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Maternal Stress During Pregnancy Predicts Infant Infectious and Noninfectious Illness

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Abstract

Objectives—To examine the association between prenatal stress and infant physical health in the first year of life within an understudied, racially and ethnically diverse, highly stressed community sample. We expected that greater stress exposure would predict higher rates of infant illness.

Study design—Low-income, racially/ethnically diverse, overweight women with low medical risk pregnancies were recruited (2011-2014) during pregnancy. Pregnancy Stressful Life Events were assessed retrospectively (mean, 11.88 months postpartum). Perceived stress was assessed twice during pregnancy (at a mean of 17.4 weeks and again at a mean of 25.6 weeks) and at 6 months postpartum. Women with live births (n = 202) were invited; 162 consented to the offspring study. Medical records from pediatric clinics and emergency departments for 148 infants were abstracted for counts of total infectious illnesses, total noninfectious illness, and diversity of illnesses over the first year of life.

Results—The final analytic sample included 109 women (mean age, 28.08 years) and their infants. In covariate-adjusted negative binomial models, maternal perceptions of stress across pregnancy were positively associated with infant illness. Each 1-point increase in average stress was associated with a 38% increase in incidence of infant infections (IRR, 1.38; 95% CI, 1.01-1.88; *P* < .05), a 73% increase in noninfectious illness (IRR, 1.73; 95% CI, 1.34-2.23; *P* < .05), and a 53% increase in illness diversity (IRR, 1.53; 95% CI, 1.25,1.88; *P* < .01); effect sizes were larger for perceived stress later in pregnancy. Stressful life events count and postnatal stress were not uniquely associated with illness.

Conclusions—In line with recommendations from the American Academy of Pediatrics to screen for maternal perinatal depression, screening and support for stress reduction during pregnancy may benefit both maternal and child health.

Accumulating evidence shows that early life psychosocial stress "gets under the skin" to impact physical health.[1–3] Fetal programming theories identify pregnancy as a particularly sensitive period for offspring exposure-dependent development.[4–7] Empirical studies show associations between maternal prenatal stress, defined as exposure to stressful events or the perception of experiencing stress during pregnancy, and an offspring's risk for increased rates of premature birth, low birth weight, and being small for gestational age.[8–12]

In addition to birth outcomes, a robust evidence base also shows associations with illness throughout childhood. Systematic reviews find positive associations between prenatal stress and child atopy, and meta-analytic results show prenatal stress is linked to an 60% increased risk of asthma-related outcomes throughout childhood.[13–15] Although more limited, evidence also suggests that prenatal stress affects offspring vulnerability to a range of nonatopic illnesses. In a Dutch study of 174 dyads, maternal daily cortisol and/or self-reported stress during pregnancy was associated with rates of respiratory, skin, and general illnesses and antibiotic use in infants.[16] In a predominantly Caucasian American sample, prenatal stress was found to predict greater infant respiratory, gastrointestinal, and total illnesses, and increased frequency of urgent care and emergency room visits.[17] Postnatal stress-related perturbations can affect brain function, but also a range of peripheral organs, in a manner that contributes to physiologic "allostatic load," a process that contributes to cellular wear and tear that impacts organism health broadly.[18] The accumulating evidence for associations between maternal prenatal stress and a broad range of offspring health outcomes may result from alteration of the intrauterine environment by stress-related chronic activation of the maternal hypothalamic-pituitary-adrenal (HPA) axis that affects the fetal autonomic nervous system, HPA axis, and immune system development.[19–22] Indeed, recent mechanistic work in animals points to the manner in which perinatal stress physiology can decrease offspring CD8 T-cell function, increasing susceptibility to both tumor growth and bacterial infection, suggesting impact on a wide range of offspring health outcomes.[23] Because the fetal and infancy periods are understood to be sensitive periods for the development of organs and system function, it follows that prenatal exposure to stress has the potential for pervasive effects.[21,24–27]

Apart from using Swedish or Danish hospital registry data, most research outside of atopic outcomes is based on potentially biased maternal or family report of infant health.[16,17,28–31] Much of the evidence is derived from European samples or samples with little social adversity (eg, highly educated, predominantly higher income), with some exceptions for atopic outcomes.[17,32–34] The biological effects of acute, occasional stressors differ from the effects of chronic stress activation, which is more common in communities experiencing high adversity.[35] Finally, most existing studies do not reflect the diverse racial/ethnic makeup of the US population of childbearing-age women (the primary US study evidence was drawn from a sample that was 83% White, non-Hispanic), limiting generalizability.[17]

