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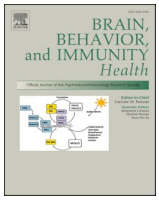

Contributions of maternal prenatal infection and antibiotic exposure to offspring infection and risk for allergic respiratory conditions through age 5

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A B S T R A C T

Objectives: To determine if maternal prenatal infection increases risk of offspring postnatal infections through age 5 or diagnosis of respiratory allergy at age 5, independent of prenatal/postnatal antibiotic exposure. To evaluate if frequency of offspring infections mediates an association between prenatal infection and respiratory allergy at age 5.

Study design: Secondary data analyses were performed from the Child Health and Development Studies (CHDS), a prospective, longitudinal birth cohort that enrolled pregnant women from 1959 to 1966 (N = 19,044 live births). The sample included a subset of mother-offspring dyads ($n = 2062$) with abstracted medical record data from the prenatal period through age 5 that included information on antibiotic use, infection, and offspring respiratory allergy.

Results: Second trimester maternal infection was associated with an increased risk of offspring infection (IRR = 1.23; 95% CI = 1.09–1.39; $p = 0.001$). No significant direct associations were detected between prenatal infection and diagnosis of offspring respiratory allergy. Offspring infection (OR = 1.17; 95% CI = 1.13–1.20; $p < 0.001$) and antibiotic exposure (OR = 1.28; 95% CI = 1.22–1.33; $p < 0.001$) were significantly associated with a diagnosis of offspring respiratory allergy. Respiratory allergy diagnosis risk was greater with increasing offspring infection exposure and antibiotics. There was a significant indirect effect of second trimester maternal infection on offspring respiratory allergy, due to infections and not antibiotic use, via offspring infection, indicating a partially mediated effect.

Conclusion: Prenatal maternal infection may contribute to increase risk for early childhood infections, which in turn, may increase risk for allergic conditions.

Accumulating data, primarily from preclinical studies, provides evidence of a link between prenatal infection and enduring alterations in offspring immune processes. Specifically, results suggest that prenatal maternal immune activation (MIA) may induce fetal inflammatory responses, evidenced by heightened expression of maternal and fetal pro-inflammatory cytokines (Boksa, 2010; Mandal et al., 2013; Patternson, 2009; Simões e Siva et al., 2020). Prenatal MIA is associated with persistent altered offspring immune profiles (Mandal et al., 2011, 2013; Estes and McAllister, 2016; Hsiao and Patterson, 2012; Ponzio et al., 2013). As such, prenatal MIA may induce a long-lasting offspring pro-inflammatory phenotype in offspring characterized by robust responses to subsequent postnatal immune challenges (Mandal et al., 2013; Simões e Siva et al., 2020; Ponzio et al., 2013). Despite this evidence from animal models, few studies have examined this hypothesis in humans. The majority of human studies have focused on the association between maternal prenatal infection and offspring immune alterations in relation to risk for offspring psychopathology (Patternson, 2009; Fineberg and Ellman, 2013; Miller et al., 2013; Patterson, 2011; Mac Giollabhui et al., 2019). Several psychiatric disorders may originate, in part, during fetal development, suggesting maternal prenatal infection may 'prime' the fetal brain and immune system, increasing vulnerability to immune-mediated diseases (Bale et al., 2010; Bilbo and Schwarz, 2009; Gumusoglu and Stevens, 2019; Merlot et al., 2008; Page, 2018). Less attention has been given to the impact of maternal prenatal infection on offspring immune-related physical health outcomes (Fineberg and Ellman, 2013; Deng et al., 2018; Patternson, 2011; Raison et al., 2006).

To our knowledge, only three human studies have examined the relationship between maternal prenatal infection and risk of offspring infection (Betts et al., 2014; Blomstrom et al., 2016; Cohen et al., 2019), none of which addressed timing of prenatal infections on offspring illness, despite evidence that timing of prenatal infection differentially

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predicts offspring outcomes (Fineberg and Ellman, 2013; Brown and Derkits, 2010). In one study, maternal self-report at birth of prenatal vaginal infection predicted offspring illness susceptibility (i.e., maternal report of frequency of medical attention and symptoms of infection) during the first six months of life (Betts et al., 2014). However, this study used non-specific measurement of infant illness and narrow assessment of prenatal infection, which did not include other common prenatal infections. In the second study, using national register data, increased childhood hospitalization risk was found among offspring of mothers with a hospital diagnosis of prenatal viral or bacterial infection (Blomstrom et al., 2016). Similarly, a population-based cohort analysis found maternal urinary tract infection (UTI) in pregnancy may influence offspring susceptibility to pediatric infections (Cohen et al., 2019). Despite including a range of clinically diagnosed maternal and childhood infections, questions remain as to the relationship between less severe forms of prenatal infection (i.e., not requiring hospitalization) and risk of offspring infection.

Several other meta-analyses (Baron et al., 2020a; Zhu et al., 2016) and systematic reviews (Baron et al., 2020a) have demonstrated associations between maternal prenatal infection and offspring immune outcomes (e.g., asthma and related allergic disorders) (Algert et al., 2011; Calvani et al., 2004; Collier et al., 2013; Hughes et al., 1999; Xu et al., 1999). Early life viral respiratory infections appear to be associated with the development and exacerbation of childhood asthma and allergic disease (Bacharier et al., 2012; Beigelman and Bacharier, 2016; Busse et al., 2010; Jackson et al., 2008; Kusel et al., 2007; Sigurs et al., 2005; Zomer-Kooijker et al., 2014). Yet, no studies have examined whether childhood infection partially mediates or enhances the relationship between maternal prenatal infection and development of allergic respiratory conditions in offspring. Complicating these findings, prenatal antibiotic exposure has been linked to increased risk of the development of offspring allergic disorders, including childhood asthma (Jedrychowski et al., 2006; McKeever et al., 2002; Rusconi et al., 2007; Stensballe et al., 2013; Baron et al., 2020b) and infection-related hospitalization (Miller et al., 2018; Gestels and Vandenplas, 2023). Further, a handful of studies have demonstrated associations between antibiotic exposure in early life and risk of developing childhood asthma (Baron et al., 2020b; Kozyrskyj et al., 2007; Kuo et al., 2013; Marra et al., 2009; Murk et al., 2011; Risnes et al., 2011). Debate remains as to the role of pre- and postnatal antibiotic exposure in the development of childhood allergic disorders, due to inconsistent findings (Kuo et al., 2013; Murk et al., 2011) and failure to detect an association after controlling for confounding factors (e.g., presence of childhood infection). (Celedon et al., 2004; Mai et al., 2010; Su et al., 2010; Wickens et al., 2008).

