total	49.0 $\pm$ 12.0
BASC-2 t-scores ^c (median $\pm$ IQR)	
Attention Problems	49.5 $\pm$ 18.0
Hyperactivity	47.0 $\pm$ 13.0

^a Assessed using the Crisis in Family Systems-Revised survey, possible range: 0–11.

^b Maternal active smoking or self-reported exposure to second hand smoke for ≥ 1 h per week during pregnancy.

^c Defined as: 1) symptoms of and/or medication use for asthma, and/or 2) symptoms of atopic dermatitis, and/or 3) doctor diagnosed allergic rhinitis during the antenatal period.

^d t-scores are standardized to have a mean $\pm$ sd of 50 $\pm$ 10.

The majority of mothers were African American (28%) or Hispanic (59%). At the time of delivery, more than two thirds (68%) of mothers had only a high school education or less and 29% either smoked or reported exposure to cigarette smoke for one hour per week or more during pregnancy. One third (34%) of mothers included in the analysis were ever diagnosed with an atopic disease, with 21% reporting active symptoms during the antenatal period. Participants with postnatal follow-up data that were excluded from the analysis (n = 599), which was largely due to missing neurobehavioral data, did not significantly differ from those included on maternal atopic status or any covariate of interest.

T-scores for the CPRS-R and BASC-2 assessments are provided in Table 1. Scores were right skewed across all subscales examined with median values ranging from 47 to 51. Approximately 10% of children had CPRS-R scores above the threshold for clinically significant risk (ADHD index: 10%, DSM-IV Inattentive: 10%, DSM-IV Hyperactive-Impulsive: 12%, DSM-IV Total: 11%). On the BASC-2, which uses a higher cut-off (t-score of 70 versus 65) to screen for clinical risk, only 2% of children met the criteria for the Attention Problems and Hyperactivity scales. Scores were moderately to highly correlated between subscales designed to measure ADHD subtypes (CPRS-R Inattentive vs. BASC-2 Attention Problems: $\rho = 0.65$, $p < 0.0001$; CPRS-R DSM-IV Hyperactive-Impulsive vs. BASC-2 Hyperactive: $\rho = 0.71$, $p < 0.0001$, see Supplemental Table 1 for correlation coefficients for all comparisons).

As expected given that the CPRS-R is sex-standardized, we did not detect significant t-score differences between boys and girls. On the BASC-2, which is age, but not sex-standardized, median Hyperactivity and Attention Problem scores were slightly higher among boys (48 and 50, respectively) compared to girls (47 and 49, respectively); however, these differences were not statistically significant.

As illustrated by Fig. 1, results from quantile regression at the 50th percentile suggest maternal active antenatal atopy is associated with more ADHD-related behaviors among children, as indicated by higher

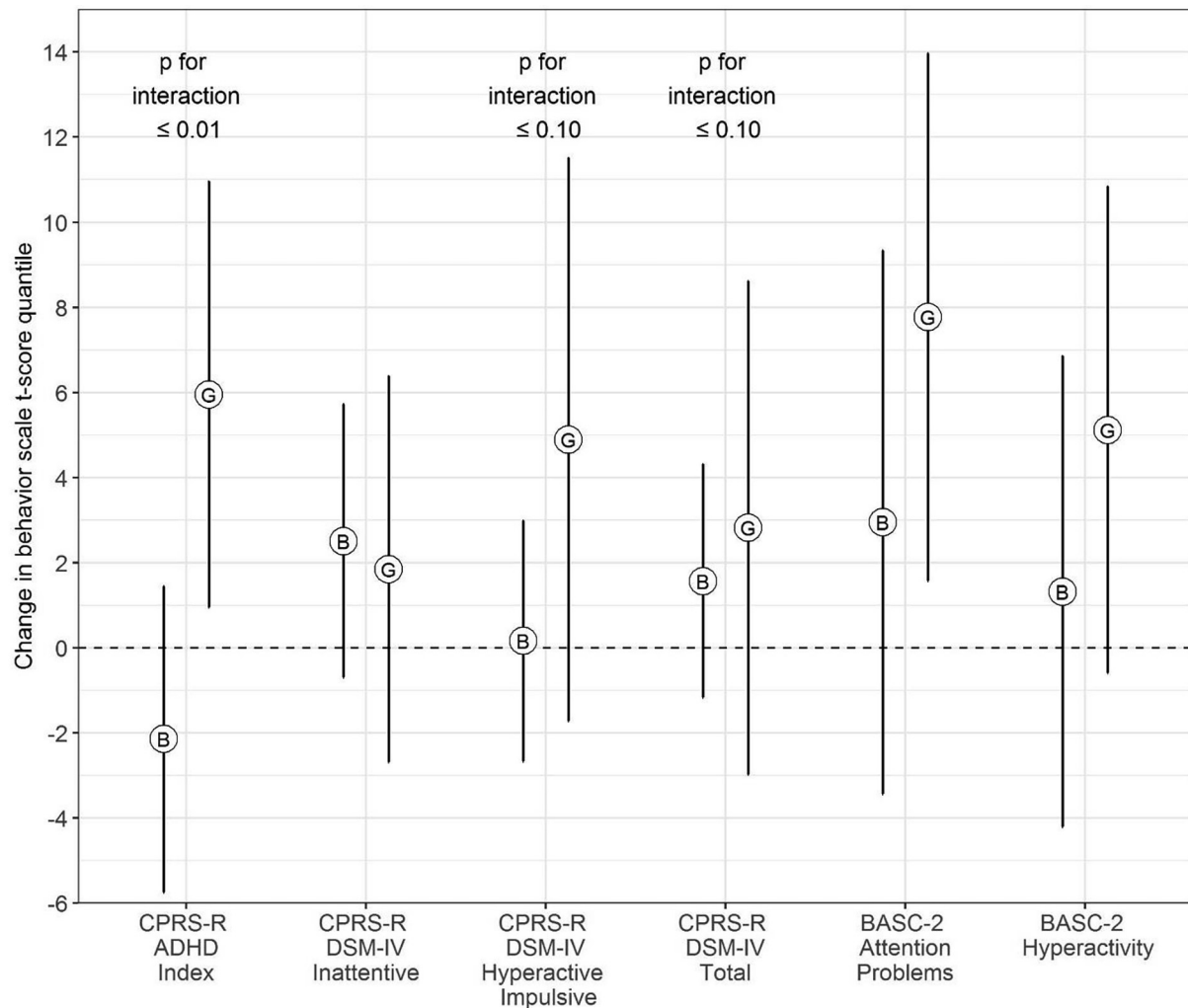


Fig. 1. Associations between maternal atopy during or within the year before pregnancy and symptoms of ADHD among school-aged girls and boys ($n = 250$). A positive change indicates more problem behaviors. B = boys, G = girls. Associations modeled using quantile regression at the median outcome percentile. Circles represent the change in behavior scale t-score quantile among children born to mothers with versus without active antenatal asthma and/or other atopic disorders. All models adjusted for: child age at neurodevelopmental testing, maternal age at delivery, maternal race/ethnicity, maternal education, prenatal exposure to cigarette smoke and negative life event domain score.

scores across CPRS-R and BASC-2 subscales. This association reached statistical significance at the $p = 0.05$ level for the CPRS-R ADHD index and also significantly varied by sex (girls: $\beta = 5.96$, 95% CI = 0.95, 10.96; boys: -2.14 , 95% CI = -5.75 , 1.45, p -interaction: 0.01).