The current study expands this literature by studying a racially and ethnically diverse sample of low-income, pregnant, urban US women. We examined associations between maternal reports of subjective stress and objective stressful event exposure and medical provider diagnoses of infant infectious and noninfectious illness across the first year of life. We hypothesized that maternal stress during pregnancy would be associated with an increased incidence of both types of physical illness. In addition, given the potentially broad ranging impact of stress-related fetal programming of offspring HPA axis, autonomic nervous system, and immune function, in addition to increased frequency of certain types of illness (eg, recurrent infections), we expected that offspring of mothers with higher stress during pregnancy would experience a greater diversity of types of illness in infancy (eg, more likely to have a variety of infectious and chronic illnesses). Given mixed evidence for varying effects related to timing of stress, we also examined potential differences between early vs later pregnancy stress.[36–39]

Methods

The Stress, Eating, and Early Development (SEED) study is a longitudinal study designed to investigate the associations between prenatal stress and weight gain on child health and development.[37,40] SEED participants were drawn from a larger study testing an intervention to prevent excessive gestational weight gain in overweight and obese pregnant women.[41,42] Inclusion criteria were that women be 18-45 years of age, 8-23 weeks pregnant with a singleton, have a body mass index of 25-40 kg/m^2, incomes of 500% or less of the Federal Poverty Level, and be English speaking. Women were excluded if they had medical conditions that may interfere with baseline body composition or maternal gestational weight gain, or were currently taking antidepressants, antipsychotics, opiate drugs, corticosteroids, or medications related to weight loss or diabetes. Institutional review boards approved the study protocols at all participating study sites and written informed consent was collected from mothers.

Recruitment and participant flow details for the pregnancy study and SEED study have been published previously.[37,42,43] Of the 215 women enrolled in the original study, 202 mothers (94%) and their offspring were eligible to enroll in the SEED follow-up study of children's cardiometabolic and stress physiology risk factors, and 162 (80%) enrolled. Details of determination of the final analytic sample for those with illness outcome data (n = 109) are provided in the Appendix (available at www.jpeds.com). Sample characteristics are in Table I (available at www.jpeds.com).

Determination of Infant Illness

Illness in the first year of life was assessed through medical records abstraction (MRA) of information related to diagnoses and medications prescribed at each visit during the observation window (details provided in the Appendix). Diagnosis codes included are listed in Table I. MRA was conducted by medical students and research assistants trained and supervised by an experienced pediatrician and a clinical psychologist researcher. Because lower income families disproportionately rely on emergency services for routine and

preventive care healthcare needs, all primary care and emergency room visits during the first year of life were included.[44,45]

Surgical procedures (eg, circumcision) and any accidents (eg, injury-related stitches) were excluded from all summary scores. A detailed summary of methods for the creation of outcome variables is included in the Appendix, and all diagnosis codes and their assignment to summary variables are listed in Table I. A total infectious illness count was created by summing a subset of diagnoses identified as infectious. This score reflects the total number of occurrences of discrete infections, not simply the number of times infections were observed in visit records so that a repeat incidence of a specific infection code (eg, upper respiratory infection) within 30 days of the first incidence was only included in the count if it was ascertained to be a new, discrete infection. A parallel score of noninfectious illness count was created in a similar manner, but using the noninfectious codes, including atopic illnesses. Finally, to explore whether overall variation in illness types would provide a useful indicator of broad-ranging impact of stress on infant health, we created a total unique illness count—illness diversity—combining codes from both the infectious and noninfectious illness summary scores; however, in this score, repeated occurrences of the same diagnosis code across the year of abstraction counted only once into the total score.

Maternal Stress

Our measures of stress are documented in detail elsewhere.[37,42] Maternal report of stressful life events that occurred during pregnancy was assessed, retrospectively, via phone calls conducted approximately 12 months post partum (mean, 11.88 ± 5.52 months) using a list of 14 events and situations adapted from the Centers for Disease Control and Prevention Pregnancy Risk Assessment Monitoring System postpartum survey.[46] Participants were asked to respond yes or no to statements about experiences with major illness, death of loved ones, being a victim of crime, relationship problems, housing difficulties, legal issues and financial problems during pregnancy (stressful life event reported sums range, 0-8; 14% reported no events, 39% reported 1-2 events, and 47% reported ≥3 events; scores were square root transformed to reduce slight skewness). Although there was some delay between the events occurring during pregnancy and report of those events, such measures of specific major life events are thought to have limited recall bias and be accurate over a span of years. [47]

The Cohen Perceived Stress Scale (PSS) is a widely used, highly reliable and valid, 10-item self-report questionnaire that assesses the extent to which individuals perceive their lives as "unpredictable," "uncontrollable," and "overloaded" over the previous month (as opposed to reactions to a specific event) on a 5-point scale.[48] The PSS was assessed prospectively twice during pregnancy (earlier mean, 17.4 ± 4.2 weeks; and later mean, 25.6 ± 4.5 weeks), which on average occurred during the second and third trimesters, and again at roughly 6 months post partum. Mean scores were computed as long as greater than 75% of the items were answered. The 2 prenatal time points were highly correlated ($r = .66$) and were averaged to create a single measure of prenatal perceived stress.

