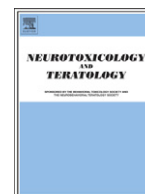




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Upper respiratory infection during pregnancy and neurodevelopmental outcomes among offspring



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ABSTRACT

Objective: Maternal infection during pregnancy is associated with psychiatric disorders among offspring. The aim of this study was to investigate associations between upper respiratory infection (URI) in pregnancy and measures of cognitive and behavioral outcomes in child offspring.

Materials and methods: A longitudinal study of 534 mother-child pairs with information regarding prenatal exposures collected through an interview conducted on average one year after delivery and subsequent participation in a childhood cognitive and psychosocial assessment between the ages 5–12 years. Childhood cognition was measured using the Peabody Picture Vocabulary Test (PPVT-III) and the Beery-Buktenica Test of Visual Motor Integration-Fifth Edition (VMI-5) and behavioral function measured using the Child Behavior Checklist (CBCL) and teacher-report using the Teacher Report Form (TRF). Adjusted mean differences (adjMD) in outcome measures were calculated between mothers reporting the presence or absence of a URI during pregnancy.

Results: URI during pregnancy was not associated with the two measures of cognition given to offspring, but was associated with modest increases in total behavioral problems reported by mothers (adjMD: 3.72; CI: 1.91–5.54) and teachers (adjMD: 2.74; CI: 0.97–4.50). We observed differences in CBCL and TRF scores based on timing of URI: infections in mid-pregnancy (lunar months 4–5) were associated with poorer scores than were infections in early pregnancy (lunar months 2–3).

Conclusions: In general, URI in pregnancy was not associated with decrements in childhood cognition, but may be associated with behavior problems.

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1. Introduction

Prenatal brain development entails a complex set of processes and is a highly sensitive period of development. The importance of the prenatal environment in influencing neurodevelopmental outcomes in infancy, childhood, and adulthood is becoming increasingly better understood (Bale et al., 2010; Richetto and Riva, 2014). There is mounting evidence to suggest that maternal influences on the prenatal environment, including stress, malnutrition, medications, and infections, play a fundamental role in later behavioral and cognitive functioning in offspring (Richetto and Riva, 2014).

Maternal infection during pregnancy has been studied in relation to the development of psychiatric disorders in the offspring, particularly

schizophrenia, autism spectrum disorders (ASD) and attention deficit/hyperactivity disorder (ADHD) (Betts et al., 2014; Brown, 2012; Khandaker et al., 2013; Richetto and Riva, 2014; Werenberg Dreier et al., 2016). Maternal exposure to herpes simplex virus-2 (Buka et al., 2008), influenza (Brown et al., 2004), bacterial infection (Sorensen et al., 2009), rubella (Brown et al., 2000a), and toxoplasmosis (Brown et al., 2005) have all been associated with an increased risk of schizophrenia in adult offspring. In addition, there is a suggestive link between maternal exposure to influenza (Atladottir et al., 2012), bacterial infections (Atladottir et al., 2010), and rubella (Deykin and MacMahon, 1979) to ASD in offspring and between genitourinary infections and ADHD (Werenberg Dreier et al., 2016; Silva et al., 2014).

The mechanism by which a maternal infection impacts neurodevelopmental outcomes in offspring is hypothesized to involve maternal immune activation involving antibodies and cytokines (Buka et al., 2001; Dammann and Leviton, 1997; Brown, 2012). Maternal immune activation has also been hypothesized to result in cognitive impairments, although few human studies on this topic exist (Richetto and Riva, 2014). The timing of infection during pregnancy has also been suggested to play an important role, yet few studies have

Abbreviations: CBCL, Child behavior checklist; LMP, last menstrual period; (adj)MD, (adjusted) mean difference; PPVT, peabody picture vocabulary test; TRF, teacher report form; URI, upper respiratory infections; VMI, Beery-Buktenica test of visual motor integration-fifth edition.

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distinguished infections by trimester (Atladdottir et al., 2010; Werenberg Dreier et al., 2016). Treatment of infection is another important component since studies have linked medications, specifically acetaminophen and antibiotics, with neurodevelopmental outcomes, including ASD and ADHD (Liew et al., 2014; Liew et al., 2015; Brandlistuen et al., 2013; Thompson et al., 2014; Atladdottir et al., 2012). Lastly, the influence of infection on a range of neurodevelopmental measures in childhood, such as subclinical effects, in contrast to a specific clinical diagnosis, has not been addressed.

Upper respiratory infection (URI) is the most commonly reported infection during pregnancy, with an estimated 49.6% of women in the United States being affected at some point during periconception and pregnancy (Collier et al., 2009). URIs are self-limiting infections most commonly caused by viruses, including rhinoviruses, coronaviruses, and influenza (Monto, 2002). Despite its common occurrence, few studies have investigated the role of maternal respiratory infections during pregnancy on child neurodevelopment (Brown et al., 2000b).