Girls born to mothers with antenatal atopy also fell into significantly higher BASC-2 Attention Problem quantiles; however, this finding did not significantly vary by sex at the p -value ≤ 1.0 level (girls: $\beta = 7.77$, 95% CI = 1.57, 13.97). In unadjusted models and sociodemographic-only adjusted models subset on girls, associations were generally in the same direction and similar or stronger across subscales except for the BASC-2 Attention Problems scale, for which it was attenuated. Among boys, results across unadjusted and adjusted models did not substantially vary and did not reach statistical significance (Supplemental Material Table 2a–c).

Across behavioral rating scale subtests, the odds of scoring above the threshold for clinically significant risk were consistently higher among children born to mothers with versus without active antenatal atopy (range of adjusted odds ratios (aORs) across subtests: 1.25–2.76); however, these associations did not reach statistical significance (see Table 2 and Supplemental Material Fig. 1).

4. Discussion

We used multivariable quantile regression to prospectively assess the relation between maternal antenatal active asthma, atopic dermatitis and/or allergic rhinitis and ADHD-related behaviors among maternal-child pairs in a lower-income, ethnically mixed urban pregnancy cohort in the northeastern United States. We found girls born to mothers with an active atopic disorder during the antenatal period displayed significantly more problem behaviors associated with ADHD compared to girls born to mothers without active atopy; we did not observe significant associations among boys. We additionally found that across behavioral rating scale subtests, a higher proportion of children born to mothers with versus without active antenatal atopy scored above the threshold used for screening clinically significant risk. This suggests that, at the population level, the upward shift (more problem behaviors) in behavioral rating scale scores attributable to active maternal atopy before and/or during pregnancy may have substantial consequences for children already scoring in the mildly atypical range, which may be especially consequential for minority children in the United States, who have been shown to receive poorer ADHD care quality and treatment continuity compared to white children (Coker et al., 2016; Cummings et al., 2017).

Table 2

Percent of children with t-scores in the clinically significant range, as defined by the CPRS-R (t-score > 65) and BASC-2 (t-score > 70) administrative manuals, stratified by maternal active atopy during the antenatal period (n = 250).

		No atopy (79%)	Yes atopy (21%)	aOR (95% CI)
CPRS-R	ADHD Index	9.1	11.5	1.29 (0.46, 3.66)
	DSM-IV Inattentive	9.6	11.5	1.25 (0.44, 3.57)
	DSM-IV Hyperactive-Impulsive	10.6	17.3	1.68 (0.68, 4.20)
	DSM-IV Total	9.6	15.4	1.64 (0.63, 4.28)
BASC-2	Hyperactivity	2.0	3.8	2.76 (0.41, 18.32)
	Attention Problems	1.5	3.8	2.40 (0.25, 23.26)

Adjusted for child age at neurodevelopmental testing, maternal age at delivery, maternal race/ethnicity, maternal education, prenatal exposure to cigarette smoke and negative life event domain score.

Multiple lines of evidence support maternal immune activation as a putative mechanism underlying these findings. Asthma and atopic disorders are characterized by pro-inflammatory states, which have been shown to trigger an inflammatory response in the placenta and may activate microglia, resident immune cells of the brain, in the fetal central nervous system (Bilbo and Schwarz, 2012; Bilbo et al., 2018). Fetal microglia play a critical role in neurodevelopmental processes, including axon guidance, synaptic pruning and the removal of apoptotic cells (Bilimoria and Stevens, 2015; Paolicelli et al., 2011). Activated microglia release pro-inflammatory cytokines and other proteins, which can be toxic to neurons at high levels (Deverman and Patterson, 2009; Nakanishi, 2003; Urakubo et al., 2001) and have the potential to disrupt brain development during sensitive windows, leading to increased risk for neurobehavioral and cognitive disorders (Bilbo and Schwarz, 2009; Garay and McAllister 2010). For example, in murine and non-human primate models, animals exposed to maternal immune activation during gestation present with endophenotypes that mirror human neurodevelopmental disorders, including autism and schizophrenia (Bauman et al., 2014; Weir et al., 2015). In observational human studies, decades of research have linked infection arising from various insults during pregnancy with increased risk of these disorders (Brown, 2012; Miller et al., 2013). Fewer mechanistic and clinical studies have investigated associations between antenatal pro-inflammatory states and ADHD-related behaviors. In the only human study to measure early life inflammatory markers in relation to ADHD, twins with higher ADHD symptom scores at approximately age 9 years had significantly higher transplacentally acquired *Pneumococcus* polysaccharide14 (PnPs14) antibody levels in blood spots taken 5 days after birth compared to his/her same-sex twin pair (Bilenberg et al., 2011). A similar finding with *Cytomegalovirus* (CMV) antibody titer levels was detected among girls only, but no associations were detected for several other infectious agents (Bilenberg et al., 2011).

Our finding that girls may be more vulnerable to maternal antenatal atopy during fetal development is supported by evidence of fetal-sex specific changes in the maternal immune milieu during pregnancy (Enninga et al., 2015; Taylor et al., 2018). Research has found asthmatic women carrying a female, but not male, fetus have a higher risk of asthma flares (Clifton, 2006), as well as upregulation of placental inflammatory and allergic mediators (Scott et al., 2009). Previous research also suggests females born to mothers with asthma-related immune activation may be at greater risk for poor fetal growth and low birthweight, potentially due to sex-specific immune influences on placental cortisol metabolism (Murphy et al., 2003). In turn, low birthweight is a risk factor for adverse neurobehavioral development and may partially explain our finding of a greater association between antenatal asthma and ADHD symptoms among girls. Recent research from a cohort of 3749 maternal-child pairs in Brazil found girls born small for gestational age presented with attention difficulties at 4 years; corresponding findings were not detected among boys (Murray et al., 2015). Alternatively, given the higher prevalence of ADHD among boys,

it is plausible their enhanced susceptibility to other risk factors may attenuate the additional risk conferred by maternal active atopy during the antenatal period.