Covariates

Gestational age and birthweight and maternal parity (primiparous vs multiparous) were obtained via labor and delivery medical records. Participants reported total household income, which was converted to percent of US federal poverty level, adjusted for reported household size.[49] Depression symptoms were assessed twice during pregnancy and at 6-month postpartum using the sum of the 9-item Patient Health Questionnaire, commonly used in primary care settings and validated in pregnant women, and postnatal depression and perceived stress (PSS) were considered for covariate inclusion.[50,51] We also included whether or not SEED mothers had participated in a prenatal stress management intervention tested in the parent study designed to prevent excessive weight gain during pregnancy, as well as maternal report of smoking during pregnancy.[42]

Statistical Analyses

Analyses were performed using R version 4.0.0 (The R Foundation, Vienna, Austria). Descriptive statistics were calculated for demographic characteristics and study variables. Initial comparisons were made between our MRA data sample and the remaining sample without abstraction to assess representativeness and potential bias; subsequent analyses include only those with MRA data. A P value of less than .05 was used as the threshold for determination of significance. Spearman-Rank correlations assessed bivariate associations between prenatal stress/depression with illness outcomes. Pearson correlations assessed covariation among the measures of stress and depressive symptoms, as well as intercorrelations among the outcomes. Negative binomial regression models examined the covariate-adjusted effects of prenatal stress on the child illness outcomes. Because of potential problems introduced by multicollinearity, models were initially performed separately for each perceived stress and depressive symptoms variable, then coefficients were compared when both measures were included. Finally, to explore sensitivity to exposure timing, we tested independently reports of stress coming from earlier vs later pregnancy.

Results

Table II presents sample characteristics, showing comparability of the MRA data sample and those without sufficient medical records data on demographic characteristics, as well as considerable variability in the number of discrete infectious illnesses and diversity of illnesses. Of note, mothers without MRA data reported significantly higher prenatal stress and postnatal depression. The frequencies of the 10 most common diagnoses are presented in Table III (available at www.jpeds.com).

Table IV and Table V present bivariate relations within maternal stress measures and between model variables and the infant illness outcomes, respectively. Moderate intercorrelations longitudinally within PSS (rs = 0.57-0.62) provide reference for limiting our interpretation to coefficients derived from separate models. Final models were adjusted for the effects of poverty, gestational age, and birth weight to improve comparability with the published literature. In addition, maternal parity was included as a covariate. Because maternal participation in the prenatal intervention (although designed to prevent excessive

maternal weight gain during pregnancy, it did not affect maternal gain) was not associated with illness outcomes, and its inclusion did not affect model results, it was omitted from final models to preserve power. Although we intended to covary for maternal smoking during pregnancy, only 5 women within our analytic sample endorsed this variable, inclusion of this variable led to loss of 3 subjects owing to missing data, and study findings were not changed by its inclusion; thus, it was not retained in final models.

Although we considered the potential confounding influence of maternal prenatal and postnatal depression in our models, PSS across timepoints was moderately to strongly correlated with depression across timepoints ($r = 0.57$-0.69), which caused collinearity concerns. However, postnatal depression was uncorrelated with illness outcomes, and because neither prenatal nor postnatal depression predicted either outcome in covariate-adjusted models, depression was dropped from models. Prenatal PSS, but not 6-month postnatal PSS, was correlated with outcomes; thus, owing to collinearity concerns, postnatal PSS was not included in the final models. Prenatal stressful life events was not associated with either outcome, although it approached significance for illness diversity (Table V). The discrete infection count was correlated ($r = 0.35$) with the discrete noninfectious illness counts. Illness diversity was correlated ($r = 0.68$) with the infection count ($r = 0.87$) and with the noninfectious illness count; the moderate and high correlations suggested it did not provide particularly novel information, so analyses with this variable were pursued only in an explanatory manner to enhance interpretation of the outcome data.