The present study used prospectively collected, longitudinal cohort data to investigate the role of maternal prenatal infection in the development of offspring infection and allergic respiratory conditions. We hypothesized that prenatal infection, independent of prenatal antibiotic exposure, would increase risk for offspring infection and respiratory allergy risk. Further, we predicted that offspring infection would partially mediate the relationship between prenatal infection and offspring allergic respiratory conditions.

1. Methods

1.1. Participants

Secondary data analyses were approved by the Institutional Review Boards at the Public Health Institute, University of California-Los Angeles (UCLA) and Temple University. Participants were drawn from the Child Health and Development Studies (CHDS), a prospective, longitudinal cohort study that enrolled pregnant women from 1959 to 1966 (N = 19,044 live births) in Alameda County, California and some surrounding areas. CHDS recruited pregnant women receiving obstetric care through the Kaiser Foundation Health Plan (van den Berg et al., 1988).

Current study participants were drawn from a subset of the CHDS cohort, including offspring with abstracted medical record data from birth (n = 4188). Within this subset of CHDS children, additional record abstractions were conducted on children who had 1) severe congenital anomalies (n = 718), 2) non-severe congenital anomalies (n = 702), or 3) certain selected disabilities (n = 482). These children, and an additional 54 children with no post-birth medical record data, were excluded from analyses. Some mothers had multiple offspring in the sample; therefore, one member of each sibling set was randomly selected to eliminate non-independent observations (n = 170 removed), resulting in a final analytical sample of 2062 mother/child pairs (see Fig. 1 for a flow chart of the sample selection). See Table 1 for demographic characteristics and Table 2 for comparative demographics between our sample and the remainder CHDS live births.

1.2. Maternal infection and antibiotic exposure during pregnancy

Maternal medical events occurring six months prior to the women's last menstrual period until after delivery, including presence and timing of prenatal infections, were abstracted from Kaiser medical records. Diagnoses of infection were identified according to the International Classification of Diseases, Seventh Edition (ICD-7; see Table 6). Infection variables were collapsed across categories (i.e., viral, bacterial, other) and a single dichotomous infection variable was created to indicate presence or absence of at least one infection in each trimester, similar to previous studies (Cheslack-Postava and Brown, 2022).

Type, timing, and frequency of oral antibiotics taken in response to infection during pregnancy were recorded. Oral antibiotics were limited to broad-spectrum antibiotics, specifically tetracyclines, sulfonamides, select penicillins (e.g., Ampicillin), and select macrolides (e.g., erythromycin). These exposures were recorded because these agents act on a wide-range of disease-causing bacteria in comparison to narrow-spectrum agents (Sarpong and Miller, 2015), at least 11 types of broad-spectrum antibiotics are known to cross the placenta (Nahum et al., 2006), and they have been classified similarly in related studies (McKeever et al., 2002; Kozyrskyj et al., 2007; Borg and Camilleri, 2019). Frequency of broad-spectrum antibiotic use by trimester was summed and examined as a continuous variable.

1.3. Offspring childhood infection and antibiotic exposure

Diagnosed conditions, treatments, and prescriptions from birth to ages 9–12 (abstractions from 1960 to 1972) were abstracted from medical records of offspring's visits to Kaiser pediatric clinics, specialty clinics, and hospitalizations. Participant attrition increased gradually over subsequent study years leading to substantial missing data by middle childhood; therefore, the presence of childhood infections (identified according to 2-digit ICD-8 codes, see Table 6) and/or antibiotic exposure was limited to the first 5 years of life. Frequency of childhood infections and antibiotic exposures during this period were summed and examined as continuous variables. Offspring antibiotic use was limited to treatment with broad-spectrum antibiotics.

1.4. Offspring childhood respiratory conditions

Diagnoses indicating the presence of offspring *'Respiratory Allergy'* at age 5 were used. A diagnosis of *'Respiratory Allergy'* was identified according to a 2-digit ICD-8 code that was modified to capture the morbidity experience of young children, encompassing: wheezing or allergic bronchitis, asthmatic bronchitis, asthma, or hay fever.

1.5. Data analysis

All analyses were performed using IBM SPSS (v25). Statistical significance was based on two-tailed tests with $p < 0.05$. Bivariate relationships were examined between study variables and maternal age,