Our findings are also supported by results from several large-scale, population-based cohorts linking maternal immune-related disorders and infectious states with increased risk of ADHD-like behaviors in children. In the largest study, which used national registry data from 2.3 million Norwegians, researchers found maternal diagnosis (ever) with asthma and several other immune-related diseases was significantly associated with a higher odds of ADHD among children (asthma aOR: 1.5, 95% CI: 1.4–1.6; rheumatoid arthritis aOR: 1.7, 95% CI: 1.5–1.9; hypothyroidism: aOR 1.2, 95% CI: 1.1–1.4; type 1 diabetes aOR: 1.6, 95% CI: 1.3–2.0; multiple sclerosis aOR: 1.8, 95% CI: 1.2–2.5) (Instanes et al., 2017). The authors did not detect statistically significant interactions with child sex; however, across the diseases studied associations were consistently stronger among girls. Similarly, the Generation R cohort of 3139 Dutch families found elevated maternal thyroid autoantibody titers during pregnancy were associated with a significantly higher risk of attention deficit and hyperactivity problem behaviors even after adjusting for maternal thyroid parameters (aOR: 1.56, 95% CI: 1.14–2.14) (Ghassabian et al., 2012). Likewise, using a registry-based case-control study design, researchers found 12,991 Australian children diagnosed with and prescribed medication for ADHD were significantly more likely (aOR: 1.37, 95% CI: 1.21–1.55) to be born to mothers who experienced at least one urinary tract infection during pregnancy compared 30,071 control children (Silva et al., 2014). Finally, among 84,721 United States children enrolled in Medicaid, researchers found maternal genitourinary infection during pregnancy was significantly associated with increased odds of ADHD (aOR: 1.29, 95% CI: 1.23–1.35) (Mann and McDermott, 2011). Despite variation in the diseases and infections investigated, these studies, in concert with our findings, collectively support an association between maternal immune activation during pregnancy and child symptoms of ADHD.

In the present analysis we did not adjust models for potential mediating variables, but rather acknowledge some of the effect we observe may be acting through intermediate pathways. Specifically, we did not adjust for child early life asthma, which has been shown to be comorbid with ADHD and may share underlying etiologies (Grizenko et al., 2015; Fasmer et al., 2011; Schmitt et al., 2010). For example, microglia that colonize the fetal brain during early prenatal development self-renew across the lifespan without contribution from peripheral hematopoietic stem cells (Ginhoux et al., 2013). This suggests inflammation-triggered activation of immature microglia during prenatal development may not only contribute to disrupted brain development, but could also program these cells and their progeny to be more reactive to future immune challenges. Likewise, we did not adjust for preterm birth or small size for gestational age, which have been previously associated with maternal asthma and other atopic disorders (Mendola et al., 2013; Murphy et al., 2011; Murphy, 2006) and are

established risk factors for adverse neurobehavioral outcomes, including ADHD phenotypes (Coghill et al., 2011; Halmoy et al., 2012; Henriksen et al., 2015; Silva et al., 2014). In contrast, we did adjust models for exposure to cigarette smoke during pregnancy, which is also an established risk factor for ADHD and related problem behaviors (Linnet et al., 2003), and has been linked to reduced corticosteroid response (Tomlinson, 2005) and poorer symptom control among asthmatics (Chaudhuri et al., 2008; Eisner and Iribarren, 2007; Siroux et al., 2000), including during pregnancy (Murphy et al., 2010), which may result in an enhanced inflammatory milieu (Chen and Stress, 2007). We also adjusted models for maternal negative life events as stress has been associated with asthma exacerbations across the lifecourse, including during pregnancy (Brunst et al., 2017; Sandberg et al., 2004). Less research has investigated associations between stress and ADHD; however, a large, prospective cohort of 2140 mother–child pairs found children born to mothers who experienced a major stressful event during pregnancy or reported a high level of perceived stress were significantly more likely to receive an ADHD diagnosis (Okano et al., 2018). Additionally, research has shown that children with ADHD have lower cortisol levels and maladaptive cortisol responses to acute stress exposure (Corominas et al., 2012; Pauli-Pott et al., 2017). While the use of topical steroids during pregnancy has not been linked to an increased risk of adverse perinatal outcomes, given these preliminary findings, research investigating prenatal exposure to these medications in relation to stress-response programming and related adverse neurobehavioral development, such as ADHD, warrants further study (Chi et al., 2013; Chi and Wang, 2015).

This is the first study to examine the association between antenatal atopy and ADHD symptoms in a lower-income, ethnically mixed sample at higher risk for both asthma, atopy and untreated ADHD symptoms. In addition to rich covariate data, our prospective study design allowed us to evaluate maternal symptoms during the vulnerable prenatal period without relying on maternal recall across a multi-year time frame. Similarly, despite our relatively small sample size for examining sex-specific effects, we observed a consistent pattern whereby associations between antenatal active asthma and/or other atopic disorders and adverse neurobehavioral outcomes were strongest among girls. Unfortunately, we were unable to examine interactions with other potential modifying factors or confounding variables, such as maternal body mass index (BMI), which previous research has linked with both an increased risk for maternal asthma (Baffi et al., 2015) and child ADHD diagnosis (Andersen et al., 2018). While the majority of children in our sample (73%) were younger than the average age of ADHD diagnosis in the United States (7 years), results from other prospective studies demonstrate early childhood scores on standardized neurobehavioral assessments predict persistent problem behaviors and more definitive characterization of ADHD during middle to late childhood (von Stauffenberg and Campbell, 2007). Unfortunately, we did not collect information on paternal asthma or atopic disorders; however, we do not anticipate paternal status to directly impact the intrauterine inflammatory environment, which we hypothesize underlies the associations described here. Additionally, it is possible for exposure misclassification if mothers did not accurately report atopy symptoms or were unaware of sub-clinical disease. Future research that is able to better characterize atopy (e.g. by review of medical records and/or measurement of biological markers) is needed to reinforce the preliminary findings reported here. Likewise, our measure of ADHD was based on maternal report of symptoms rather than physician diagnosis. Unfortunately, we did not measure maternal diagnosis with or symptomatology of a mood disorder at the time of neurobehavioral reporting. Previous research suggests that mothers with depressive symptoms more frequently report behavioral problems among their children (Ordway, 2011) and maternal depression has been linked with adult-onset asthma (Brunner et al., 2014). Given these relationships, it is possible our findings suffer from residual confounding by unmeasured maternal depression or other mood disorders. Similarly, ADHD is

known to be co-morbid with several psychological (e.g., anxiety) and behavioral (e.g., oppositional defiant disorder) disorders in children (Reale et al., 2017), thus, it is possible that our findings with ADHD symptoms reflect a more general vulnerability to psychopathology.

Future studies designed to examine clinical diagnosis of ADHD in relation to maternal atopy are needed to better understand the public health impact of our findings. This study was conducted in an urban environment and was comprised of a largely minority (African American/Hispanic) demographic. Our results may not be generalizable to rural populations of differing sociodemographic makeup, for whom sources and triggers of atopy may vary.

