Relationships among Maternal Stress and Depression, Type 2 Responses, and Recurrent Wheezing at Age 3 Years in Low-Income Urban Families

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Abstract

Rationale: Maternal depression and prenatal and early life stress may influence childhood wheezing illnesses, potentially through effects on immune development.

Objectives: To test the hypothesis that maternal stress and/or depression during pregnancy and early life are associated with recurrent wheezing and aeroallergen sensitivity and altered cytokine responses (enhanced type 2 or reduced virus-induced cytokine responses) from stimulated peripheral blood mononuclear cells at age 3 years.

Methods: URECA (Urban Environment and Childhood Asthma) is a birth cohort at high risk for asthma ($n = 560$) in four inner cities. Maternal stress, depression, and childhood wheezing episodes were assessed by quarterly questionnaires beginning at birth. Logistic and linear regression techniques were used to examine the relation of maternal stress/depression to recurrent wheezing and peripheral blood mononuclear cell cytokine responses at age 3 years.

Measurements and Main Results: Overall, 166 (36%) children had recurrent wheeze at age 3 years. Measures of maternal perceived stress at Years 2 and 3 were positively associated with recurrent wheeze ($P < 0.05$). Maternal depression (any year) was significantly associated with recurrent wheezing ($P \leq 0.01$). These associations were also significant when considered in a longitudinal analysis of cumulative stress and depression ($P \leq 0.02$). Neither stress nor depression was significantly related to aeroallergen sensitization or antiviral responses. Contrary to our original hypothesis, prenatal and Year 1 stress and depression had significant inverse associations with several type 2 cytokine responses.

Conclusions: In urban children at high risk for asthma, maternal perceived stress and depression were significantly associated with recurrent wheezing but not increased atopy or reduced antiviral responses.

Keywords: atopy; inner city; stress; depression; wheezing

Minority children who grow up in urban neighborhoods with high rates of poverty have a higher prevalence of childhood asthma and are at risk for higher morbidity due to

asthma relative to other children (1–3). Recurrent wheezing is common in preschool-aged children (4, 5). Recurrent wheezing and allergic sensitization comprise the two

strongest risk factors for asthma (6). Children 0–4 years of age, diagnosed with asthma, have the greatest health care utilization, including the highest rate of outpatient asthma office

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At a Glance Commentary

Scientific Knowledge on the

Subject: Prior studies have shown that maternal stress and depression during pregnancy and in early life are associated with subsequent risk of wheeze in early childhood. However, there is relatively little information about how prenatal and postnatal stress affects cytokine responses and the development of recurrent wheeze and asthma. In the URECA (Urban Environment and Childhood Asthma) cohort, we have previously reported that prenatal stress is associated with altered innate and adaptive immune responses in stimulated cord blood cytokine responses. In the same cohort, we have also identified significant positive associations between maternal stress and/or depression and recurrent wheeze at 1 year of age.

What This Study Adds to the

Field: This study demonstrates that, in urban families, low socioeconomic status with a family history of atopy, maternal stress, and depression are positively associated with recurrent wheezing in children at age 3 years, and neither stress nor depression augment allergic sensitization or type 2 cytokine responses at age 3 years.

visits and hospitalizations (4, 5, 7), among all age groups.

Low-income families living in urban neighborhoods are often exposed to stressful life events (8), which may have long-term consequences on respiratory health. For example, maternal stress and depression during pregnancy and in early life are associated with subsequent risk of wheeze in early childhood (9–13). Cytokine responses of blood cells can be assessed during childhood as a marker of immune status. Environmental factors, such as increased caregiver psychological stress, may modify immune function and cytokine production (12, 14). There is relatively little information about how prenatal and postnatal stress affects cytokine responses and the development of recurrent wheeze and asthma. There is only limited information about how prenatal stress affects the development of cytokine responses, an

important indicator of immune development, throughout childhood (12, 14, 15). After birth, early-life chronic caregiver stress has been associated with increased tumor necrosis factor- α and reduced IFN- γ responses by stimulated peripheral blood mononuclear cells (PBMCs) (12). Carlsson and colleagues (14) have also shown that, in PBMCs collected from 5-year-old children with high stress within the family, there is increased antigen-induced production of a variety of cytokines, including tumor necrosis factor- α and IFN- γ , compared with cytokine responses from 5-year-old children without high stress within the family.