Results of the covariate-adjusted negative binomial regression models for both outcomes, each modeled 3 times to examine exposure timing effects, are displayed in parallel in Table VI. Perceived stress assessed during pregnancy was significantly positively related to all 3 illness outcomes in infants across the first year of life, with apparent exposure timing effects. Each 1-point greater average prenatal stress was associated with a 38% increase in number of infections (IRR, 1.38; 95% CI, 1.01-1.88; $P < .05$). This finding seems to be driven by perceived stress later in pregnancy, when an additional point on reported stress was associated with a 55% increase in infections (IRR, 1.55, 95% CI, 1.18-2.03; $P < .01$); earlier pregnancy stress was not associated. In a similar manner, each 1-point greater average prenatal stress was associated with a 73% increase in number of noninfectious illnesses (IRR, 1.73; 95% CI, 1.34-2.23; $P < .01$). This association was also driven by perceived stress later in pregnancy, when an additional point on reported stress was associated with a 83% increase in number of different types of illness (IRR, 1.83, 95% CI, 1.43, 2.35; $P < .01$). Consistent with patterns for the 2 discrete total illness count types, each 1-point greater average prenatal stress was associated with a 53% increase in illness diversity (IRR, 1.53; 95% CI, 1.25, 1.88; $P < .01$). This association was also driven by perceived stress later in pregnancy, when an additional point on reported stress was associated with a 60% increase in number of different types of illness (IRR, 1.60, 95% CI, 1.32, 1.93; $P < .01$).

The count of stressful event types occurring during pregnancy, however, was not related to outcomes, either alone, or while simultaneously adjusted for perceived stress. Although not of primary interest, given the moderate intercorrelations between stress and depression in this sample and the clinical need to discern depression effects from those of stress, we also ran covariate-adjusted models that included (one at a time) prenatal depressive symptoms

and postnatal perceived stress. In these sensitivity models, neither depression nor postnatal stress were significantly related to infant illness above the effects of prenatal stress reports (results not shown); thus, ultimately, those variables were not retained in models because multicollinearity among predictors may distort or inflate coefficients for perceived stress.

Discussion

Maternal perceptions of stress during pregnancy, within a racially and ethnically diverse sample of low-income women, were associated with their infants' frequency of both infectious and noninfectious illnesses, assessed via medical records. Results seemed to be driven by stress in the latter one-half of pregnancy and were present after adjusting for income and key infant characteristics. Of note, postnatal perceived stress was not related to infant illness outcomes, and prenatal and postnatal depression were also not predictive, despite all being moderately correlated with prenatal stress. This finding suggests specificity in the qualities of the maternal distress exposure (reports of high stress and lack of control vs depressed mood) and developmental timing for offspring matter. Our findings, using objective infant illness data that minimize shared reporter and social desirability bias, strengthen confidence in similar findings from previous studies that relied on mothers' report of both stress and children's health.[17] Our study further demonstrates these associations within a racially/ethnically diverse, lower socioeconomic status US urban study population—a population at high risk for exposure to stress and high rates of infant illness.

Observing an association after adjusting for postpartum stress suggests that maternal stress during pregnancy contributes to health in the first year of life, independent of postnatal experience. There are a variety of potential mechanisms for prenatal transmission. A rich literature demonstrates how maternal experiences of stress have myriad effects on her biology, in manners that affect development of the fetal HPA axis.[21,52–54] A growing literature reviews prenatal stress effects on offspring immune system development, including gut microbiota related to gastrointestinal symptoms and allergic reactions.[20,21,55–57] We have previously found that prenatal stress was associated with infant autonomic nervous system reactivity in this sample, consistent with accumulating evidence in this realm.[21,37] This factor may also play a role in stress-reactive illness development. Accumulating evidence, such as associations between maternal prenatal stress and epigenetic regulation of FKBP5, which has been linked to inflammation and both mental and physical health disorders, point to underlying molecular processes with functional consequences that could impact myriad health outcomes.[25,58–61] Evidence of such broad associations with offspring brain and organ development and function, coupled with increasing understanding of the organ crosstalk and associated inflammatory processes that contribute to pathogenesis, are in line with our findings here, which show maternal stress associations with incidence of a range of offspring illness types—both infectious and noninfectious.[18,62]

Although moderately correlated with infection count, and highly correlated with noninfectious illness count, the diversity measure was calculated to capture something slightly different. The significant association of stress with this outcome suggests that maternal stress not only predicts increased incidence of both infectious and noninfectious illness, but that it also predicts whether a child has multiple different types of illnesses,

rather than just a high frequency of recurring illness. This factor broadens the interpretation of the findings and is in alignment with other evidence for wide-ranging systemic effects of perturbed stress response systems, potentially bridging immunologic, cardiovascular, neurohormonal, and limbic changes, via an intergenerational pathway.[18,25,63]