While we were able to control for many potential confounders, it remains a challenge to draw conclusions about the causal nature of the observed atopy-ADHD relationship given potential overlapping pathways underlying these conditions, including common genetic predisposition and joint exposure to shared environmental factors. For example, children prenatally exposed to maternal atopy are also more likely to be exposed to treatments for these diseases, such as the use β -2-Adrenergic receptor agonists (β 2AAs) for asthma control. Given the relatively small size of our sample we were not able to explore the impact of medication use; previous research investigating the role of β 2AAs during pregnancy has concluded positive associations observed between β 2AAs and ADHD are likely attributable to underlying maternal asthma (Liang et al., 2017).

Our work supports a growing body of evidence indicating that maternal disorders associated with pro-inflammatory states, particularly when active around the time of pregnancy, may be a risk factor for development of ADHD-like symptoms in children. Given the central role of immune pathways, it is critical that future studies are designed to measure more direct correlates of active asthma and other atopic disorders in pregnant women, for example, using lung function, serologies, and high-throughput assays of immune biomarkers.

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Declaration of Competing Interest

The authors have no competing financial conflicts of interest.

References

- American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders. fifth ed, 2013.
- Andersen, C.H., Thomsen, P.H., Nohr, E.A., Lemcke, S., 2018. Maternal body mass index before pregnancy as a risk factor for ADHD and autism in children. *Eur. Child Adolesc. Psychiatry* 27 (2), 139–148. <https://doi.org/10.1007/s00787-017-1027-6>. Epub 2017/07/18; PubMed PMID: 28712019.
- Baffi, C.W., Winnica, D.E., Holguin, F., 2015. Asthma and obesity: mechanisms and clinical implications. *Asthma Res Pract.* 1, 1. <https://doi.org/10.1186/s40733-015-0001-7>. Epub 2015/06/04; PubMed PMID: 27965756 PMCID: PMC4970376.
- Bauman, M.D., Iosif, A.M., Smith, S.E., Bregere, C., Amaral, D.G., Patterson, P.H., 2014. Activation of the maternal immune system during pregnancy alters behavioral development of rhesus monkey offspring. *Biol. Psychiatry* 75 (4), 332–341. <https://doi.org/10.1016/j.biopsych.2013.06.025>. Epub 2013/09/10; PubMed PMID: 24011823.
- Berry, C.A., Quinn, K.A., Portillo, N., Shalowitz, M.U., 2006. Reliability and validity of the Spanish version of the Crisis in Family Systems-Revised. *Psychol. Rep.* 98 (1), 123–132. <https://doi.org/10.2466/pr0.98.1.123-132>. Epub 2006/05/06; PubMed PMID: 16673963.
- Beyerlein, A., 2014. Quantile regression-opportunities and challenges from a user's perspective. *Am J Epidemiol.* 180 (3), 330–331. <https://doi.org/10.1093/aje/kwu178>. Epub 2014/07/06; PubMed PMID: 24989240.
- Biederman, J., Faraone, S.V., 2005. Attention-deficit hyperactivity disorder. *Lancet* 366 (9481), 237–248. [https://doi.org/10.1016/S0140-6736\(05\)66915-2](https://doi.org/10.1016/S0140-6736(05)66915-2). Epub 2005/07/