The URECA (Urban Environment and Childhood Asthma) birth cohort was established to identify effects of stress and other environmental stimuli on early immune development, and on clinical outcomes, such as allergy, recurrent wheeze, and asthma. In URECA, we previously reported that prenatal stress is associated with altered innate and adaptive immune responses in stimulated cord blood cytokine responses (16). In the same cohort, we have also identified significant positive associations between maternal stress and/or depression and wheeze at 1 year of age (17). In this cohort, we have also described factors related to recurrent wheeze at age 3 years in urban children, such as low annual family income and lower birth weight and gestational age of the child (18). On the basis of these findings, we hypothesized that maternal stress and/or depression in the first 3 years would be associated with recurrent wheezing at age 3 years. Moreover, we hypothesized that maternal stress and/or depression would be associated with enhanced type 2 or reduced viral-induced cytokine responses at age 3 years. To test these hypotheses in the URECA birth cohort study, we prospectively measured maternal stress and depression starting in the prenatal period and continuing until age 3 years, and tested for relationships with the following outcomes measured at age 3 years: recurrent wheeze, allergic sensitization, and cytokine responses from PBMCs. Some of the results of this study have been previously reported in the form of an abstract (19).

Methods

Study Population

The design, methods, and study population of the URECA study have been previously

reported in detail (20). URECA is a longitudinal birth cohort study in four U.S. urban areas: Baltimore, Boston, New York City, and St. Louis. Selection criteria included living in a census tract with more than 20% of families below the poverty level, mother or father of the index child with a history of allergic rhinitis, eczema, and/or asthma, and gestational age of 34 weeks or greater. Expectant families were recruited during the prenatal period, and written informed consent was obtained. Every mother underwent a prenatal study visit (60% in the third trimester of pregnancy, and most of the remainder in the second trimester). Maternal questionnaires were administered prenatally and every 3 months after birth. Clinic visits occurred at 12, 24, 33, and 36 months. Between February 2005 and March 2007, 1,850 families were screened, 889 met eligibility criteria, and 560 were enrolled.

Study Assessments

Maternal depressive symptoms were ascertained annually using the Edinburgh Postnatal Depression Scale, which has been validated for detecting depression in the prenatal as well as postpartum periods (21). Maternal perceived stress was assessed quarterly by the four-item Perceived Stress Scale, which measures the degree to which respondents believe their lives were unpredictable, uncontrollable, and overwhelming in the preceding month (22). The quarterly responses were averaged across each year.

The physiologic effects of stress may be greatest when adverse events are experienced across multiple domains. We used a composite measure of external stressors, which includes difficult life circumstances (i.e., stressful life events), financial strain, neighborhood violence, and housing problems, as previously detailed (16, 17). Principal component factor analysis was used to combine the items on the individual scales in the stress battery and to extract a reduced number of factors to represent different domains of stress (16). Resultant factors represented three contexts related to individual-level stressors and ecological-level strains related to housing problems and neighborhood problems. Cumulative measures of stress and depression were created by summing the responses across the four time points. To create a composite stress score, each subscale was divided into tertiles and given

values of 1 (low), 2 (medium), and 3 (high) exposure, and the tertile values were summed across the three factors (range, 3 [low on all domains] to 9 [high on all domains]).

An additional questionnaire administered annually measured coping (21–25). The brief COPE questionnaire is composed of 16 questions that measure coping strategies (25). Within the COPE questionnaire, three subscales measure emotion-focused strategies, problem-based strategies, and dysfunctional coping strategies (26).

Definitions

The primary outcome for the study was recurrent wheeze, defined as at least two episodes of wheezing during the first 3 years of life, with at least one episode during the third year, as assessed by a standardized questionnaire administered every 3 months to the child's caretaker. The mother or primary caretaker was asked, "Since the last time we talked, has your child's chest ever made a wheezing or whistling sound?" Also considered in the definition of "wheezing" were hospitalizations and health care provider visits (emergency room, doctor's office, urgent care, or clinic visits), where the mother indicated that one of the reasons for the visits was a wheezing illness, asthma exacerbation, or reactive airway disease.