The aim of this study is to investigate the association between URI during pregnancy and child cognitive development, on the Peabody Picture Vocabulary Test (PPVT-III) and the Beery-Buktenica Test of Visual Motor Integration-Fifth Edition (VMI-5) and psychosocial development on the Child Behavior Checklist (CBCL) and the Teacher Report Form (TRF) and to determine if such associations differ by timing in pregnancy, duration of infection, or treatment. The CBCL and TRF are not designed to provide clinical diagnoses, but studies have demonstrated that these tests can be used to discriminate children with diagnoses such as ASD and ADHD with moderate to high accuracy (Ooi et al., 2011; So et al., 2013; Graetz et al., 2001).

2. Methods

Eligible participants were children whose mothers previously participated in a case-control study of risk factors for hemifacial microsomia (HFM). The case-control study included children born between 1996 and 2002 and enrolled mother-child pairs within 36 months of delivery. This study has previously been described in detail (Werler et al., 2004; Collett et al., 2011). Mothers of the children included in that study were contacted to participate in a follow-up study when their child reached 5 to 6 years of age. The present study is restricted to control children, or those without a malformation. This study was approved by the Institutional Review Board at Boston University and was completed in compliance with HIPAA standards.

3. Upper respiratory infection

Data on URI were collected through a maternal telephone interview conducted by trained study nurses one year after delivery, on average (range = 2 weeks to 3 years). Women were asked to report episodes of URI, including cold, flu, or sinusitis, which occurred at any point from their last menstrual period (LMP) through the 5th lunar month of pregnancy. URI events that began in lunar month 6 or afterwards were not captured in the interview, since the interview was initially focused on risk factors for HFM, which develops in early pregnancy. Reports of a URI during the first lunar month post-LMP were removed from the primary analysis as this period includes the preconception window and implantation period ($n = 36$). We also performed a sensitivity analysis including these women.

Women who reported a URI were subsequently prompted about timing during pregnancy, duration, symptoms, and treatment of the reported infection. Timing of URI onset was categorized into two mutually exclusive groups; 1) early pregnancy (lunar months 2–3) and 2) mid-pregnancy (lunar months 4–5). Duration of the reported infection was categorized as short (1–9 days) or long (≥ 10 days), based on clinical data indicating the symptoms usually resolve within 10 days. Data on specific symptoms of the URI, including self-reported fever and self-reported flu, were also collected.

Medications reported for treatment of URI were classified based on active ingredient or class using the Boston University Slone Drug Dictionary (Boston University Slone Epidemiology Center Slone Drug Dictionary), a computerized coding system that includes codes for prescription and non-prescription drugs, dietary supplements, and other natural products. The following medication categories were created 1) pseudoephedrine/decongestants, 2) acetaminophen, 3) guaifenesin, 4) antibiotics, and 5) antihistamines. Due to the possibility of treatment with multiple medications and multiple components within a medication, these groups are not mutually exclusive.

4. Outcome measures

4.1. Neurodevelopmental outcomes

Child cognition was assessed using the Peabody Picture Vocabulary Test (PPVT-III) and perceptual-motor skills were measured by the Beery-Buktenica Test of Visual Motor Integration-Fifth Edition (VMI-5). The PPVT-III is a norm-referenced measure of receptive vocabulary. Respondents are presented with increasingly difficult vocabulary words and shown four target pictures. They are asked to point to the picture that best represents the word. Reliability is excellent, and convergent validity is supported by strong correlations with other measures of verbal ability and prediction of academic achievement (Dunn and Dunn, 1997). Higher scores on this test indicate better receptive vocabulary in the child.

The VMI-5 is a norm-referenced measure of perceptual motor abilities. Respondents copy a series of 24 increasingly difficult geometric designs which are scored for accuracy by an examiner. The VMI-5 has good reliability, including strong test-retest stability and inter-scoring reliability among diverse examiners. Validity of the VMI-5 is supported by convergence with other measures of visual perception and low correlations with verbal measures (Beery and Beery, 2004). Higher scores indicate better perceptual motor abilities.

4.2. Behavioral outcomes

Behavioral adaptation was measured using instruments from the Achenbach System of Empirically Based Assessments (ASEBA), the parent report Child Behavior Checklist (CBCL) and the Teacher Report Form (TRF). The CBCL provides measures of parent-reported externalizing behavior problems (e.g. hyperactive, noncompliant, disruptive) and internalizing behavior problems (e.g. shy, withdrawn, despondent). The TRF captures teacher impressions of children's behavioral and emotional problems in these same domains and is the companion instrument to the CBCL. The current study used three summary scores from the CBCL and the TRF; internalizing, externalizing, and total problems and eight syndrome scales; anxious/depressed, withdrawn/depressed, somatic, social, thought, attention, rule-breaking, and aggressive. Both have well-established reliability and validity (Achenbach and Rescorla, 2001). Higher scores on this battery of tests indicate worse behavior problems in children.