- 19; PubMed PMID: 16023516.
- Bilbo, S.D., Schwarz, J.M., 2012. The immune system and developmental programming of brain and behavior. *Front. Neuroendocrinol.* 33 (3), 267–286. <https://doi.org/10.1016/j.ynfrne.2012.08.006>. Epub 2012/09/18; PubMed PMID: 22982535; PMCID: PMC3484177.
- Bilbo, S.D., Schwarz, J.M., 2009. Early-life programming of later-life brain and behavior: a critical role for the immune system. *Front. Behav. Neurosci.* 3, 14. <https://doi.org/10.3389/fnbeh.2009.0014.2009>. Epub 2009/09/10; PubMed PMID: 19738918; PMCID: PMC2737431.
- Bilbo, S.D., Block, C.L., Bolton, J.L., Hanamsagar, R., Tran, P.K., 2018. Beyond infection – Maternal immune activation by environmental factors, microglial development, and relevance for autism spectrum disorders. *Exp Neurol.* 299 (Pt A), 241–251. <https://doi.org/10.1016/j.expneurol.2017.07.002>. Epub 2017/07/13; PubMed PMID: 28698032; PMCID: PMC5723548.
- Bilenberg, N., Hougaard, D., Norgaard-Pedersen, B., Nordenbaek, C.M., Olsen, J., 2011. Twin study on transplacental-acquired antibodies and attention deficit/hyperactivity disorder – a pilot study. *J. Neuroimmunol.* 236 (1–2), 72–75. <https://doi.org/10.1016/j.jneuroim.2011.04.012>. Epub 2011/05/24; PubMed PMID: 21601295.
- Bilimoria, P.M., Stevens, B., 2015. Microglia function during brain development: New insights from animal models. *Brain Res.* 1617, 7–17. <https://doi.org/10.1016/j.brainres.2014.11.032>. Epub 2014/12/03; PubMed PMID: 25463024.
- Boulanger-Bertolus, J., Pancaro, C., Mashour, G.A., 2018. Increasing role of maternal immune activation in neurodevelopmental disorders. *Front. Behav. Neurosci.* 12, 230. <https://doi.org/10.3389/fnbeh.2018.00230>. Epub 2018/10/23; PubMed PMID: 30344483; PMCID: PMC6182081.
- Brown, A.S., 2012. Epidemiologic studies of exposure to prenatal infection and risk of schizophrenia and autism. *Dev Neurobiol.* 72 (10), 1272–1276. <https://doi.org/10.1002/dneu.22024>. Epub 2012/04/11; PubMed PMID: 22488761; PMCID: PMC3435457.
- Brunner, W.M., Schreiner, P.J., Sood, A., Jacobs Jr., D.R., 2014. Depression and risk of incident asthma in adults. The CARDIA study. *Am J Respir Crit Care Med.* 189 (9), 1044–1051. <https://doi.org/10.1164/rccm.201307-1349OC>. Epub 2014/01/25; PubMed PMID: 24456492; PMCID: PMC4098106.
- Brunst, K.J., Rosa, M.J., Jara, C., Lipton, L.R., Lee, A., Coull, B.A., Wright, R.J., 2017. Impact of maternal lifetime interpersonal trauma on children's asthma: mediation through maternal active asthma during pregnancy. *Psychosom Med.* 79 (1), 91–100. <https://doi.org/10.1097/PSY.0000000000000354>. Epub 2016/07/01; PubMed PMID: 27359172; PMCID: PMC5182122.
- Chaudhuri, R., McSharry, C., McCoard, A., Livingston, E., Hothersall, E., Spears, M., Lafferty, J., Thomson, N.C., 2008. Role of symptoms and lung function in determining asthma control in smokers with asthma. *Allergy* 63 (1), 132–135. <https://doi.org/10.1111/j.1398-9995.2007.01538.x>. Epub 2007/12/07; PubMed PMID: 18053022.
- Chen, E., Miller, G.E., 2007. Stress and inflammation in exacerbations of asthma. *Brain Behav Immun.* 21 (8), 993–999. <https://doi.org/10.1016/j.bbi.2007.03.009>. Epub 2007/05/12; PubMed PMID: 17493786; PMCID: PMC2077080.
- Chi, C.C., Wang, S.H., Mayon-White, R., Wojnarowska, F., 2013. Pregnancy outcomes after maternal exposure to topical corticosteroids: a UK population-based cohort study. *JAMA Dermatol.* 149 (11), 1274–1280. <https://doi.org/10.1001/jamadermatol.2013.5768>. Epub 2013/09/06; PubMed PMID: 24005903.
- Chi, C.C., Wang, S.H., Wojnarowska, F., Kirtschig, G., Davies, E., Bennett, C., 2015. Safety of topical corticosteroids in pregnancy. *Cochrane Database Syst Rev.* 10. <https://doi.org/10.1002/14651858.CD007346.pub3>. CD007346. Epub 2015/10/27; PubMed PMID: 26497573.
- Chiu, Y.H., Coull, B.A., Sternthal, M.J., Kloog, I., Schwartz, J., Cohen, S., Wright, R.J., 2014. Effects of prenatal community violence and ambient air pollution on childhood wheeze in an urban population. *J. Allergy Clin. Immunol.* 133 (3). <https://doi.org/10.1016/j.jaci.2013.09.023>. 713–22 e4. Epub 2013/11/10. PubMed PMID: 24200349; PMCID: PMC3943665.
- Clifton, V., 2006. Maternal asthma during pregnancy and fetal outcomes: potential mechanisms and possible solutions. *Curr. Opin. Allergy Clin. Immunol.* 6 (5), 307–311. <https://doi.org/10.1097/01.all.0000244788.28789.dd>. Epub 2006/09/07; PubMed PMID: 16954781.
- Coghill D, Bazian L, Faron S, Nigg J, Sonuga-Barke E, Rohde L. A systematic review of the causes of attention deficit hyperactivity disorder (ADHD): an evidence report. In: Health LDO, editor. London, UK 2011.
- Coker, T.R., Elliott, M.N., Toomey, S.L., Schwebel, D.C., Cuccaro, P., Tortolero Emery, S., Davies, S.L., Visser, S.N., Schuster, M.A., 2016. Racial and ethnic disparities in ADHD diagnosis and treatment. *Pediatrics* 138 (3). <https://doi.org/10.1542/peds.2016-0407>. Epub 2016/08/25. PubMed PMID: 27553219; PMCID: PMC5684883.
- Conners, C., 1997. *Conners' Rating Scales – Revised (CRS-R) User's Manual*. Multi-Health Systems Inc, North Tonawanda, NY.
- Corominas, M., Ramos-Quiroga, J.A., Ferrer, M., Saez-Francas, N., Palomar, G., Bosch, R., Casas, M., 2012. Cortisol responses in children and adults with attention deficit hyperactivity disorder (ADHD): a possible marker of inhibition deficits. *Atten Defic Hyperact Disord.* 4 (2), 63–75. <https://doi.org/10.1007/s12402-012-0075-5>. Epub 2012/05/12; PubMed PMID: 22576746.
- Cummings, J.R., Ji, X., Allen, L., Lally, C., Druss, B.G., 2017. Racial and ethnic differences in ADHD treatment quality among medicaid-enrolled youth. *Pediatrics* 139 (6). <https://doi.org/10.1542/peds.2016-2444>. Epub 2017/06/01. PubMed PMID: 28562259; PMCID: PMC5470500 conflicts of interest to disclose.
- Deverman, B.E., Patterson, P.H., 2009. Cytokines and CNS development. *Neuron* 64 (1), 61–78. <https://doi.org/10.1016/j.neuron.2009.09.002>. Epub 2009/10/21; PubMed PMID: 19840550.
- Eisner, M.D., Iribarren, C., 2007. The influence of cigarette smoking on adult asthma outcomes. *Nicotine Tob. Res.* 9 (1), 53–56. <https://doi.org/10.1080/14622200601078293>. Epub 2007/03/17; PubMed PMID: 17365736.