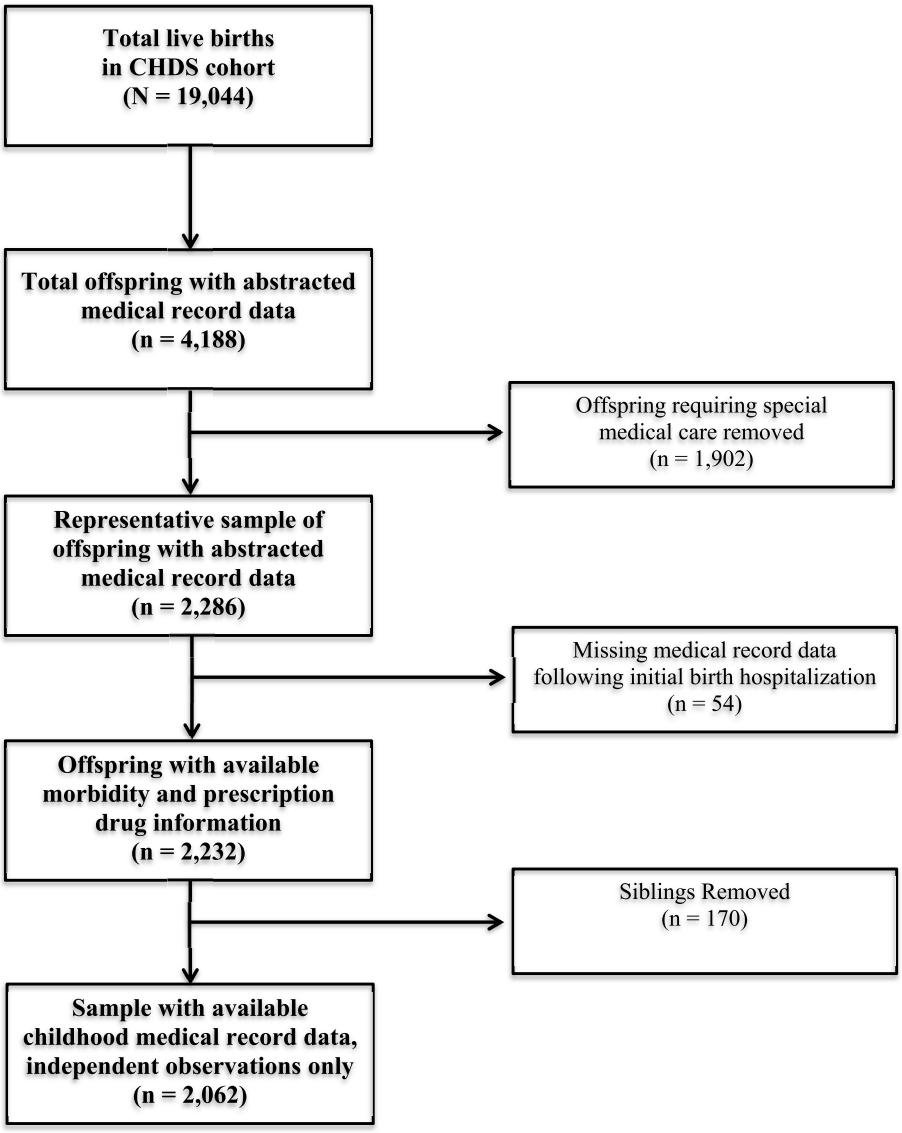

Fig. 1. Flow chart of participants in analytic sample.

maternal race (Black participants vs. not Black participants), parity, delivery type (vaginal vs. caesarian), gestational age (weeks from last menstrual period to birth), birth weight, and offspring sex. Variables significantly correlated with at least one independent variable and at least one dependent variable were added as covariates in statistical models. Maternal education at birth (high school degree or below vs. above high school) was controlled for in analyses as a representative of socioeconomic status, given its strong correlation with other measures of SES (e.g., income) in the sample and frequent use as a proxy for postnatal adversity (Fineberg et al., 2016; Schlotz and Phillips, 2009).

Negative binomial regressions (Hilbe, 2011) were conducted to evaluate the association between each trimester of prenatal infection and frequency of offspring infection, as well as offspring antibiotic exposure, in separate models controlling for covariates. These analyses were repeated using prenatal antibiotic exposure by trimester as the predictor variable. Model results were reported using Incidence Rate Ratios (IRR). Separate logistic regressions also were conducted to determine whether presence of prenatal infection by trimester, childhood infection frequency, the interaction between prenatal and offspring infection, and/or frequency of childhood antibiotic exposure predicted allergic respiratory conditions in offspring at age 5, controlling for covariates. Models were adjusted for maternal diagnosis of asthma or chronic bronchitis anytime during pregnancy, as maternal asthma is associated with risk of offspring asthma (Burke et al., 2003).

Two sensitivity analyses were performed to evaluate the potential confounding effect of antibiotic exposure on the relationship between prenatal infection and offspring infection, and the relationship between offspring infection and allergic respiratory conditions. One analysis was restricted to mothers who had no antibiotic exposure during pregnancy. The second analysis was restricted to offspring with no exposure to antibiotics during the first 24 months of life (analyses restricted to offspring without antibiotic exposure during the first 5 years of life resulted in a sample size too small to interpret). Multicollinearity was assessed among the infection and antibiotic study variables using variance inflation factor (VIF) and examination of the correlation matrix. Study variables with a correlation greater than 0.5 or a VIF greater than 5 were not included together as predictors in regression models.

To test whether frequency of offspring infection partially mediated the relationship between prenatal infection and offspring allergic respiratory conditions at age 5, Preacher and Hayes SPSS indirect bootstrapping macro for mediation was used (Preacher and Hayes, 2008). Of note, this method allows for the investigation of indirect pathways even in the absence of a direct effect (O'Rourke and MacKinnon, 2018). Significant mediation was determined if the 95% bias-corrected

Table 1
Demographic and clinical characteristics of analytic Sample (n = 2062).

Demographics	Overall Sample (N = 2062)
Offspring Sex, *n* (%)	
Male	974 (47.2)
Female	1088 (52.8)
Maternal Race, *n* (%)	
African American	458 (22.3)
Non-African American	1597 (77.7)
Maternal Education, *n* (%)	
Less than or equal to H.S.	1051 (51.7)
Greater than H.S.	982 (48.3)
Parity, *n* (%)	
First child	390 (18.9)
Second child	493 (23.9)
Third or more child	1178 (57.2)
Delivery Type, *n (%)*	
Vaginal	1961 (95.7)
Caesarian Section	88 (4.3)
Maternal Age, *M (SD)*	28.2 (5.9)
Birth Weight (g), *M (SD)*	3374.1 (503.7)
Gestational Age, *M (SD)*	40.1 (2.2)
Maternal Infection, *n (%)*	
Trimester 1	291 (14.1)
Trimester 2	346 (16.8)
Trimester 3	285 (13.8)
Maternal Antibiotic Exposure, *n (%) (%)n(%)*	
Trimester 1	102 (4.9)
Trimester 2	98 (4.8)
Trimester 3	98 (4.8)
Offspring Infection, *n (%) [M (SD)]*	1969 (95.5) [8.08 (5.32)]
Offspring Antibiotic, *n (%) [M (SD)]*	1733 (84.0) [3.62 (3.22)]
Respiratory Allergy at age 5, *n (%)*	180 (8.7)

Note. For the present study sample, the following variables had missing data: maternal race (n = 7); maternal education (n = 29); parity (n = 1); delivery type (n = 13); maternal age (n = 6); gestational age (n = 19). Gestational age = weeks from last menstrual period to birth; Maternal infection = presence of any infection by trimester; Maternal antibiotic exposure: frequency of antibiotic use by trimester; Offspring infection = frequency of infection 0–5 years of age; Offspring antibiotic = Frequency of antibiotic use 0–5 years of age.