5. Statistical analysis

Demographic and clinical characteristics were summarized using frequencies for women who did or did not report a URI during early pregnancy and included maternal race/ethnicity (white non-Hispanic, black non-Hispanic, Hispanic, other), maternal age (<25 years, 25–34 years, ≥ 35 years), annual household income ($\leq \$25,000$, $\$25,001$ – $\$35,000$, $\$35,001$ – $\$65,000$, $> \$65,000$), pre-pregnancy BMI (<18.5, 18.5–24, 25–29, ≥ 30), maternal education (≤ 12 years, 13–15 years, ≥ 16 years), and smoking during pregnancy (yes, no).

Average mean scores on the cognitive tests, PPVT-III and VMI-5, and the behavior assessment tools, CBCL and TRF, were calculated for children prenatally exposed and unexposed to URI. Mean scores were

also calculated for groups categorized by timing of URI onset, duration of URI, symptoms (fever or flu), and treatment. Adjusted linear regression models were used to calculate adjusted mean differences (adjMD) and 95% confidence intervals (CI) for all URI categorizations using children unexposed to URI as the reference. Potential confounders were identified a priori based on reported associations with infection during pregnancy and childhood neurodevelopment and included maternal race, age, and education. Household income was also considered, but due to missing data for approximately 6% of subjects and correlation with other confounders (race, age, and education), it was not included. Maternal smoking during pregnancy and maternal pre-pregnancy BMI were also considered as potential confounders and were tested using a change-in-estimate approach. Neither covariate materially altered results.

Analyses were performed using SAS Software Version 9.3 and the GLM procedure (SAS Institute, Cary, NC).

6. Results

Of the 839 control subjects in the original study, 570 (68%) participated in the follow-up study. Participants were more likely to be white, non-Hispanic, have higher educational attainment, and higher household income than non-participants. Among the 534 mother-child pairs included in this study after exclusions, 39.5% ($n = 211$) of mothers reported a URI in early pregnancy. Compared to mothers without a URI, those with a URI were more likely to be white, non-Hispanic (80.6% vs. 72.1%), <25 years of age (21.8% vs. 19.2%), and have ≥ 16 years of education (46.9% vs. 44.3%). They were also more likely to have a BMI ≥ 30 and smoke during pregnancy (Table 1).

Maternal exposure to URI was not associated with substantial differences in child receptive vocabulary skills (PPVT-III scaled score; adjMD: 1.34, 95% CI: $-1.16, 3.84$) or visual motor abilities (VMI-5 scaled score; adjMD: 0.32, 95% CI: $-1.65, 2.28$) compared to those unexposed to URI. URI was associated with an increase in total behavior problems

Table 1
Demographic characteristics of women with and without a reported URI.

| Characteristics | URI (N = 211) | | No URI (N = 323) | |
|-----------------------------------|---------------|------|------------------|------|
| | n | % | n | % |
| Maternal race/ethnicity | | | | |
| White non-Hispanic | 170 | 80.6 | 233 | 72.1 |
| Black non-Hispanic | 16 | 7.6 | 32 | 9.9 |
| Other | 4 | 1.9 | 17 | 5.3 |
| Hispanic | 21 | 10.0 | 41 | 12.7 |
| Maternal age at delivery | | | | |
| <25 years | 46 | 21.8 | 62 | 19.2 |
| 25–34 years | 125 | 59.2 | 209 | 64.7 |
| ≥ 35 years | 40 | 19.0 | 52 | 16.1 |
| Maternal education (years) | | | | |
| ≤ 12 | 65 | 30.8 | 97 | 30.0 |
| 13–15 | 47 | 22.3 | 83 | 25.7 |
| ≥ 16 | 99 | 46.9 | 143 | 44.3 |
| Household income | | | | |
| $\leq \$25,000$ | 33 | 15.6 | 54 | 16.7 |
| \$25,001–\$35,000 | 26 | 12.3 | 37 | 11.5 |
| \$35,001–\$65,000 | 62 | 29.4 | 104 | 32.2 |
| $> \$65,000$ | 80 | 37.9 | 108 | 33.4 |
| Missing | 10 | 4.7 | 20 | 6.2 |
| Marital status | | | | |
| Married/living with father | 190 | 90.0 | 286 | 88.5 |
| Widowed/divorced/separated | 21 | 10.0 | 37 | 11.5 |
| Pre-pregnancy body mass index | | | | |
| <18.5 | 7 | 3.3 | 11 | 3.4 |
| 18.5–24.9 | 126 | 59.7 | 206 | 63.8 |
| 25.0–29.9 | 43 | 20.4 | 69 | 21.4 |
| ≥ 30 | 33 | 15.6 | 31 | 9.6 |
| Missing | 2 | 1.0 | 6 | 1.9 |
| Maternal smoking during pregnancy | | | | |
| Yes | 35 | 16.6 | 49 | 15.2 |
| No | 176 | 83.4 | 274 | 84.8 |