- Enninga, E.A., Nevala, W.K., Creedon, D.J., Markovic, S.N., Holtan, S.G., 2015. Fetal sex-based differences in maternal hormones, angiogenic factors, and immune mediators during pregnancy and the postpartum period. *Am J Reprod Immunol.* 73 (3), 251–262. <https://doi.org/10.1111/aji.12303>. Epub 2014/08/06; PubMed PMID: 25091957; PMCID: PMC4317383.
- Enriquez, R., Griffin, M.R., Carroll, K.N., Wu, P., Cooper, W.O., Gebretsadik, T., Dupont, W.D., Mitchel, E.F., Hartert, T.V., 2007. Effect of maternal asthma and asthma control on pregnancy and perinatal outcomes. *J. Allergy Clin. Immunol.* 120 (3), 625–630. <https://doi.org/10.1016/j.jaci.2007.05.044>. Epub 2007/07/31; PubMed PMID: 17658591.
- Estes, M.L., McAllister, A.K., 2016. Maternal immune activation: Implications for neuropsychiatric disorders. *Science* 353 (6301), 772–777. <https://doi.org/10.1126/science.aag3194>. Epub 2016/08/20; PubMed PMID: 27540164; PMCID: PMC5650490.
- Fasmer, O.B., Riise, T., Eagan, T.M., Lund, A., Dilsaver, S.C., Hundal, O., Oedegaard, K.J., 2011. Comorbidity of asthma with ADHD. *J. Atten Disord.* 15 (7), 564–571. <https://doi.org/10.1177/1087054710372493>. Epub 2010/06/25; PubMed PMID: 20574059.
- Fleming, M., Fitton, C.A., Steiner, M.F.C., McLay, J.S., Clark, D., King, A., Mackay, D.F., Pell, J.P., 2017. Educational and health outcomes of children treated for attention-deficit/hyperactivity disorder. *JAMA Pediatr.* 171 (7). <https://doi.org/10.1001/jamapediatrics.2017.0691>. e170691. Epub 2017/05/02; PubMed PMID: 28459927.
- Garay, P.A., McAllister, A.K., 2010. Novel roles for immune molecules in neural development: implications for neurodevelopmental disorders. *Front Synaptic Neurosci.* 2, 136. <https://doi.org/10.3389/fnsyn.2010.00136>. Epub 2010/01/01; PubMed PMID: 21423522; PMCID: PMC3059681.
- Ghassabian, A., Bongers-Schokking, J.J., de Rijke, Y.B., van Mil, N., Jaddoe, V.W., de Muinck Keizer-Schrama, S.M., Hooijkaas, H., Hofman, A., Visser, W., Roman, G.C., Visser, T.J., Verhulst, F.C., Tiemeier, H., 2012. Maternal thyroid autoimmunity during pregnancy and the risk of attention deficit/hyperactivity problems in children: the Generation R Study. *Thyroid* 22 (2), 178–186. <https://doi.org/10.1089/thy.2011.0318>. Epub 2011/12/20; PubMed PMID: 22175242; PMCID: PMC3271370.
- Ginhoux, F., Lim, S., Hoeftel, G., Low, D., Huber, T., 2013. Origin and differentiation of microglia. *Front Cell Neurosci.* 7, 45. <https://doi.org/10.3389/fncel.2013.00045>. Epub 2013/04/26; PubMed PMID: 23616747; PMCID: PMC3627983.
- Graham, A.M., Rasmussen, J.M., Rudolph, M.D., Heim, C.M., Gilmore, J.H., Styner, M., Potkin, S.G., Entringer, S., Wadhwa, P.D., Fair, D.A., Buss, C., 2018. Maternal systemic interleukin-6 during pregnancy is associated with newborn amygdala phenotypes and subsequent behavior at 2 years of age. *Biol. Psychiatry* 832, 109–119. <https://doi.org/10.1016/j.biopsych.2017.05.027>. Epub 2017/07/30; PubMed PMID: 28754515; PMCID: PMC5723539.
- Grieken, N., Osmanliu, E., Fortier, M.E., Joob, R., 2015. Increased Risk of Asthma in Children with ADHD: role of prematurity and maternal stress during pregnancy. *J. Can. Acad. Child Adolesc. Psychiatry* 24 (2), 109–115 Epub 2015/09/18. PubMed PMID: 26379722; PMCID: PMC4558981.
- Halmoy, A., Klungsoyr, K., Skjaerven, R., Haavik, J., 2012. Pre- and perinatal risk factors in adults with attention-deficit/hyperactivity disorder. *Biol. Psychiatry* 71 (5), 474–481. <https://doi.org/10.1016/j.biopsych.2011.11.013>. Epub 2011/12/28; PubMed PMID: 22200325.
- Henriksen, L., Wu, C.S., Secher, N.J., Obel, C., Juhl, M., 2015. Medical augmentation of labor and the risk of ADHD in offspring: a population-based study. *Pediatrics* 135 (3), e672–e677. <https://doi.org/10.1542/peds.2014-1542>. Epub 2015/02/11; PubMed PMID: 25667242.
- Instanes, J.T., Halmoy, A., Engeland, A., Haavik, J., Furu, K., Klungsoyr, K., 2017. Attention-deficit/hyperactivity disorder in offspring of mothers with inflammatory and immune system diseases. *Biol Psychiatry* 81 (5), 452–459. <https://doi.org/10.1016/j.biopsych.2015.11.024>. Epub 2016/01/27; PubMed PMID: 26809250.
- Knuesel, I., Chicha, L., Britschgi, M., Schobel, S.A., Bodmer, M., Hellings, J.A., Toovey, S., Prinssen, E.P., 2014. Maternal immune activation and abnormal brain development across CNS disorders. *Nat. Rev. Neurol.* 10 (11), 643–660. <https://doi.org/10.1038/nrneuro.2014.187>. Epub 2014/10/15; PubMed PMID: 25311587.
- Koenker, R., Bassett Jr., G., 1978. Regression quantiles. *Econometrics* 46 (1), 33–50.
- Kurinczuk, J.J., Parsons, D.E., Dawes, V., Burton, P.R., 1999. The relationship between asthma and smoking during pregnancy. *Women Health* 29 (3), 31–47. https://doi.org/10.1300/J013v29n03_03. Epub 1999/08/31; PubMed PMID: 10466509.
- Liang, H., Chen, J., Miao, M., Christensen, J., Dalsgaard, S., Yuan, W., Li, J., 2017. In utero exposure to beta-2-adrenergic receptor agonist and attention-deficit/hyperactivity disorder in children. *Eur. Child Adolesc. Psychiatry* 26 (7), 847–856. <https://doi.org/10.1007/s00787-017-0956-4>. Epub 2017/02/12; PubMed PMID: 28185095.
- Linnet, K.M., Dalsgaard, S., Obel, C., Wisborg, K., Henriksen, T.B., Rodriguez, A., Kotimaa, A., Moilanen, I., Thomsen, P.H., Olsen, J., Jarvelin, M.R., 2003. Maternal lifestyle factors in pregnancy risk of attention deficit hyperactivity disorder and associated behaviors: review of the current evidence. *Am. J. Psychiatry* 160 (6), 1028–1040. <https://doi.org/10.1176/appi.ajp.160.6.1028>. Epub 2003/06/05; PubMed PMID: 12777257.
- Mann, J.R., McDermott, S., 2011. Are maternal genital/urogenital infection and pre-eclampsia associated with ADHD in school-aged children? *J. Atten Disord.* 15 (8), 667–673. <https://doi.org/10.1177/1087054710370566>. Epub 2010/09/15; PubMed PMID: 20837984.
- Matsui, E.C., Hansel, N.N., McCormack, M.C., Rusher, R., Breysse, P.N., Diette, G.B., 2008. Asthma in the inner city and the indoor environment. *Immunol Allergy Clin North Am.* 28 (3), 665–686. <https://doi.org/10.1016/j.jac.2008.03.004>. x. Epub 2008/06/24; PubMed PMID: 18572113; PMCID: PMC5516633.
- Mendola, P., Laughon, S.K., Mannisto, T.I., Leishear, K., Reddy, U.M., Chen, Z., Zhang, J., 2013. Obstetric complications among US women with asthma. *Am J Obstet Gynecol.* 208 (2). <https://doi.org/10.1016/j.ajog.2012.11.007>. 127 e1-8. Epub 2012/11/20. PMID: 23159695; PMCID: PMC3557554.