Table 2
Comparative demographics for analytic sample and CHDS not in analytic sample (Total n = 19,044).

Demographics	Analytic Sample	CHDS Not in Analytic Sample	*p*-value
	n = 2062	n = 16,982	
Offspring Sex, *n* (%)			<0.0001
Male	974 (47.2)	8769 (51.6)	
Female	1088 (52.8)	8213 (48.4)	
Maternal Race, *n* (%)			<0.0001 < 0.0001
African American	458 (22.3)	4347 (25.6)	
Non-African American	1597 (77.7)	12,358 (72.8)	
Maternal Education, *n* (%)			0.43
Less than or equal to H.S.	1051 (51.7)	7227 (50.8)	
Greater than H.S.	982 (48.3)	6996 (49.2)	
Parity, *n* (%)			<0.0001
First child	390 (18.9)	5077 (27.7)	
Second child	493 (23.9)	4482 (24.5)	
Third or more child	1178 (57.2)	8745 (47.8)	
Delivery Type, *n (%)*			0.56
Vaginal	1961 (95.7)	16,189 (96.0)	
Caesarian Section	88 (4.3)	679 (4.0)	
Maternal Age, *M (SD)*	28.2 (5.9)	26.9 (6.13)	<0.0001
Birth weight (g), *M (SD)*	3374.1 (503.7)	3285.3 (580.5)	<0.0001
Gestational age, *M (SD)*	40.1 (2.2)	39.9 (2.8)	.001

Note. For the present study sample, the following variables had missing data: maternal race (n = 7); maternal education (n = 29); parity (n = 1); delivery type (n = 13); maternal age (n = 6); gestational age (n = 19).
For CHDS mother/child pairs not in the present study sample, the following variables had missing data: maternal race (n = 277); maternal education (n = 2759); parity (n = 740); delivery type (n = 114); maternal age (n = 170); birth weight (n = 1); gestational age (n = 288).

bootstrap confidence interval (CI) did not include zero.

2. Results

2.1. Bivariate analyses of study variables

In bivariate analyses (Table 3), maternal race, gestational age, and parity were associated with at least one independent and dependent variable, and so were added as covariates in all analyses, in addition to maternal education. Of note, offspring infection was significantly correlated with T1 (r = 0.7; $p < 0.01$) and T2 (r = 0.12; $p < 0.01$) infection and T1 antibiotic use (r = 0.05; $p < 0.05$), but not T3 infection nor T2 or T3 antibiotic use. Offspring antibiotic use followed a similar pattern and was significantly correlated with T1 (r = 0.07; $p < 0.01$) and T2 (r = 0.13; $p < 0.01$) infection and T1 antibiotic use (r = 0.05; $p < 0.05$). Offspring infection and antibiotic use were significantly correlated (r = 0.81; $p < 0.01$). Lastly, respiratory allergy was significantly correlated with offspring antibiotic use (r = 0.25; $p < 0.01$) and infection (r = 0.23; $p < 0.01$) but not any of the prenatal infections nor antibiotic use timepoints.

2.2. Maternal infection as a predictor of offspring early childhood infection or antibiotic exposure

Adjusted regression analyses indicated that presence of maternal prenatal infection during the first and second trimesters were associated with higher frequencies of offspring infection from birth through age 5 (Table 4). Inspection of multicollinearity among maternal prenatal infection and prenatal antibiotic variables revealed no indication that predictor variables were highly correlated. Analyses were further adjusted for first and second trimester prenatal antibiotic exposure, respectively. Findings linking prenatal infection during the second trimester to offspring infection remained significant after controlling for prenatal antibiotic exposure (IRR = 1.23; 95% CI = 1.08–1.40; $p = 0.002$); however, first trimester findings were no longer significant (IRR = 1.14; 95% CI = 1.00–1.31; $p = 0.069$). There were no significant associations between prenatal antibiotic exposure during any trimester and offspring infection. Prenatal infection during the first and second trimesters was significantly associated with higher frequencies of offspring antibiotic exposure from birth through age 5 (Table 4).

2.3. Maternal infection, offspring infection or antibiotic exposure as predictors of offspring early childhood allergic respiratory conditions

Adjusted and unadjusted logistic regression analyses are presented in Table 5. There were no significant associations between maternal prenatal infection during any trimester and offspring respiratory allergy at age 5; these findings remained after adjusting models for offspring infection. No significant interactions for predicting respiratory allergy were found between prenatal infection by trimester and offspring infection. Adjusted analyses indicated that higher frequencies of both offspring infection and antibiotic exposure from birth through age 5 were associated significantly with a diagnosis of offspring respiratory allergy at age 5 (Table 7). Supplementary analyses (Table 7) suggested evidence of a dose-response relationship between offspring infection, offspring antibiotic exposure, and diagnosis of respiratory allergy at age 5. Given multicollinearity between offspring infection and offspring antibiotic exposure (r = 0.81, VIF = 2.89), these variables could not be examined together in relation to offspring risk of allergic respiratory

Table 3
Bivariate associations of study variables (n = 2062).