according to both mother-report (CBCL Total T-score; adjMD: 3.72, 95% CI: 1.91, 5.54) and teacher-report (TRF Total T-score; adjMD: 2.74, 95% CI: 0.97, 4.50) after adjustment for maternal race, age, and education. An analysis of the subdomains of the CBCL and TRF showed the greatest differences in scores for attention problems and aggressive behavior. The inclusion of women reporting a URI in the first lunar month slightly attenuated the mean difference for most of the domains (Table 2).

In general, the associations between URI and behavioral outcomes were stronger for infections occurring in mid-pregnancy than in early pregnancy, when both were compared to children of mothers without a URI. The adjusted mean difference for total behavior problems was 5.14 (95% CI: 2.75, 7.54) according to mother-report and 4.18 (95% CI: 1.89, 6.47) for teacher-report for infections in mid-pregnancy. The corresponding differences for infection in early pregnancy were attenuated to 2.85 (95% CI: 0.35, 5.34) and 0.74 (95% CI: $-1.68, 3.16$), respectively (Table 3). There was little difference in PPVT and VMI-5 scores based on timing of infection and confidence intervals for these results were wide.

Average differences in scores based on duration of infection were small, with the exception of the CBCL. The adjusted mean difference between URI and behavior problems was greater for children of mothers with long duration of URI (CBCL adjMD: 4.85, 95% CI: 2.50, 7.21). Similar differences were also observed for the scales of internalizing and externalizing behavior problems. VMI-5 scores were lower, though not significantly, among mothers with long duration of URI than for mothers with short duration of illness (adjMD: -0.73 , 95% CI: $-3.30, 1.85$) (Table 4).

URI accompanied by fever or flu was also assessed. In general, URI plus self-reported flu ($n = 28$) was associated with poorer behavioral outcomes. Total and externalizing behavioral problems were notably higher in offspring of mother's reporting flu, although the number of mother's reporting flu was small. URI with fever only ($n = 26$) was also associated with increased behavior problems compared to children of mothers with no URI, but differences were smaller in general and the confidence intervals included the null value (Table 5).

Among women with a URI, 69% ($n = 145$) used medication or supplements for treatment. The most common medications reported for treatment included acetaminophen (44%), pseudoephedrine/decongestants (28%), and antibiotics (22%). Women that treated their URI were more likely to be white, non-Hispanic (86% vs. 68%) and have ≥ 16 years of education (49% vs. 42%) compared to women that did not treat (data not shown). VMI-5 scores were lower among those exposed to antihistamines (adjMD: -2.12 , 95% CI: $-6.84, 2.60$), although the confidence intervals were wide and demonstrated considerable overlap with the other treatment groups and URI without treatment group. Behavioral problems according to maternal report were worse when URI was treated with guaifenesin (CBCL adjMD: 8.90, 95% CI: 4.09, 13.91) or antibiotics (CBCL adjMD: 5.45, 95% CI: 1.65, 9.26). Compared to results for URI without treatment, treatment with acetaminophen was associated with poorer behavioral outcomes according to mother-report, but not teacher-report. In general, there were no large differences in cognitive or psychosocial outcomes between treatment with specific medications and URI compared with no treatment (Table 6).

7. Discussion

Upper respiratory infection during early and mid-pregnancy was moderately associated with more behavioral problems, as reported by mothers and teachers, when the children were assessed at ages 5 through 12. In general, associations between URI and cognitive outcomes, specifically measures of receptive vocabulary and visual-motor abilities, were not observed. The associations between URI and behavioral outcomes were most pronounced for infections occurring during mid-pregnancy. The ability of infection to influence neurodevelopmental outcomes in

Table 2
Mean difference in neurodevelopmental test scores of children among mothers with and without URI.