Allergic sensitization at 3 years of age was defined as the presence of one or more positive (≥ 0.35 kU/L) serologic test results for allergen-specific IgE, or one or more positive allergy skin tests. A positive skin test reaction is defined as a mean wheal size at least 3 mm larger than the saline control. The IgE panel at 3 years of age consisted of milk, egg, peanut, German cockroach, dust mites, dog, cat, mouse, and *Alternaria* (ImmunoCAP; Phadia, Uppsala, Sweden). Children underwent skin prick testing at age 33 months (Multi-Test II; Lincoln Diagnostics, Decatur, IL) for the following 14 indoor and outdoor allergens (Greer Laboratories, Lenoir, NC): *Alternaria tenuis*, American and German cockroach mix, *Aspergillus* mix, cat hair, *Dermatophagoides farinae*, *D. pteronyssinus*, dog epithelia, German cockroach, mouse epithelia, *Penicillium notatum*, ragweed mix, rat epithelia, Timothy grass, and tree pollen (white oak at St. Louis and Baltimore sites; birch mix at Boston).

Cytokine Responses

Blood mononuclear cells from the 36-month visit were separated from fresh peripheral blood by density gradient centrifugation at each of four study sites (27). After separation, PBMCs were incubated with a panel of specific stimuli selected to activate specific innate (including respiratory viruses), adaptive, and polyclonal responses (see Table E1 in the online supplement), as previously described (28, 29). Supernatant fluids from PBMC cultures were frozen in aliquots and sent to a central laboratory for cytokine analysis. Selected cytokines (Table E1) were measured by multiplex ELISA (Milliplex; Millipore, Billerica, MA). These assays were carefully standardized across the four clinical sites; technicians attended centralized training sessions and used the same equipment and centrally prepared stimulants and reagents, and performance was assessed yearly by analysis of a blood sample that was split and analyzed at each of the sites (27). A type 1 (Th1) immune response was defined by the cytokine, IFN- γ , and a type 2 (Th2) immune response was defined by the cytokines, IL-4, IL-5, and IL-13.

Statistical Analysis

Demographic comparisons between children with or without recurrent wheeze were tested using Wilcoxon tests or *t* tests for continuous data and chi-square tests for categorical data. Variables previously identified as being related to psychological stress and recurrent wheezing, as well as relevant demographic and clinical characteristics, were examined as potential confounders (16, 29). Univariate and multivariate logistic regression was performed to determine the association of perceived stress score, depression score, and composite stress measured at each year and cumulatively with both recurrent wheezing and allergic sensitization at age 3 years. All stress and depression measures were standardized (using sample mean and SD) before examining the regression models with clinical outcomes, to easily compare the magnitude of the estimates across different scales. First-order interactions were tested between stress/depression and allergic sensitization in the prediction of recurrent wheeze, but were found to be nonsignificant. We also considered that coping skills might have potentially been in the pathway through which stress might contribute to recurrent wheeze, and we

explored this using a mediation analysis. This was performed using a four-step approach with several linear and logistic regression models to determine if coping skills mediated the relationship between stress or depression and recurrent wheeze, and if depression mediated the relationship between stress and recurrent wheeze (30). This was followed up with a test for partial mediation, using the techniques described by Iacobucci, which employs both linear and logistic regression models (31). Relationships between cytokine expression and perceived stress score, depression score, and composite stress were examined using linear regression; cytokine values were log transformed due to their skewed distributions. Variables remained in the final models if they were statistically significant ($P < 0.05$). All models were adjusted for maternal race/ethnicity (strongly correlated with study site), child's sex, prenatal smoking, maternal smoking during the first year of the child's life, birth season, child's birth weight, number of previous live births, and maternal asthma. To minimize the false discovery rate when testing several hypotheses, we employed the adaptive Benjamini and Hochberg linear step-up procedure to our prespecified hypotheses. Statistical analyses were performed on SAS Version 9.4 (SAS Institute, Cary, NC) and the R system for statistical computing (version 3.2.2; R Foundation for Statistical Computing, Vienna, Austria). Significance was set at *P* less than 0.05.