Measure	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
1: T1 Infection	–	.09**	.02	.37**	.07**	.01	.07**	.07**	.00	.01	.02	−.01	−.01	.02	.02	.02	.00
2: T2 Infection		–	.05*	.04	.30**	.05*	.12**	.13**	.02	.01	.01	.03	−.01	.03	−.01	.01	−.01
3: T3 Infection			–	.00	.04	.32**	.03	.04	.00	.00	.01	.00	.07**	.03	−.03	.01	−.02
4: T1 Antibiotic				–	.05*	.03	.05*	.05*	.03	.00	.03	.00	.01	.06*	.00	−.03	.01
5: T2 Antibiotic					–	.10**	.04	.03	−.02	−.02	−.02	.01	−.02	.02	.03	−.02	.03
6: T3 Antibiotic						–	.03	.04	−.02	.00	.01	.00	.04	.04	−.01	−.02	−.04
7: Offspring Infection							–	.81**	.23**	−.03	.01	.04	.09**	−.11**	.02	−.18**	.08**
8: Offspring Antibiotic								–	.25**	−.03	.01	.05*	.07**	−.04	.03	−.16**	.07**
9: Resp Allergy age 5									–	−.04	−.01	−.02	−.01	−.04	.01	.05*	.02
10: Offspring Sex (Female)										–	.01	−.17**	.00	.02	.04	.02	.03
11: Delivery (Vaginal)											–	.01	.06**	−.01	−.05*	−.04	.03
12: Birth weight (g)												–	.38**	.09**	.04	−.13**	.03
13: Gestational Age													–	−.03	−.04	−.15**	.02
14: Parity (≥3)														–	.44**	.13**	−.10**
15: Maternal Age															–	−.01	−.14**
16: Maternal Race (AA)																–	−.08**
17: Education (>H.S.)																	–

Note: Pearson correlations and chi-square tests measured associations between two continuous variables and two categorical variables, respectively; Analysis of variance (ANOVA) measured associations between one continuous variable and one categorical variable; The following variables had missing data: gravida age (n = 6); parity (n = 1); maternal education (n = 29); maternal race (n = 7); delivery type (n = 13); gestational age (n = 19); Probability: *$p < 0.05$; **$p < 0.01$.T1 = Trimester 1; T2 = Trimester 2; T3 = Trimester 3; T1/T2/T3 Infection = presence of any maternal infection during trimester; Offspring Infection = Frequency of infection 0–5 years of age; Antibiotic = Frequency of broad spectrum antibiotic exposure during trimester or 0–5 years of age; Resp Allergy = diagnosis of offspring respiratory allergy at age 5; Gestational Age = weeks from last menstrual period to birth; Parity (≥3) = Parity (Three or more children); Maternal Race (AA) = Maternal Race (African American); Education (>H.S) = Maternal Education at birth (Greater than High School Education); Delivery type reference category is caesarian section; Parity reference category is first child; Race reference category is Non-African American; Maternal Education reference category is less than or equal to high school.

Table 4
Binomial regression models predicting offspring infection and antibiotic exposure in childhood (n = 2062) due to maternal infection or antibiotic exposure.

Exposure	Frequency of Offspring Infection (birth – 5 years)					
	Unadjusted			Adjusted		
	IRR	95% CI	*p*-value	IRR	95% CI	*p*-value
Maternal Infection						
T1 Infection	1.14	1.0–1.30	0.051	1.15	1.01–1.31	**0.038**
T2 Infection	1.22	1.08–1.38	**0.001**	1.23	1.09–1.39	**0.001**
T3 Infection	1.07	0.93–1.22	0.348	1.06	0.93–1.22	0.369
Maternal Antibiotic						
T1 Antibiotic	1.12	0.93–1.34	0.221	1.11	0.92–1.33	0.281
T2 Antibiotic	1.11	0.92–1.35	0.277	1.11	0.92–1.35	0.277
T3 Antibiotic	1.08	0.89–1.31	0.421	1.08	0.89–1.31	0.466
Exposure	Frequency of Offspring Antibiotic Exposure (birth – 5 years)					
	Unadjusted			Adjusted		
	IRR	95% CI	*p*-value	IRR	95% CI	*p*-value
Maternal Infection						
T1 Infection	1.19	1.03–1.36	**0.015**	1.19	1.04–1.37	**0.014**
T2 Infection	1.31	1.16–1.49	**<0.001**	1.32	1.16–1.50	**<0.001**
T3 Infection	1.10	0.96–1.27	0.165	1.09	0.95–1.26	0.214
Maternal Antibiotic						
T1 Antibiotic	1.17	0.97–1.42	0.101	1.15	0.95–1.39	0.161
T2 Antibiotic	1.12	0.91–1.37	0.280	1.10	0.90–1.35	0.353
T3 Antibiotic	1.15	0.94–1.4	0.191	1.12	0.91–1.37	0.295

Note: Adjusted analyses controlled for maternal education, maternal race, gestational age, and parity. Maternal Infection = presence of any infection during trimester; T1 = Trimester 1; T2 = Trimester 2; T3 = Trimester 3; Maternal Antibiotic = frequency of antibiotic exposure during trimester; IRR = Incident Rate Ratios; CI = Confidence Interval; p values < 0.05 are shown in bold.

conditions.

2.4. Sensitivity analyses for Maternal Antibiotic exposure

Among mothers with no antibiotic exposure during pregnancy, there remained an association with respect to second trimester infection and offspring infection (n = 248; IRR = 1.22, 95% CI = 1.05–1.40; $p = 0.007$). An association that approached significance was observed between first trimester infection and offspring infection (n = 189; IRR = 1.18, 95% CI = 1.00–1.38; $p = 0.047$). Additionally, when restricting analyses to children without exposure to antibiotics from birth to 24 months, offspring infection during this period remained related significantly to diagnosis of allergic respiratory conditions at age 5 (n = 28; OR = 1.34, 95% CI = 1.06–1.71; $p = 0.017$).

2.5. Mediation analyses

Bootstrapping analyses for indirect effects indicated that the number of offspring infections from birth through age 5 significantly partially mediated the relationship between prenatal second trimester infection and offspring diagnosis of respiratory allergy at age 5 (Bias-Corrected CI: 0.1502–0.3682).

3. Discussion

This is the first human study to find that maternal prenatal exposure to infection, specifically during the second trimester, is associated with subsequent increases in diagnoses of offspring infection from birth through age 5. A similar, non-significant association was found between first trimester infection and offspring infection; however, no association was observed with third trimester infection or prenatal antibiotic exposure. Further, frequencies of both offspring infection and antibiotic

Table 5
Logistic regressions predicting offspring respiratory allergy diagnosis at age 5 due to maternal infection and/or offspring infection, or offspring antibiotic exposure.