| Test | URI/No URI | Mean (SD) scaled score | | Mean Difference (95% CI) | | |
|---------------------|------------|------------------------|--------------|--------------------------|--------------------------------|------------------------------------|
| | | URI | No URI | Crude | Adjusted: primary ^a | Adjusted: sensitivity ^b |
| PPVT-III | 177/261 | 107.5 (13.6) | 105.7 (14.0) | 1.72 (−0.93, 4.37) | 1.34 (−1.16, 3.84) | 0.71 (−1.75, 3.18) |
| VMI-5 | 177/260 | 96.9 (10.6) | 96.5 (10.3) | 0.28 (−1.71, 2.28) | 0.32 (−1.65, 2.28) | 0.32 (−1.62, 2.26) |
| CBCL | | Mean (SD) T-score | | | | |
| Total | 210/320 | 49.5 (10.2) | 45.8 (10.4) | 3.60 (1.80, 5.40) | 3.72 (1.91, 5.54) | 3.22 (1.49, 4.95) |
| External | 210/320 | 49.5 (10.1) | 46.8 (9.4) | 2.64 (0.94, 4.33) | 2.77 (1.06, 4.48) | 2.27 (0.64, 3.90) |
| Internal | 210/320 | 49.8 (9.4) | 47.3 (9.8) | 2.46 (0.77, 4.14) | 2.54 (0.86, 4.22) | 2.15 (0.55, 3.76) |
| Anxious/depressed | 210/320 | 54.2 (6.1) | 53.1 (5.3) | 1.14 (0.15, 2.12) | 1.16 (0.17, 2.15) | 0.93 (0.00, 1.86) |
| Withdrawn/depressed | 210/320 | 53.3 (4.9) | 52.3 (4.2) | 1.04 (0.26, 1.82) | 1.07 (0.29, 1.86) | 1.04 (0.28, 1.80) |
| Somatic complaints | 210/320 | 54.2 (5.6) | 54.1 (5.6) | 0.14 (−0.84, 1.11) | 0.18 (−0.81, 1.16) | 0.04 (−0.89, 0.98) |
| Social problems | 210/320 | 53.5 (4.6) | 53.0 (5.1) | 0.50 (−0.36, 1.36) | 0.54 (−0.32, 1.40) | 0.33 (−0.47, 1.13) |
| Thought problems | 210/320 | 54.4 (6.0) | 53.3 (5.3) | 1.11 (0.14, 2.09) | 1.15 (0.16, 2.13) | 1.01 (0.06, 1.95) |
| Attention problems | 210/320 | 54.5 (6.1) | 52.6 (4.5) | 1.87 (0.96, 2.77) | 1.90 (0.98, 2.82) | 1.92 (1.00, 2.83) |
| Rule-breaking | 210/320 | 53.9 (5.4) | 52.7 (4.0) | 1.27 (0.47, 2.07) | 1.32 (0.51, 2.13) | 1.21 (0.43, 2.00) |
| Aggressive behavior | 210/320 | 54.2 (6.5) | 52.8 (4.9) | 1.44 (0.46, 2.41) | 1.50 (0.52, 2.49) | 1.17 (0.24, 2.10) |
| TRF | | | | | | |
| Total | 187/282 | 49.8 (10.1) | 47.1 (9.1) | 2.61 (0.85, 4.37) | 2.74 (0.97, 4.50) | 2.70 (1.01, 4.38) |
| External | 187/282 | 49.8 (9.0) | 47.1 (8.4) | 2.35 (0.83, 3.88) | 2.47 (0.95, 3.99) | 2.66 (1.20, 4.12) |
| Internal | 187/282 | 49.1 (9.5) | 47.2 (7.7) | 1.48 (−0.16, 3.12) | 1.52 (−0.14, 3.18) | 1.34 (−0.23, 2.92) |
| Anxious/depressed | 187/282 | 54.3 (6.2) | 53.0 (4.1) | 1.29 (0.35, 2.23) | 1.28 (0.33, 2.23) | 1.11 (0.21, 2.01) |
| Withdrawn/depressed | 187/282 | 52.8 (4.5) | 52.6 (4.6) | 0.15 (−0.68, 0.99) | 0.16 (−0.68, 1.01) | 0.16 (−0.65, 0.96) |
| Somatic complaints | 187/282 | 52.7 (5.3) | 52.0 (4.7) | 0.64 (−0.27, 1.56) | 0.56 (−0.36, 1.48) | 0.49 (−0.39, 1.36) |
| Social problems | 187/282 | 54.2 (5.6) | 53.1 (4.8) | 1.14 (0.19, 2.10) | 1.11 (0.14, 2.07) | 1.04 (0.13, 1.96) |
| Thought problems | 187/282 | 53.4 (6.0) | 52.3 (4.5) | 1.11 (0.16, 2.07) | 1.12 (0.15, 2.08) | 0.96 (0.03, 1.90) |
| Attention problems | 187/282 | 52.4 (6.1) | 53.0 (5.1) | 1.23 (0.21, 2.24) | 1.32 (0.30, 2.33) | 1.24 (0.28, 2.21) |
| Rule-breaking | 187/282 | 53.2 (5.3) | 52.4 (4.7) | 0.82 (−0.10, 1.74) | 0.85 (−0.06, 1.77) | 0.90 (0.02, 1.78) |
| Aggressive behavior | 187/282 | 53.7 (6.4) | 52.3 (4.5) | 1.41 (0.42, 2.40) | 1.44 (0.45, 2.43) | 1.53 (0.57, 2.49) |

PPVT-III: Peabody Picture Vocabulary Test; VMI-5: Beery-Buktenica Test of Visual Motor Integration-Fifth Edition; CBCL: Child Behavior Checklist; TRF: Teacher Report Form.