- Meyer, U., 2014. Prenatal poly(i:C) exposure and other developmental immune activation models in rodent systems. *Biol. Psychiatry* 75 (4), 307–315. <https://doi.org/10.1016/j.biopsych.2013.07.011>. Epub 2013/08/14; PubMed PMID: 23938317.
- Miller, B.J., Culpepper, N., Rapaport, M.H., Buckley, P., 2013. Prenatal inflammation and neurodevelopment in schizophrenia: a review of human studies. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* 42, 92–100. <https://doi.org/10.1016/j.pnpb.2012.03.010>. Epub 2012/04/19; PubMed PMID: 22510462.
- Murphy, V.E., Gibson, P.G., Giles, W.B., Zakar, T., Smith, R., Bisits, A.M., Kessell, C.G., Clifton, V.L., 2003. Maternal asthma is associated with reduced female fetal growth. *Am. J. Respir. Crit. Care Med.* 168 (11), 1317–1323. <https://doi.org/10.1164/rccm.200303-374OC>. Epub 2003/09/23; PubMed PMID: 14500261.
- Murphy, V.E., Clifton, V.L., Gibson, P.G., 2006. Asthma exacerbations during pregnancy: incidence and association with adverse pregnancy outcomes. *Thorax* 61 (2), 169–176. <https://doi.org/10.1136/thx.2005.049718>. Epub 2006/01/31; PubMed PMID: 16443708; PMCID: PMC2104591.
- Murphy, V.E., Clifton, V.L., Gibson, P.G., 2010. The effect of cigarette smoking on asthma control during exacerbations in pregnant women. *Thorax* 65 (8), 739–744. <https://doi.org/10.1136/thx.2009.124941>. Epub 2010/07/16; PubMed PMID: 20627905.
- Murphy, V.E., Namazy, J.A., Powell, H., Schatz, M., Chambers, C., Attia, J., Gibson, P.G., 2011. A meta-analysis of adverse perinatal outcomes in women with asthma. *BJOG* 118 (11), 1314–1323. <https://doi.org/10.1111/j.1471-0528.2011.03055.x>. Epub 2011/07/14; PubMed PMID: 21749633.
- Murray, E., Matijasevich, A., Santos, I.S., Barros, A.J., Anselmi, L., Barros, F.C., Stein, A., 2015. Sex differences in the association between foetal growth and child attention at age four: specific vulnerability of girls. *J. Child Psychol. Psychiatry* 56 (12), 1380–1388. <https://doi.org/10.1111/jcpp.12422>. Epub 2015/04/17; PubMed PMID: 25879754.
- Nakanishi, H., 2003. Microglial functions and proteases. *Mol. Neurobiol.* 27 (2), 163–176. <https://doi.org/10.1385/MN:27:2:163>. Epub 2003/06/05; PubMed PMID: 12777686.
- Okano, L., Ji, Y., Riley, A.W., Wang, X., 2018. Maternal psychosocial stress and children's ADHD diagnosis: a prospective birth cohort study. *J. Psychosom. Obstet. Gynaecol.* 1–9. <https://doi.org/10.1080/0167482X.2018.1468434>. Epub 2018/05/24; PubMed PMID: 29790815; PMCID: PMC6251762.
- Ordway, M.R., 2011. Depressed mothers as informants on child behavior: methodological issues. *Res. Nurs. Health* 34 (6), 520–532. <https://doi.org/10.1002/nur.20463>. Epub 2011/10/04; PubMed PMID: 21964958 PMCID: PMC3207031.
- Paolicelli, R.C., Bolasco, G., Pagani, F., Maggi, L., Scianni, M., Panzanelli, P., Giustetto, M., Ferreira, T.A., Guiducci, E., Dumas, L., Ragozzino, D., Gross, C.T., 2011. Synaptic pruning by microglia is necessary for normal brain development. *Science* 333 (6048), 1456–1458. <https://doi.org/10.1126/science.1202529>. Epub 2011/07/23; PubMed PMID: 21778362.
- Pauli-Pott, U., Schloss, S., Ruhl, I., Skoluda, N., Nater, U.M., Becker, K., 2017. Hair cortisol concentration in preschoolers with attention-deficit/hyperactivity symptoms—roles of gender and family adversity. *Psychoneuroendocrinology* 86, 25–33. <https://doi.org/10.1016/j.psyneuen.2017.09.002>. Epub 2017/09/15; PubMed PMID: 28910602.
- Pawankar, R., Canonica, G.W., Holgate, S.T., Lockey, R.F., 2012. Allergic diseases and asthma: a major global health concern. *Curr. Opin. Allergy Clin. Immunol.* 12 (1), 39–41. <https://doi.org/10.1097/ACI.0b013e32834ec13b>. Epub 2011/12/14; PubMed PMID: 22157151.
- Rasmussen, J.M.A.M., Graham, S., Entringer, J.H., Gilmore, M., Styner, D.A., Fair, P.D., Wadhwa, C., 2018. Buss Maternal Interleukin-6 concentration during pregnancy is associated with variation in frontolimbic white matter and cognitive development in early life. *Neuroimage*. <https://doi.org/10.1016/j.neuroimage.2018.04.020>. Epub 2018/04/15; PubMed PMID: 29654875; PMCID: PMC6181792.
- Reale, L., Bartoli, B., Cartabia, M., Zanetti, M., Costantino, M.A., Canevini, M.P., Termine, C., Bonati, M., Lombardy, A.G., 2017. Comorbidity prevalence and treatment outcome in children and adolescents with ADHD. *Eur. Child Adolesc. Psychiatry* 26 (12), 1443–1457. <https://doi.org/10.1007/s00787-017-1005-z>. Epub 2017/05/21; PubMed PMID: 28527021.
- Reynolds, C., Kamphaus, R., 2004. *Behavior Assessment System for Children (BASC-2) Manual*, second ed. Pearson, Minneapolis, MN.
- Rudolph, M.D., Graham, A.M., Feczko, E., Miranda-Dominguez, O., Rasmussen, J.M., Nardos, R., Entringer, S., Wadhwa, P.D., Buss, C., Fair, D.A., 2018. Maternal IL-6 during pregnancy can be estimated from newborn brain connectivity and predicts future working memory in offspring. *Nat. Neurosci.* 21 (5), 765–772. <https://doi.org/10.1038/s41593-018-0128-y>. Epub 2018/04/11; PubMed PMID: 29632361; PMCID: PMC5920734.
- Sandberg, S., Jarvenpää, S., Penttinen, A., Paton, J.Y., McCann, D.C., 2004. Asthma exacerbations in children immediately following stressful life events: a Cox's hierarchical regression. *Thorax* 59 (12), 1046–1051. <https://doi.org/10.1136/thx.2004.024604>. Epub 2004/11/26; PubMed PMID: 15563703; PMCID: PMC1746895.
- Schmitt, J., Buske-Kirschbaum, A., Roessner, V., 2010. Is atopic disease a risk factor for attention-deficit/hyperactivity disorder? A systematic review. *Allergy* 65 (12), 1506–1524. <https://doi.org/10.1111/j.1398-9995.2010.02449.x>. Epub 2010/08/19; PubMed PMID: 20716320.