Predictor	Offspring Respiratory Allergy at Age 5					
	Unadjusted			Adjusted		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Maternal Infection						
(i) T1 Infection	1.03	0.67–1.59	0.893	0.87	0.55–1.37	0.543
Offspring Infection x T1[a]	–	–	–	1.17	1.13–1.20	**<0.001**
(ii) T2 Infection	1.17	0.79–1.74	0.428	0.85	0.56–1.29	0.441
Offspring Infection x T2[a]	–	–	–	1.17	1.13–1.21	**<0.001**
(iii) T3 Infection	0.96	0.61–1.50	0.843	0.86	0.54–1.38	0.528
Offspring Infection x T3[a]	–	–	–	1.17	1.13–1.20	**<0.001**
Offspring Infection	1.15	1.12–1.18	**<0.001**	1.17	1.13–1.20	**<0.001**
Offspring Antibiotic	1.25	1.20–1.30	**<0.001**	1.28	1.22–1.33	**<0.001**

Note: Adjusted analyses controlled for maternal education, maternal race, gestational age, parity, and maternal diagnosis of asthma or chronic bronchitis during pregnancy; p values < 0.05 are shown in bold. Maternal Infection = presence of any infection during trimester; T1 = Trimester 1; T2 = Trimester 2; T3 = Trimester 3; Offspring Infection = Frequency of infection 0–5 years of age; Offspring Antibiotic = Frequency of broad-spectrum antibiotic exposure 0–5 years of age; OR = Odds Ratio; CI = Confidence Interval.

[a] Analyses further controlled for offspring infection; estimated associations of offspring infection by trimester are shown.

exposure from birth through age 5 were associated significantly with a diagnosis of respiratory allergy in children at age 5 in a dose-related manner. Although the direct relationship was insignificant, a significant indirect effect of maternal second trimester infection on offspring diagnosis of respiratory allergy at age 5 via offspring infection was found, indicating a partially mediated effect. Sensitivity analyses suggested that our results primarily were due to infections and not antibiotic use, given that findings were replicated when restricting analyses to samples of mothers or offspring without antibiotic exposure. Similarly, associations established in primary analyses remained after controlling for antibiotic exposure, suggesting that maternal prenatal infection is an independent risk factor for offspring infection, as is offspring infection for risk of allergic respiratory conditions at age 5.

Our findings of an association between maternal prenatal infection and offspring infection are consistent with previous research in humans and animals models (Betts et al., 2014; Blomstrom et al., 2016; Cohen et al., 2019; Jacobsen et al., 2021). Nonetheless, this is the first human study to demonstrate that timing of maternal prenatal infection, specifically during mid-, and possibly early, gestation, may be important in portending risk for offspring infection. Our results also provide support for findings linking offspring infection to increased risk of allergic respiratory conditions, like asthma (Beigelman and Bacharier, 2016; Sigurs et al., 2005; Celedon et al., 2004; Mai et al., 2010; Wickens et al., 2008; Ramsey et al., 2007). Although the underlying mechanisms remain unclear, prenatal exposure to maternal infection, as well as offspring antibiotic exposure from birth to 5 years, may disrupt the offspring's developing immune system, predisposing them to dysfunctional immune responses that increase the risk of more frequent infections (suboptimal responses) and subsequently greater allergy and asthma risk (inappropriately exaggerated responses) (Rosas-Salazar and Hartert, 2020). Evidence suggests that children who develop asthma by school age exhibit aberrant immune responses to pathogenic bacteria, characterized by increases in several inflammatory cytokines (Larsen et al., 2014). One theory is that abnormal immune responses to pathogenic bacteria colonizing the offspring's airway during early life might lead to chronic airway inflammation and subsequent asthma (Larsen et al., 2014). Mice models have begun to test this hypothesis, with one study showing that chronic maternal immune activation (MIA) from respiratory infections can contribute to the onset of offspring lung disease (Kim et al., 2008). It is well established that prenatal maternal infection, both viral and bacterial, can contribute to MIA and consequentially fetal immune cell activation (Jacobsen et al., 2021). There is also a possibility that individuals with asthma are more prone to infection due to their impaired innate immunity against bacteria (Habibzay et al., 2012); however, this alternative explanation does not account for the significant relationship between prenatal infection and diagnosis of allergic respiratory conditions seen in this study. Future research is necessary to clarify these mechanisms and the temporal precedence of events.

Further, our results highlight a possible second trimester vulnerability to maternal infection on lasting consequences for offspring health. Identifying the role of prenatal exposure timing is an area of importance in epidemiological pregnancy research (Rice and Mein, 2020), and there has been some support of a second trimester vulnerability to infection in the literature. For example, past work from our team has shown that the second trimester of pregnancy is a critical period for the adverse effects of maternal infection on fetal neurodevelopment and risk of offspring depression (Brown et al., 2004; Murphy et al., 2017; Ellman et al., 2008) Less research has been done on the role on prenatal maternal infection on offspring physical health. This being said, more research is needed to clarify the role of timing of prenatal maternal infection on later offspring physical health (San Martín-González et al., 2023).

Our findings do not preclude the possibility that antibiotic exposure during pregnancy and/or early childhood may be an independent risk factor for offspring illness, given our results linking childhood antibiotic exposure to the diagnosis of respiratory allergy at age 5. Antibiotics have been linked to alterations in gut microbiota, the collection of microorganisms populating the intestine with an integral role in immune development (Francino, 2016; Langdon et al., 2016). Disturbances to microbiota in early life may have long-lasting consequences on health and disease (Francino, 2014; Sprockett et al., 2018). In animal models, studies have demonstrated that such disturbances during pregnancy can contribute to an increased risk of offspring allergic disease and asthma (Gao et al., 2021) and that a healthy microbiota during pregnancy can actually decrease risk of asthma in offspring (Li et al., 2020). Nevertheless, this study helps strengthen conclusions that pre- and postnatal infection may play an important role in the development of offspring infections and allergic respiratory conditions, above and beyond antibiotic exposure.