Results

Study Population and Recurrent Wheeze

Of the 560 children in the URECA cohort, 478 (85%) remained in the study at age 3 years, 467 (83%) had sufficient data to assess recurrent wheeze, and 420 (75%) had either skin test or IgE measured to classify allergic sensitization. Adaptive and polyclonal immune response data at Year 3 were available from 422 of the 467 URECA participants (90%), whereas innate and antiviral cytokine response data at Year 3 were available from 419 of the 467 URECA participants (90%). The main characteristics of the study participants are summarized in Table 1. Of all the study participants in this analysis, 166 (36%) had recurrent wheeze at age 3 years. Recurrent wheeze at age 3 years was significantly and positively associated

Table 1. Characteristics of Study Participants

Characteristic	Overall (n = 467)	Recurrent Wheeze, 36% (n = 166)	No Recurrent Wheeze, 64% (n = 301)	P Value*
Maternal demographics and smoking				
Mother completed high school	58% (273)	55% (92)	61% (181)	0.35
Mother married	14% (64)	13% (21)	14% (43)	0.72
Household income < \$15,000	69% (321)	75% (124)	65% (197)	0.05
Mother smoked while pregnant [†]	18% (83)	24% (39)	15% (44)	0.02
Mother smoked in first year of child's life	44% (203)	49% (81)	41% (122)	0.10
Number of previous live births	1.3 ± 1.5	1.5 ± 1.7	1.1 ± 1.3	0.03
Maternal asthma/allergy				
Mother has asthma [†]	40% (186)	47% (77)	37% (109)	0.04
Mother has hay fever/allergies [†]	46% (209)	47% (76)	45% (133)	0.71
Mother is atopic	71% (313)	72% (112)	70% (201)	0.74
Child demographics				
Child's race/ethnicity				0.19
Black	71% (333)	72% (120)	71% (213)	
Hispanic	20% (92)	16% (27)	21% (65)	
Other	9% (42)	12% (19)	8% (23)	
Child's sex: male	51% (240)	56% (93)	49% (147)	0.16
Child's birth				
Birth season				0.70
January–March	24% (113)	27% (45)	23% (68)	
April–June	25% (117)	25% (42)	25% (75)	
July–September	30% (138)	28% (46)	30% (92)	
October–December	21% (99)	20% (33)	22% (66)	
C-section delivery	33% (154)	36% (60)	31% (94)	0.33
Child's birth weight, g	3,258.0 ± 504.4	3,203.8 ± 567.0	3,287.9 ± 464.6	0.10
Gestational age, wk	38.8 ± 1.5	38.4 ± 1.6	39.0 ± 1.4	<0.01

Descriptive statistics are shown as % (n) or mean ± SD.

*P values are from chi-squared test (if categorical) or *t* test (if continuous).

[†]Questions were asked during pregnancy.

with household income less than \$15,000 ($P = 0.05$), prenatal smoking ($P = 0.02$), number of previous live births ($P = 0.03$), and maternal asthma ($P = 0.04$). There was a trend toward a positive relationship between recurrent wheezing and maternal smoking in the first year of life ($P = 0.10$). Compared with children without recurrent wheeze at age 3 years, children with recurrent wheeze at age 3 years had significantly lower birth weight ($P < 0.01$) and a trend toward lower gestational age ($P = 0.10$). Children included in the primary analysis (with complete follow-up data on wheeze) compared with those lost to follow up had slightly greater birth weight ($P = 0.04$) and gestational age ($P = 0.04$, Table E2).

Relationship between Stress or Depression and Recurrent Wheeze

Stress and/or depression was significantly and positively associated with maternal race/ethnicity, maternal education, prenatal smoking, mother's age at time of birth, child's birth weight and birth season,

number of previous live births, maternal asthma, and maternal smoking in the first year of the child's life (data not shown).

The median depression score was highest at the prenatal visit (7.0 [interquartile range (IQR) = 3.0–12.0]) and then was stable in Years 1–3 (Table E3). Similarly, the median perceived stress score was also greatest at prenatal visit (6.0 [IQR = 3.0–8.0]). Median composite stress scores were stable across time (6.0 [IQR = 5.0–8.0]).

We examined the association of measures of stress/depression at each year with recurrent wheeze at age 3 years (Figure 1A). Maternal perceived stress at Years 2 and 3 was significantly associated with increased odds of recurrent wheezing at age 3 years (odds ratios [ORs] ranged from 1.28 to 1.29; $P = 0.02$ –0.03). There was a similar association between depression from the first year of life to age 3 years and recurrent wheezing at age 3 years (ORs ranged from 1.30 to 1.54; all $P < 0.02$). Individual and composite measures of external stressors were also

significantly associated with increased odds of recurrent wheeze at age 3 years, including composite stressors at Year 3 (OR = 1.36; $P = 0.006$), neighborhood factors at Year 2 (OR = 1.28; $P = 0.05$), and hardship factors at Years 2 and 3 (OR = 1.84 and 2.00; $P = 0.009$ and $P = 0.002$, respectively). All relationships between stress, depression, and recurrent wheeze persisted when controlling for multiple comparisons.