The stronger associations later in gestation suggest that the timing of perceived stress during pregnancy is important to its potential effects on the developing fetus. This factor may relate to gestational timing-specific alterations in maternal hormones, which are understood to be stress responsive, that shift across pregnancy.[7] Additionally, although the initial development of the immune system largely occurs in the first trimester, the transplacental passage of maternal antibodies starts at 16 weeks of gestation, with the majority of IgG passage occurring in the final 4 weeks of pregnancy.[64] Maternal IgG provides protection for the first several months of life. Animal studies have shown that chronic prenatal stress in late pregnancy is associated with decreased levels of maternal and male neonatal IgG, decreased innate immune cell function, and decreased offspring white blood cell counts at birth and in the months after.[22,65,66] Relatedly, higher anxiety in later pregnancy has been associated with decreased human infant adaptive immune response to vaccines.[67] These studies suggest that prenatal stress in later pregnancy may affect offspring immunity by compromising maternal immune function and antibody production, and by altering the newborn's immune system in a durable way.

Exposure to prenatal stress is not deterministic, however, and many factors contribute to variation in organism response and probabilities of risk.[25] Postnatal factors and interventions can promote infant health and buffer the impact of earlier adversities, and our findings lend support to evidence that prenatal protective factors or interventions also have the potential to buffer infants from harm or remediate negative outcomes.[18,26,68–74]

Several limitations should be noted. Although we provide much-needed data on low-income women of diverse racial and ethnic backgrounds, our restricted sample type and size may limit the generalizability of our findings to other populations. Our maternal sample was limited to overweight and obese mothers, though this aligns with the weight status of 60%-68% of American women of childbearing age (20-44 years of age) during our enrollment period, with figures being even greater among African Americans (81%), Hispanic/Latina (78%) and Mexican American (84%) women in the population.[75] Indeed, our sample may be more representative in this domain than are typical research samples. Further, there is potential bias in who takes their infants to the doctor regularly and the possibility of missing illnesses during the first year of life for which families did not seek medical attention, and our analytic restriction to those with 6 documented visits available for abstraction may not have fully addressed this factor. Women without pediatric medical record data reported higher levels of prenatal stress, which may reflect lower rate of return of medical record release forms or greater instability in care providers leading to irregular or challenging records access, thus results found here with this subsample of slightly less stressed mothers may underestimate potential effects. In addition, we previously found that greater maternal perinatal depression was associated with increased frequency of visits to pediatric medical providers; however, because postnatal maternal stress and depression were not associated with the illness outcomes studied here, differences in those factors that might

affect likelihood of visiting the doctor would not seem to affect our findings.[76] Our inability to adjust for infant postnatal exposure to household smoking is a limitation, although maternal smoking during pregnancy was very low in this sample (4.5%; consistent with low regional rates of smoking in general) and its inclusion in analyses did not alter findings. Last, we acknowledge that there may be variability in individual pediatrician's diagnosis documentation practices that could affect total illness counts.

Conclusions

Overall, the results of this study point to the importance of considering maternal stress during pregnancy, especially women's self-report of their stress level, when attempting to understand the etiology of good health in infancy and beyond. Our focus on children's health outcomes is relevant to macrolevel public health and economic policy work, but is also important on a more microlevel for child health clinicians. Identifying the broad reach of maternal stress on a range of child health outcomes can improve prevention and assessment for pediatric patients, potentially decreasing illness and costs to individuals and society. Optimal pediatric healthcare services may be best achieved by attending to the familial context, including parental stress and mental health, in addition to providing treatment that is focused on children's physical symptoms and concerns. A recent policy statement from the American Academy of Pediatrics argues that primary care providers are optimally positioned to conduct screenings, reduce stigma, and provide referrals to improve parent mental health, although adequate education and training in these areas is lacking, as are resources to refer families to and to help families to navigate those referrals.[77] Early screenings and referrals for maternal stress (and associated mental health problems) could be feasibly incorporated into pediatric healthcare settings, in addition to coordination with obstetric settings the mother is connected to before birth, and provision of support within the primary care setting, contributing to wide-ranging benefits for mothers, infants, and pediatric healthcare resource use, it is possible that prenatal stress associations like those observed here may have life course implications, because poorer early life health is associated with poorer health and social functioning in adulthood.[26,78–81]

Future studies may continue to extend this research by evaluating relations in larger samples, particularly those that assess maternal biological processes that potentially serve as physiologic mediators of the associations, such as immune system, autonomic nervous system, and HPA axis function. Further, examining the potential protective moderating factors by which children might be buffered from the risk of harmful associations between a mothers' mental well-being and child health, as well as assessing the effects of maternal stress reduction interventions on their offspring's illness conditions, will be important next steps. Considering the maternal-child dyad and their interconnected well-being—postnatally and prenatally—will advance the pursuit of health for children.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Glossary

HPA	Hypothalamic-pituitary-adrenal
MRA	Medical records abstraction
PSS	Cohen Perceived Stress Scale
SEED	Stress, Eating, and Early Development

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Table I.