- Scott, N.M., Hodyl, N.A., Murphy, V.E., Osei-Kumah, A., Wyper, H., Hodgson, D.M., Smith, R., Clifton, V.L., 2009. Placental cytokine expression covaries with maternal asthma severity and fetal sex. *J. Immunol.* 182 (3), 1411–1420 Epub 2009/01/22 PubMed PMID: 19155488.
- Shalowitz, M.U., Berry, C.A., Rasinski, K.A., Dannhausen-Brun, C.A., 1998. A new measure of contemporary life stress: development, validation, and reliability of the CRISYS. *Health Serv. Res.* 33 (5 Pt 1), 1381–1402 Epub 1998/12/29. PubMed PMID: 9865225; PMCID: PMC1070321.
- Silva, D., Colvin, L., Hagemann, E., Bower, C., 2014. Environmental risk factors by gender associated with attention-deficit/hyperactivity disorder. *Pediatrics* 133 (1), e14–e22. <https://doi.org/10.1542/peds.2013-1434>. Epub 2013/12/04; PubMed PMID: 24298003.
- Simpson, B.M., Custovic, A., Simpson, A., Hallam, C.L., Walsh, D., Marolia, H., Campbell, J., Woodcock, A., 2001. NAC Manchester Asthma and Allergy Study (NACMAAS): risk factors for asthma and allergic disorders in adults. *Clin. Exp. Allergy* 31 (3), 391–399 Epub 2001/03/22; PubMed PMID: 11260150.
- Siroux, V., Pin, I., Oryszczyn, M.P., Le Moual, N., Kauffmann, F., 2000. Relationships of active smoking to asthma and asthma severity in the EGEE study. *Epidemiological study on the Genetics and Environment of Asthma. Eur Respir J.* 15 (3), 470–477 Epub 2000/04/12. PubMed PMID: 10759439.
- Spann, M.N., Monk, C., Scheinost, D., Peterson, B.S., 2018. Maternal immune activation during the third trimester is associated with neonatal functional connectivity of the salience network and fetal to toddler behavior. *J. Neurosci.* 38 (11), 2877–2886. <https://doi.org/10.1523/JNEUROSCI.2272-17.2018>. Epub 2018/03/01; PubMed PMID: 29487127; PMCID: PMC5852665.
- Tata, L.J., Lewis, S.A., McKeever, T.M., Smith, C.J., Doyle, P., Smeeth, L., West, J., Hubbard, R.B., 2007. A comprehensive analysis of adverse obstetric and pediatric complications in women with asthma. *Am. J. Respir. Crit. Care Med.* 175 (10), 991–997. <https://doi.org/10.1164/rccm.200611-1641OC>. Epub 2007/02/03; PubMed PMID: 17272783.
- Taylor, B.D., Ness, R.B., Klebanoff, M.A., Tang, G., Roberts, J.M., Hougaard, D.M., Skogstrand, K., Haggerty, C.L., 2018. The impact of female fetal sex on preeclampsia and the maternal immune milieu. *Pregnancy Hypertens.* 12, 53–57. <https://doi.org/10.1016/j.preghy.2018.02.009>. Epub 2018/04/21; PubMed PMID: 29674199; PMCID: PMC6049062.
- Thapar, A., Cooper, M., Eyre, O., Langley, K., 2013. What have we learnt about the causes of ADHD? *J. Child Psychol. Psychiatry* 54 (1), 3–16. <https://doi.org/10.1111/j.1469-7610.2012.02611.x>. Epub 2012/09/12; PubMed PMID: 22963644; PMCID: PMC3572580.
- Togias, A., Fenton, M.J., Gergen, P.J., 2010. Rotrosen D, Fauci AS. Asthma in the inner city: the perspective of the National Institute of Allergy and Infectious Diseases. *J. Allergy Clin. Immunol.* 125 (3), 540–544. <https://doi.org/10.1016/j.jaci.2010.01.040>. Epub 2010/03/17; PubMed PMID: 20226290.
- Tomlinson, J.E., McMahon, A.D., Chaudhuri, R., Thompson, J.M., Wood, S.F., Thomson, N.C., 2005. Efficacy of low and high dose inhaled corticosteroid in smokers versus non-smokers with mild asthma. *Thorax* 60 (4), 282–287. <https://doi.org/10.1136/thx.2004.033688>. Epub 2005/03/26; PubMed PMID: 15790982; PMCID: PMC1747368.
- Urakubo, A., Jarskog, L.F., Lieberman, J.A., Gilmore, J.H., 2001. Prenatal exposure to maternal infection alters cytokine expression in the placenta, amniotic fluid, and fetal brain. *Schizophr. Res.* 47 (1), 27–36 Epub 2001/02/13; PubMed PMID: 11163542.
- Vaezi, A., Haghighi, L., Beigmohammadi, F., Nojomi, M., 2017. Maternal asthma, pregnancy, delivery and birth outcomes: a retrospective cohort study. *Iran. J. Allergy Asthma Immunol.* 16 (2), 92–98 Epub 2017/06/12; PubMed PMID: 28601048.
- von Stauffenberg, C., Campbell, S.B., 2007. Predicting the early developmental course of symptoms of attention deficit hyperactivity disorder. *J. Appl. Dev. Psychol.* 28 (5–6), 536–552. <https://doi.org/10.1016/j.appdev.2007.06.011>. Epub 2007/09/01; PubMed PMID: 21836767 PMCID: PMC3153376.
- Weir, R.K., Forghany, R., Smith, S.E., Patterson, P.H., McAllister, A.K., Schumann, C.M., Bauman, R.D., 2015. Preliminary evidence of neuropathology in nonhuman primates prenatally exposed to maternal immune activation. *Brain Behav. Immun.* 48, 139–146. <https://doi.org/10.1016/j.bbi.2015.03.009>. Epub 2015/03/31; PubMed PMID: 25816799; PMCID: PMC5671487.
- Willcutt, E.G., 2012. The prevalence of DSM-IV attention-deficit/hyperactivity disorder: a meta-analytic review. *Neurotherapeutics* 9 (3), 490–499. <https://doi.org/10.1007/s13311-012-0135-8>. Epub 2012/09/15. PubMed PMID: 22976615; PMCID: PMC3441936.
- Wright, R.J., Mitchell, H., Visness, C.M., Cohen, S., Stout, J., Evans, R., Gold, D.R., 2004. Community violence and asthma morbidity: the Inner-City Asthma Study. *Am. J. Public Health* 94 (4), 625–632 Epub 2004/04/01. PubMed PMID: 15054016; PMCID: PMC1448309.
- Wright, R.J., Suglia, S.F., Levy, J., Fortun, K., Shields, A., Subramanian, S., Wright, R., 2008. Transdisciplinary research strategies for understanding socially patterned disease: the Asthma Coalition on Community, Environment, and Social Stress (ACCESS) project as a case study. *Cien Saude Colet* 13 (6), 1729–1742 Epub 2008/10/04. PubMed PMID: 18833350; PMCID: PMC2628980.
- Yuksel, H., Sogut, A., Yilmaz, O., 2008. Attention deficit and hyperactivity symptoms in children with asthma. *J. Asthma* 45 (7), 545–547. <https://doi.org/10.1080/02770900801990016>. Epub 2008/09/06; PubMed PMID: 18773323.