^a Adjusted for maternal race, age, and education

^b Includes women reporting a URI in the first lunar month (n = 36).

offspring has been suggested to be a result of maternal immune activation. The increased production on inflammatory cytokines, as a result of the mother's immune response to infection, has been hypothesized to be the mediating factor between maternal infection and neurodevelopmental disorders in the offspring (Ratnayake et al., 2013).

One study conducted among preterm infants reported an association between genitourinary tract infections and poorer scores on neurobehavioral outcomes using the Infant Toddler Social and Emotional Assessment (ITSEA) at 2 years (Lee et al., 2014), but to our knowledge ours is one of the first studies to explore maternal infection in relation to cognitive and psychosocial functioning in childhood.

Although the present analysis investigated a continuous measure of cognition and behavioral development in a non-clinic population, our findings are consistent with studies reporting associations between

infection and increased risk of psychiatric problems in children, particularly ASD, yet inconsistent with a study reporting no association between respiratory infection hospitalizations and ASD (Atladdottir et al., 2010). While diagnoses of ASD and ADHD were not available in the present study, measures found within the social, thought, attention, and withdrawn syndrome scales can be used to discriminate children with ASD with moderate to high sensitivity and specificity (Ooi et al., 2011) and high predictive values (So et al., 2013), while externalizing, attention, and aggressive scores show the greatest difference between children with ADHD and children without ADHD (Graetz et al., 2001). Thought and attention scores on both the CBCL and TRF were significantly higher among children of mothers that reported an URI in the present study, while withdrawn scores were elevated on the CBCL and social scores were elevated on the TRF. Using a clinical cutoff of a T-score of 64 for the CBCL and TRF, the proportion of our sample

Table 3
Mean difference in neurodevelopmental test scores of children by timing of URI in mothers.

| Test | Months 2–3 | Months 4–5 |
|-----------------------|---|---|
| | Adjusted mean difference (95% CI) (n = 85) ^a | Adjusted mean difference (95% CI) (N = 93) ^a |
| PPVT-III ^b | 2.18 (−1.54, 5.90) | 1.96 (−1.59, 5.51) |
| VMI-5 ^b | −0.26 (−3.01, 2.48) | 0.53 (−2.06, 3.13) |
| CBCL ^c | | |
| Total | 2.85 (0.35, 5.34) | 5.14 (2.75, 7.54) |
| External | 1.70 (−0.65, 4.04) | 3.41 (1.16, 5.66) |
| Internal | 1.63 (−0.71, 3.97) | 4.47 (2.22, 6.72) |
| TRF ^c | | |
| Total | 0.74 (−1.68, 3.16) | 4.18 (1.89, 6.47) |
| External | 1.46 (−0.64, 3.56) | 2.69 (0.70, 4.68) |
| Internal | −0.88 (−3.13, 1.37) | 3.91 (1.77, 6.04) |

Reference group is children of mothers with no URI (n = 323). PPVT-III: Peabody Picture Vocabulary Test; VMI-5: Beery-Buktenica Test of Visual Motor Integration-Fifth Edition; CBCL: Child Behavior Checklist; TRF: Teacher Report Form.

^a Adjusted for maternal race, maternal age, and maternal education.

^b Scaled scores.

^c T-scores.

Table 4
Mean difference in neurodevelopmental test scores of children by duration of URI in mothers.

| Test | Short duration (1–9 days) | Long duration (≥10 days) |
|-----------------------|--|---|
| | Adjusted mean difference (95% CI) (N = 103) ^a | Adjusted mean difference (95% CI) (N = 99) ^a |
| PPVT-III ^b | 1.32 (−1.85, 4.48) | 1.66 (−1.63, 4.94) |
| VMI-5 ^b | 0.57 (−1.88, 3.03) | −0.73 (−3.30, 1.85) |
| CBCL ^c | | |
| Total | 3.13 (0.82, 5.44) | 4.85 (2.50, 7.21) |
| External | 1.95 (−0.23, 4.12) | 4.06 (1.84, 6.28) |
| Internal | 1.54 (−0.61, 3.70) | 3.97 (1.78, 6.17) |
| TRF ^c | | |
| Total | 2.74 (0.53, 4.96) | 2.85 (0.51, 5.19) |
| External | 2.39 (0.48, 4.29) | 2.45 (0.44, 4.47) |
| Internal | 1.30 (−0.78, 3.39) | 2.34 (0.14, 4.54) |

Reference group is children of mothers with no URI (n = 323). PPVT-III: Peabody Picture Vocabulary Test; VMI-5: Beery-Buktenica Test of Visual Motor Integration-Fifth Edition; CBCL: Child Behavior Checklist; TRF: Teacher Report Form.