Diagnoses list used for MRA during first 13 months of life

Codes	Illness category	Allergies/allergic conditions
Chronic and Congenital Illnesses		
C1a	Noninfectious	Allergic rhinitis
C1b	Atopy	Allergic conjunctivitis
C1c	Atopy	Atopic dermatitis (eczema)
C1d	Noninfectious	Food allergies (specify if possible, milk protein allergy can cause GI bleeding in infants)
C1e	Noninfectious	Dermatitis, contact or allergic
C1f	Noninfectious	Hives (urticaria)
Inherited disorders/hemophilia		
C2a	Noninfectious	Cardiac malformation (specify: atrial septal defect, ventricular septal defect, tetralogy of Fallot, other)
C2b	Noninfectious	Cystic fibrosis
C2c	Noninfectious	Down syndrome
C2d	Noninfectious	Fetal alcohol syndrome
C2e	Noninfectious	Hemoglobin disorders (sickle cell anemia, or other; specify in notes)
C2f	Noninfectious	Hemophilia (not nutritionally related clotting)
Digestive system		
C3a	Noninfectious	Celiac disease
C3b	Noninfectious	Cleft palate
C3c	Noninfectious	Duodenal atresia
C3d	Noninfectious	Hirschsprung disease
C3e	Noninfectious	Pyloric stenosis
C3f	Noninfectious	Constipation, chronic
Nutrition related		
C4a	Noninfectious	Iron deficiency anemia
C4b	Noninfectious	Megaloblastic anemia (folic acid or vitamin B_{12} deficiency)
C4c	Noninfectious	Failure to thrive
C4d	Noninfectious	Other nutritional (specify; eg, feeding problems/difficulty, poor weight gain, underweight, overweight, lead toxicity, rickets, etc)
C4e	Noninfectious	Anemia, unspecified
Developmental		

Codes	Illness category	Allergies/allergic conditions
C5a	Noninfectious	Autism
C5b	Noninfectious	Developmental or speech delay (specify)
C5c	Noninfectious	Cerebral infarct/hypoxic brain injury
Orthopedic		
C6a	Noninfectious	Dysplasia of the hip, developmental
C6b	Noninfectious	Other orthopedic conditions (specify)
Other conditions		
C7a	Noninfectious	Kawasaki disease
C7b	Noninfectious	Seizure disorder
C7c	Noninfectious	Seborrheic dermatitis (seborrhea, sebopsoriasis, seborrheic eczema, dandruff, cradle cap)
C7d	Noninfectious	OTHER CONDITIONS (WRITE DETAILED NOTES)
C7e	Noninfectious	Congenital condition, other (WRITE DETAILED NOTES)
C7f	Noninfectious	Heart murmur
Acute illnesses		
L1	Atopy	Asthma/reactive airway disease/bronchospasm
L1b	Atopy	Wheezing
L2	Infection-mild	Bronchiolitis
L3	Infection-mild	Bronchitis (acute)
L4	Noninfectious	Cancer (specify: neuroblastoma, others)
L5	Infection-severe	Cellulitis
L6	Noninfectious	Constipation, not chronic
L7	Infection-mild	Conjunctivitis (pink eye)
L8	Infection-mild	Coxsackie virus (hand-foot-mouth disease)
L9	Infection-mild	Croup
L10	Infection-severe	Epiglottitis/bacterial tracheitis
L11	Infection-mild	Erythema infectiosum (slapped cheek disease) (P\parvovirus B19)
L12	Noninfectious	Febrile seizures
L13	Infection-mild	Gastroenteritis (acute diarrhea)
L14	Noninfectious	Hearing loss
L15	Infection-mild	Influenza (flu)
L16	Infection-mild	Impetigo