3.1. Strengths and limitations

Results were strengthened by use of our prospective, longitudinal design, large cohort, and robust measurement of maternal and childhood infections via medical records. Moreover, analysis of timing of prenatal and offspring infection exposure further enhanced the specificity of results. Limitations to the present study should also be noted. First, classification of antibiotic exposure was based on medical record data that assumed medication compliance. Therefore, poor drug compliance could have resulted in exposure misclassification that underestimated the effect size of antibiotic exposure. Relatedly, most mothers diagnosed with an infection during pregnancy did not receive

Table 6
Diagnoses of infections for mothers during pregnancy and offspring from birth through age 5.

	Prenatal (ICD-7)	Offspring (ICD-8)
Viral	*0391: Condylomata; Vaginal warts	*04: Viral diseases accompanied by exanthem, group I (includes chicken pox, herpes zoster, herpes simplex, viral stomatitis, vaccinia)
	[a]0810: Poliomyelitis, Late Effects of	05: Viral diseases accompanied by exanthem, group II (includes measles, rubeola, rubella, roseola, erythema infectiosum, exanthema subitem, other viral exanthem)
	[a]0820: Encephalitis, Acute and NOS	*06: Viral encephalitis
	0850: Measles; Roseola; Rubeola	07: Other specific viral diseases (includes infectious hepatitis, mumps, specific disease due to coxsackie virus, infectious mononucleosis)
	0860: German measles; Rubella	*08: Viral diseases, other and NOS (includes viremia, hand-foot-mouth disease, echo virus, viral prodrome)
	0870: Chicken pox	36: Inflammatory diseases of the eye (includes conjunctivitis, blepharitis, dacryocystitis, hordeolum, inflammation of lacrimal gland, keratitis, chalazion)
	0890: Mumps	46: Acute (upper) respiratory infection, except influenza (includes acute nasopharyngitis/common cold, sinusitis, pharyngitis, tonsillitis, **cervical adenitis, chronic post-nasal drip, coryza, **conjunctivitis with URI)
	0920: Hepatitis, infectious	47: Influenza (includes flu NOS, flu with respiratory manifestation, flu with any digestive manifestation)
	0930: Mononucleosis, infectious	48: Pneumonia/lower respiratory infection (includes viral or bacterial pneumonia, pneumonitis, bronchopneumonia, **bronchiolitis)
	4700: Cold – acute, NOS; Coryza – acute, NOS; Laryngitis – acute, NOS; Laryngo-Tracheitis – acute, NOS; Nasopharyngitis – acute, NOS; Pharyngitis – acute, NOS; Rhinitis – acute, NOS; Sore throat – acute, NOS; Tracheitis – acute, NOS; URI – acute, NOS; URI with otitis media and/or sinusitis	49: Middle respiratory infection (includes **croup, **laryngitis, **tracheitis, bronchitis, combination of above)
	4710: Sinus, infected; Sinusitis – acute, NOS	50: Other diseases of upper respiratory tract (includes hypertrophy of tonsils-adenoids, adenopathy in relation to respiratory system, lymphadenopathy in relation to respiratory system)
	4730: Tonsilitis – acute, NOS	[a]51: Other diseases of respiratory system (includes bronchiectasis, pleurisy, bronchospasm)
	4800: Influenza with pneumonia	56: Other diseases of intestine and peritoneum (includes diarrhea with constipation NOS, diarrhea and vomiting NOS)
	*4840: Influenza; Flu-like syndrome; Stomach flu	
	4920: Pneumonia, atypical or viral	
	5000: Bronchitis; Influenza with associated bronchitis	
	5122: Rhinitis, vasomotor	
	[a]5190: Pleurisy	
	*5279: Empyema; Pneumothorax; Respiratory System, Other Diseases; Viral Respiratory Infections	
Bacterial	0010: Tuberculosis	00: Intestinal infectious diseases (includes salmonella, bacillary dysentery, infectious colitis)
	0200: Syphilis	01: Tuberculosis
	0300: Gonorrhea	*02: Streptococcal infections (includes strep throat, scarlatina, beta hemolytic strep, erysipelas)
	[a]0450: Dysentery (all forms), Salmonella infections	03: Other bacterial diseases, excludes strep (includes diphtheria, whooping cough, septicemia)
	[a]0490: Food poisoning	[a]09: Congenital syphilis and venereal disease
	0510: Sore throat, Streptococcal	[a]38: Disease of ear and mastoid process except otitis media (includes otitis externa)
	*0649: Other bacterial diseases (includes diphtheria, meningococcal infections, pertussis, scarlet fever, typhoid)	[a]39: Rheumatic fever
	3910: Ear infection NOS; Otitis Media; Otitis NOS	53: Diseases of esophagus, stomach, duodenum (includes gastritis, gastroenteritis with just vomiting, vomiting NOS)
	*4030: Rhematic fever with acute rhematic heart disease; Rhematic fever without acute RHD	54: Appendicitis
	4900: Bronchopneumonia – acute, NOS; Pneumonia, not viral, pneumonitis	58: Nephritis and Nephrosis (includes acute and chronic glomerulonephritis, nephrosis)
	6050: Cystitis	59: Other diseases of urinary system (includes cystitis, pyelitis, pyelonephritis, urethritis, stricture of urethra)
	*6091: Genitourinary infection NOS; Urinary Tract Infection NOS	68: Infections of skin and subcutaneous tissue (includes boil and carbuncle, paronychia, furuncle, cellulitis with abscess, **lymphadenitis, impetigo, pyoderma, infected pilonidal dimple, ulcers, acute lymphangitis)
	6220: Pelvic Inflammatory Disease (PID); Oophoritis; Salpingitis; Endometritis	
	6300: Cervicitis – Acute, Chronis, and NOS	
Other	*0399: Other and unspecified venereal disease	11: Mycoses (includes tinea, athlete's foot, pityriasis, moniliasis, candidiasis, thrush, dermatophytosis
	*6302: Vaginitis, Trichomonas	12: Helminthiases and other parasites (includes ascariasis, trichinosis, pinworms, **lice, **scabies)
	*6303: Vaginitis, Monilia, Mycotic, Mycelia	[a]13: Other infective and parasitic diseases (includes congenital toxoplasmosis)
	*6304: Mixed vaginal infection; Vaginitis NOS	