^a Adjusted for maternal race, maternal age, maternal education.

^b Scaled scores.

^c T-scores.

Table 5
Mean difference in neurodevelopmental test scores of children by URI with fever and with flu in mothers.

| Test | Adjusted mean difference (95% CI) URI with fever ^a n = 28 | Adjusted mean difference (95% CI) URI with flu ^a n = 26 |
|-----------------------|--|--|
| PPVT-III ^b | 4.28 (−1.80, 10.35) | 5.11 (−0.64, 10.89) |
| VMI-5 ^b | −0.40 (−4.99, 4.19) | −1.60 (−5.93, 2.74) |
| CBCL ^c | | |
| Total | 3.30 (−0.90, 7.50) | 5.62 (1.56, 9.69) |
| External | 2.95 (−0.91, 6.80) | 4.97 (1.24, 8.70) |
| Internal | 3.06 (−0.82, 6.95) | 4.03 (0.27, 7.79) |
| TRF ^c | | |
| Total | 2.69 (−1.39, 6.78) | 3.12 (−0.51, 6.76) |
| External | 1.17 (−2.32, 4.65) | 3.36 (0.26, 6.45) |
| Internal | 4.65 (0.77, 8.52) | −1.47 (−4.92, 1.98) |

Reference group is children of mothers with no URI (n = 323). PPVT-III: Peabody Picture Vocabulary Test ; VMI-5: Beery-Buktenica Test of Visual Motor Integration-Fifth Edition; CBCL: Child Behavior Checklist; TRF: Teacher Report Form.

^a Adjusted for maternal race, maternal age, maternal education.

^b Scaled scores.

^c T-scores.

classified in the clinical range was 4.1% to 7.5%, respectively, suggesting that the majority of our sample reflects a normative range of psychosocial outcomes among these children.

We observed differences between URI and neurodevelopmental outcomes based on timing of infection during pregnancy, with poorer outcomes observed for infections during the fourth and fifth lunar month of pregnancy, which is largely reflective of the second trimester. Our findings are inconsistent with a study conducted in the Danish National Birth Cohort that reported no association between respiratory tract infection in any trimester of pregnancy and ASD when compared to children of mothers reporting no infections during pregnancy (Atladdottir et al., 2012). Another study reported increased risks of ASD for first trimester viral infections and second trimester bacterial infections (Atladdottir et al., 2010), but infections included were only those resulting in hospitalization. Late gestation has also been suggested to be an exceptionally vulnerable period with respect to neurodevelopment, (Bitanhirwe et al., 2010) yet lack of information on infection in the third trimester prevented us from exploring this particular question.

Observed differences between outcomes were also influenced by the presence of fever or flu, with poorer visual-motor function and behavior problems noted for children of mothers reporting flu. Prenatal exposure to influenza has previously been associated with schizophrenia and bipolar disorder in adult offspring, but little is known about its association with neurodevelopment outcomes in children. Previous studies found prolonged fever (≥ 7 days) to be associated with a 2-fold risk of autism (Atladdottir et al., 2012). While the present study did not capture information on the duration of specific symptoms of URI, 21% of mothers with a URI reported having a fever, and fever was associated with slightly worse behavior problems in offspring.

Table 6
Mean difference in neurodevelopmental test scores of children by treatment of URI in mothers.

| Test | Adjusted mean difference (95% CI) ^a | | | | | |
|-----------------------|--|------------------------|----------------------|-------------------------|--|-----------------------|
| | Antibiotics (n = 32) | Acetaminophen (n = 64) | Guaifenesin (n = 18) | Antihistamines (n = 22) | Pseudoephedrine/decongestants (n = 41) | No treatment (n = 66) |
| PPVT-III ^b | 3.86 (−1.33, 9.10) | 1.03 (−2.83, 4.90) | 0.63 (−5.71, 6.97) | 2.44 (−3.66, 8.54) | 0.57 (−4.08, 5.21) | 2.95 (−0.88, 6.78) |
| VMI-5 ^b | 0.67 (−3.52, 4.87) | 0.47 (−2.60, 3.53) | 1.33 (−3.69, 6.35) | −2.12 (−6.84, 2.60) | −1.07 (−4.68, 2.54) | 1.52 (−1.50, 4.54) |
| CBCL ^c | 5.45 (1.65, 9.26) | 4.90 (2.07, 7.73) | 8.90 (4.09, 13.91) | 2.16 (−2.30, 6.62) | 3.87 (0.49, 7.25) | 2.74 (0.01, 5.48) |
| TRF ^c | 4.48 (0.74, 8.21) | 2.77 (0.12, 5.43) | 1.96 (−2.65, 6.57) | 2.08 (−2.25, 6.40) | 3.38 (0.05, 6.71) | 3.88 (1.20, 6.56) |