Codes	Illness category	Allergies/allergic conditions
L17	Noninfectious	Intussusception
L18	Infection-severe	Meningitis, bacterial
L19	Infection-severe	Meningitis, viral
L20	Infection-severe	Osteomyelitis
L21	Infection-mild	Otitis interna, media, or externa (ear infections, swimmer's ear)
L22	Infection-mild	Pertussis (whooping cough)
L23	Noninfectious	Pityriasis rosea (type of rash)
L24	Infection-severe	Pneumonia (make a note if diagnosis says viral or bacterial, complicated)
L25	Infection-mild	Roseola
L26	Infection-mild	Scarlet fever (escalation of strep throat)
L27	Infection-severe	Staphylococcal scalded skin syndrome
L28	Infection-mild	Strep (acute pharyngitis)
L29	Infection-mild	Upper respiratory infection (URI) (cold)
L30	Infection-mild	Urinary tract infection (UTI)
L31	Noninfectious	Vomiting (emesis)
L32	Infection-mild	Yeast infection/candidiasis (diaper rash, ringworm [tinea corporis], or other)
L32a	Infection-mild	Thrush
L33	Noninfectious	OTHER (WRITE DETAILED NOTES)
L33i	Infection-mild	Other, notes reviewed, infectious
L34	Noninfectious	Rash/dermatitis, nonspecified
L34i	Infection-mild	Rash/dermatitis, nonspecified, infectious
L35	Noninfectious	Fever
L36	Noninfectious	Viral syndrome
L37	Noninfectious	Jaundice
L38	None	Umbilical hernia
L39	Noninfectious	Seizure, unspecified
L40	Noninfectious	GI/digestive disturbance (eg, gas, gastroesophageal reflux disease, reflux, black stool)
L41	Infection-severe	Abscess
L42	Infection-mild	Sinusitis/sinus infection
L43	Infection-mild	Varicella (chicken pox)
L44	Infection-mild	Oral infections, not yeast/thrush

Codes	Illness category	Allergies/allergic conditions
L45	Noninfectious	Dental problems
L46	Noninfectious	Cough, unspecified
L47	Infection-mild	Methicillin-resistant *Staphylococcus aureus*
L48	Noninfectious	Neonatal respiratory distress syndrome
L49	Noninfectious	Pneumothorax of newborn
L50	Infection-mild	Boil
L51	Infection-mild	Colitis
L52	Noninfectious	Stomatitis/canker sores
L53	Noninfectious	Vision/eye problems (specify: myopia, hyperopia, strabismus, etc)
Accidents/injuries (excluded from summary scores)		
A1		Accidental ingestion (anything)
A2		Bone fracture (specify location)
A3		Burns
A4		Cuts
A5		Head injury
A6		Non accidental trauma
A7		OTHER (WRITE DETAILED NOTES)
Surgical procedures (excluded from summary scores)		
S1		Circumcision
S2		OTHER (WRITE DETAILED NOTES)

Table II.

Descriptive information for full sample and subsamples of children with and without complete MRA

Characteristics	Full sample (n = 140-162)	Analytic subsample		t
		No MRA data (n = 35-44)	MRA data (n = 99-118)	
Infant				
Gestational age (days)	277.22 (9.92)	277.07 (10.67)	277.27 (9.67)	0.12
Birthweight (kg)	3.35 (0.46)	3.30 (0.53)	3.36 (0.43)	0.69
Female	52%	61%	49%	1.38
Ethnicity				
Hispanic	40%	30%	44%	1.68 *
Race [†]				[†]
Caucasian	16%	20%	14%	
African-American	32%	39%	30%	
Mixed/other	52%	41%	56%	
Illness (n = 109)				
Discrete infection count			2.50 (2.17) range: 0-11	
Discrete noninfectious illness count			2.68 (2.10) range: 0-8	
Illness diversity			4.50 (2.81) range: 0-12	
Maternal				
Maternal age (years)	27.89 (5.61)		28.08 (5.84)	0.19
Intervention group	45%		58%	
Parity (primiparous)	45%		46%	0.03
Married/partnered	68%		68%	0.08
Income	$26 917.49 range: $0-98 000		$22 906.93 range: $0-$86 000	1.07
Percent poverty	161.05 (159.74)		132.46 (108.77)	1.28
PSS				
Early pregnancy	1.83 (0.62)	2.03 (0.53)	1.76 (0.63)	2.49 [‡]
Late pregnancy	1.63 (0.68)	1.67 (0.69)	1.61 (0.67)	0.51
Prenatal average	1.75 (0.59)	1.88 (0.58)	1.70 (0.59)	1.69 *
Postnatal	1.50 (0.71)	1.67 (0.65)	1.44 (0.72)	1.66 *