Note. Prenatal conditions were coded based on the 4-digit International Classification of Diseases, Seventh Revision (ICD-7) with adaptions made by CHDS to provide more specificity than was allowed for in ICD-7. An * has been added to classification numbers that differ from the ICD-7 classification.
Offspring morbidity coding was based on the first two digits of the International Classification of Diseases, Eighth Revision (ICD-8). However, several changes were made by CHDS to adapt the list to the morbidity experience of young children. An * has been added to a classification number if the included diseases differed from those in the ICD-8. Single diagnoses carry a ** if they were included in a classification number which differed from the ICD-8 classification.
[a] Indicates conditions that were not observed in analytic sample.

antibiotic treatment (1791/2062, 87%), which may have limited detection of a relationship between prenatal antibiotic exposure and offspring infection. In addition, the frequency of maternal infections during each trimester were not considered in analyses, rather presence of infection was treated as a dichotomous variable. Nonetheless, our findings help disentangle the relative contributions of prenatal infection and antibiotic exposure on offspring health, especially considering the conflicting interpretations of previous findings (Miller et al., 2018; Mai et al., 2010; Chandrakumar et al., 2018; Stokholm et al., 2014). Second, we chose not to examine breastfeeding in present analyses but acknowledge that breastfeeding has been associated with a lower risk of immune-related diseases and may have protective effects on infant health and immune function (Blewett et al., 2008). In CHDS, mothers were not systematically or directly asked if/when they breastfed.

Table 7
Offspring infection by year and number of offspring infections and antibiotic exposures from birth through age 5 on incidence of offspring allergic respiratory conditions at age 5 (unadjusted and adjusted results).

	Unadjusted			Adjusted		
Exposure, by year	**OR**	**95% CI**	***p*-value**	**OR**	**95% CI**	***p*-value**
Offspring Infection						
Birth to Year 1	1.26	1.13–1.40	**<.001**	1.28	1.15–1.43	**<.001**
Year 1–2	1.27	1.15–1.40	**<.001**	1.30	1.17–1.43	**<.001**
Year 2–3	1.55	1.40–1.72	**<.001**	1.61	1.44–1.79	**<.001**
Year 3–4	1.48	1.33–1.64	**<.001**	1.54	1.37–1.71	**<.001**
Year 4–5	1.47	1.32–1.63	**<.001**	1.70	1.52–1.90	**<.001**
Offspring Antibiotic						
Birth to Year 1	1.20	1.05–1.37	**.008**	1.24	1.08–1.42	**.002**
Year 1–2	1.47	1.29–1.68	**<.001**	1.54	1.34–1.77	**<.001**
Year 2–3	1.78	1.55–2.03	**<.001**	1.85	1.61–2.13	**<.001**
Year 3–4	1.64	1.42–1.90	**<.001**	1.68	1.45–1.95	**<.001**
Year 4–5	2.03	1.74–2.37	**<.001**	2.11	1.80–2.48	**<.001**
Exposure, birth through age 5	**OR**	**95% CI**	***p*-value**	**OR**	**95% CI**	***p*-value**
No. of Infections						
≤4	1.00	–	–	1.00	–	–
5-7	3.00	1.50–6.01	**<.001**	3.36	1.63–6.94	**.001**
8-12	6.08	3.25–11.39	**<.001**	7.22	3.73–13.95	**<.001**
≥13	10.63	5.71–19.82	**<.001**	13.94	7.19–27.01	**<.001**
No. of Antibiotics						
≤1	1.00	–	–	1.00	–	–
2-3	2.18	1.56–4.11	**.016**	2.28	1.18–4.40	**.015**
4-6	5.36	2.95–9.77	**<.001**	6.41	3.43–11.97	**<.001**
≥6	9.21	5.26–16.14	**<.001**	11.65	6.45–21.04	**<.001**

Note: Offspring infection and antibiotic use frequencies were visually inspected and examined as ordered categorical variables.
Adjusted analyses controlled for maternal education, maternal race, gestational age, parity, and maternal diagnosis of asthma or chronic bronchitis during pregnancy; OR = Odds Ratio; CI = Confidence Interval; p values < 0.05 are shown in bold.

Rather, any reference to breastfeeding during a pediatric visit was noted and abstracted, leading to a limited amount of breastfeeding data. Lastly, data on family history of asthma/respiratory disease was very limited, and so was not included in analyses.

4. Conclusion

In conclusion, our study provides further evidence of the fetal origins of offspring illness, in which prenatal exposure to maternal infection may exert a long-term impact on the immune function and health of offspring. These findings have important implications for prevention and intervention strategies, as maternal episodes of infection are not uncommon and often treated in outpatient settings (Laibl and Sheffield, 2005). A better understanding of the relationship between exposure to maternal prenatal infection and the development of offspring infection and allergic disorders may inform maternal and pediatric healthcare practices.

CRediT authorship contribution statement

Shannon K. Murphy: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Madeline R. Pike:** Writing – review & editing, Conceptualization. **Emily Lipner:** Writing – review & editing, Supervision. **Seth D. Maxwell:** Writing – review & editing, Supervision, Methodology, Data curation. **Barbara A. Cohn:** Writing – review & editing, Supervision, Resources, Project administration, Investigation, Funding acquisition, Data curation. **Piera Cirillo:** Writing – review & editing, Project administration, Funding acquisition, Data curation. **Nickilou Y. Krigbaum:** Writing – review & editing, Investigation, Funding acquisition, Data curation. **Elizabeth C. Breen:** Writing – review & editing, Resources, Methodology, Investigation, Funding acquisition, Data curation. **Lauren M. Ellman:** Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Data statement

De-identified (anonymized) data are available upon request from Barbara A. Cohn, PhD, Director of the Child Health and Development Studies. Dr. Cohn, research staff, and the Institutional Review Board at the Public Health Institute will review requests. Approval of requests for de-identified (anonymized) data requires execution of a data use agreement.

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Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2024.100892.

Data availability

Data will be made available on request.

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