Reference group contains women with no treatment. PPVT-III: Peabody Picture Vocabulary Test; VMI-5: Beery-Buktenica Test of Visual Motor Integration-Fifth Edition; CBCL: Child Behavior Checklist; TRF: Teacher Report Form.

^a Adjusted for maternal race, maternal age, and maternal education.

^b Scaled scores.

^c T-scores.

In general, the role of treatment and medications for URI and cognitive outcomes in children is less clear. Associations between URI and both mother- and teacher-reported behavior problems were stronger when the infection was treated with antibiotics than when the infection was untreated. Compared to the association for untreated infection and behavioral outcomes, treatment with acetaminophen or guaifenesin was associated with poorer behavior according to mother-report only. Several studies have explored the association between acetaminophen use during pregnancy and behavioral outcomes among offspring (Liew et al., 2014; Thompson et al., 2014; Liew et al., 2015). Acetaminophen use, for any indication, has been associated with slight increases in conduct and hyperactivity problems and ASD with hyperkinetic symptoms and these associations remained when multivariate models included infection/fever as a covariate. In the present study, differences in scores among treatment groups were small and inconsistent and both treated and untreated infections were associated with increases in behavior problems.

Limitations of the present study should be noted. Data on URI was collected retrospectively by maternal self-report up to three years after delivery, which may have resulted in misclassification of exposure if URI was not accurately reported. In the present study, 16% and 17% of mothers reported having a URI during lunar months 2–3 and 4–5, respectively, compared to 22.8% and 21.9% reported for the first trimester and second trimester, respectively among participants in the National Birth Defects Prevention Study (Collier et al., 2009). Misclassification of URI with respect to timing, duration, and symptoms is also possible. It is possible that women mistook another illness with similar symptoms (i.e. allergies) for a URI. URI is an umbrella term for infections as it included flu-like illness, sinus infections, and the common cold. Due to this limitation, we were unable to explore specific infections, nor distinguish between bacterial and viral infections. Measures of URI in late pregnancy were not available, thereby restricting our ability to explore late pregnancy infection as a risk factor for neurodevelopmental outcomes and perhaps missing an etiologic relevant period. The exposure misclassification is not expected to be differential with respect to neurodevelopmental outcomes, since such outcomes were measured after the interview. We also lacked serologic confirmation of self-reported infection as well as information on the presence of other infections during pregnancy, such as genitourinary infections. Mean differences were adjusted for confounders but it is possible that residual confounding and confounding due to lack of variables, such as underlying conditions, is possible. Our sample, while representing a range of maternal demographic characteristics, had a higher educational attainment than the general US population. Lastly, mothers' CBCL reports could have been biased by their knowledge of infection during pregnancy, but this is unlikely given the long interval between pregnancy and CBCL completion.

The strengths of this study include the administration of the neurodevelopmental measures in concordance with uniform guidelines. Furthermore, the PPVT-III, VMI-5, and TRF were administered by classroom teachers who presumably had no knowledge of maternal infections in pregnancy. This study included a large sample of mother-offspring

pairs allowing for the exploration of the role of timing, duration, and treatment of URI in relation to neurodevelopment. Additionally, mothers reported URI information through a standardized in-person interview with trained study nurses including symptoms, duration, timing, and treatment, prior to assessment of neurocognitive functioning and therefore the recall of information was not influenced by the development of neurocognitive delays in offspring. While the measures used in our analysis cannot be used to diagnose specific disorders, we were able to detect small changes in neurodevelopment across a normative range of scores. While an average difference in test scores of just a few points may not be clinically meaningful on the individual level, a few points associated with such a ubiquitous exposure may have a large population impact.

In conclusion, our findings contribute to the growing body of literature demonstrating the role of prenatal exposure to infections in fetal neurodevelopment. We report alterations in behavioral outcomes with respect to maternal infections in a non-clinic based population of children, although information on infection was collected retrospectively. Future studies should focus on obtaining serial serologic data to better classify type and timing of infection as it relates to neurodevelopment and utilize an extensive neuropsychological test battery to examine all domains of function.

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