Characteristics	Full sample (n = 140-162)	Analytic subsample		t
		No MRA data (n = 35-44)	MRA data (n = 99-118)	
SLE				
SLE count	2.61 (2.09)	2.46 (2.42)	2.65 (1.99)	0.49
Squareroot SLE count	1.42 (0.76)	1.30 (0.88)	1.46 (0.72)	1.11
Depression (PHQ)				
Early pregnancy	7.14 (4.93)	8.38 (4.96)	6.67 (4.86)	1.96*
Late pregnancy	5.42 (4.37)	6.09 (4.95)	5.15 (4.09)	1.16
Prenatal average	6.41 (4.10)	7.35 (3.85)	6.05 (4.16)	1.79*
Postnatal	4.53 (4.00)	6.34 (4.04)	3.93 (3.82)	3.19§

PHQ, Patient Health Questionnaire-9; *PSS*, Perceived Stress Scale; *SLE*, stressful life events. Values are mean (SD) unless otherwise noted.

*
$P < .10$.

‡
$P < .05$.

§
$P < .01$.

†
Race categories do not significantly differ between subsamples (χ^2[df = 2] = 2.93; $P = .23$).

Table III.

Frequencies of the ten most common diagnoses found during first year of life (n = 98)

Diagnoses	Count	Percent
Upper respiratory infection	116	15.76
Atopic dermatitis	80	10.87
Yeast infection/candidiasis	55	7.47
Other nutritional (eg, feeding problems/difficulty, poor weight gain, underweight, overweight, rickets)	44	5.98
Rash/dermatitis, nonspecified	39	5.30
Other (noninfectious) illness not otherwise specified	38	5.16
Jaundice	34	4.62
Seborrheic dermatitis (seborrhea, sebopsoriasis, seborrheic eczema, dandruff, cradle cap)	30	4.08
Other chronic conditions not otherwise specified	29	3.94
Otitis interna, media, or externa	27	3.67

Diagnoses noted as "other" were not given a unique diagnosis code.

Table IV.

Pearson correlations among perceived stress and stressful experiences during pregnancy and postnatal period (range, 84-107)

	PSS - early	PSS - late	PSS - average	PSS - postnatal
PSS - early	-			
PSS - late	0.57*			
PSS - average	0.90*	0.90*	-	
PSS - postnatal	0.59*	0.62*	.66*	-
SLE	0.20†	0.25†	0.26*	0.10

SLE, stressful life events.

*
$P < .01$.

†
$P < .05$.

Table V.

Spearman rank correlations among study variables and illness outcomes

	Illness outcomes		
Covariates/predictors	**Discrete infection count**	**Discrete noninfectious count**	**Diversity of illness types**
Gestational age	0.14	−0.06	0.04
Birth weight	0.04	**−0.21**[*]	−0.12
Parity (multiparous)	−0.09	−0.16[†]	−0.16
Percent poverty	−0.12	−0.17[†]	**−0.21**[*]
Postnatal PSS	−0.04	0.19[†]	0.14
Prenatal SLE count	0.12	0.11	0.15
Prenatal PSS (average)	0.09	**0.32**[‡]	**0.28**[‡]

SLE, stressful life events.

[*] $P < .05$.

[†] $P < .10$.

[‡] $P < .01$.

Table VI.

Results of negative binomial regression models predicting infectious illness count, noninfectious illness count, and illness diversity, comparing effects of average prenatal, early prenatal and later prenatal perceived stress

	Infectious illness count			Noninfectious illness count			Illness diversity		
	Prenatal perceived stress exposure period			Prenatal perceived stress exposure period			Prenatal perceived stress exposure period		
Models	**Avg**	**Early**	**Late**	**Avg**	**Early**	**Late**	**Avg**	**Early**	**Late**
No.	99	98	86	99	98	86	99	98	86
Predictors									
SLE count	1.13	1.16	1.17	0.85	0.91	0.85	0.96	1.02	0.92
PSS- average	**1.38**[*]			**1.73**[†]			**1.53**[†]		
PSS- early		1.10			**1.39**[†]			**1.26**[*]	
PSS- late			**1.55**[†]			**1.83**[†]			**1.64**[†]
% Poverty	0.99[§]	0.99	0.99	**1.00**[†]	**1.00**[*]	**1.00**[†]	**0.99**[†]	**0.99**[†]	**0.99**[†]
Parity (multi)	1.01	1.04	1.09	0.75[§]	0.74[§]	0.73[§]	0.81[§]	0.82	0.83
Gestational age	1.02[§]	1.02	**1.03**[*]	1.00	1.00	0.99	1.01	1.00	1.01
Birth weight	1.10	1.07	1.02	0.78	0.74	0.96	0.94	0.91	1.04

SLE, stressful life events.

[*]
P < .05.

[†]
P < .01.

[§]
P < .10.