Because allergic sensitization in infancy is a significant risk factor for recurrent wheeze, we next tested whether stress and depression were positively related to allergic sensitization. Contrary to our hypothesis, there were nonsignificant trends for inverse associations between perceived stress score and composite stressors measured at age 1 year and sensitivity to aeroallergens at age 3 years (ORs = 0.75 and 0.77; Figure 1B). In contrast to findings with recurrent wheeze, there were no significant associations between maternal depression at any time point and sensitivity to aeroallergens at age 3 years.

Figure 1. Associations (odds ratios and 95% confidence intervals [CIs]) between stress and depression at each year and clinical outcomes at age 3 years. Relationships with recurrent wheeze are depicted in A, and relationships with atopy are shown in B. Solid circles indicate $P < 0.05$ after adjustment for mother's race/ethnicity, prenatal smoking, maternal smoking in the first year of the child's life, maternal asthma, child's birth weight, birth season, number of previous live births, and child's sex.

Relationships with recurrent wheeze persisted in an analysis examining cumulative measures of stress and depression across all four time points (Table E4; perceived stress: OR = 1.22, $P = 0.03$; depression: OR = 1.29, $P = 0.001$). Cross-sectional relationships were generally strongest for stress measured in the second and third years, whereas associations between cumulative measures of stress or depression and recurrent wheeze were generally weaker than those for Years 2

and 3. These analyses were replicated for subjects with complete data for all four time points, and the results were similar (data not shown).

Mediation of Effects of Stress and Depression by Coping Mechanisms

Adaptive coping mechanisms can attenuate or modify adverse effects of stress. Therefore, we tested whether assessments of maternal coping mechanisms buffered relationships between stress and recurrent

wheezing. There was evidence of partial mediation with respect to dysfunctional coping skills and both perceived stress ($P = 0.04$) and composite stressors ($P = 0.03$), indicating that a relatively small, but significant, indirect effect exists, and indicates that coping skills account for some of the relationship between stress/depression and wheezing.

Relationship between Stress and Cytokine Responses

Relationships between depression, perceived stress, and composite external stressors with the risk of recurrent wheeze suggested that stress and depression might either inhibit virus-induced IFN responses or promote development of type 2 responses. To test these hypotheses, yearly measurements of composite external stress and maternal depression were examined in relation to cytokine responses of PBMCs obtained at 3 years of age. There were no significant relationships between maternal stress or depression and cytokine responses to rhinovirus or respiratory syncytial virus.

Contrary to our initial hypothesis, there were a number of significant inverse associations between stress or depression and type 2 responses at age 3 years. For example, maternal depression, perceived stress, and composite external stressors were negatively related to some type 2 (IL-4, IL-5, and IL-13) responses to polyclonal and antigenic stimuli (Figure 2B). These relationships were most prominent for exposures occurring during the prenatal period or in the first year of life (Figure 2B).

Discussion

The goal of this study was to define relationships between exposure to external stressors and maternal perceived stress and depression in early life with respect to recurrent wheezing and allergic sensitization measured at age 3 years. Our results demonstrate that the composite measure of external stressors was significantly associated with recurrent wheezing, and this was most pronounced for exposures when the children were 3 years of age. Multiple types of stressors were assessed, and those related to personal hardships had the strongest relationship with wheezing. Similarly, perceived stress in Years 2 and 3 was positively related to recurrent wheeze. Furthermore, postnatal

Figure 2. Association (β estimates) between stress and depression at each year and cytokine responses at age 3 years. Innate and antiviral responses are shown in A, and adaptive and polyclonal responses in B. All cytokine responses have been log (base 10) transformed before inclusion in the model. Blue represents a positive association ranging from 0 to 3, and red represents a negative association ranging from -3 to 0, which can be interpreted as the resulting stress and depression increase/decrease associated with a 1-log-unit change in the immune response. The intensity of the color represents the strength of the association, and statistically significant relationships after correction for multiple comparisons are marked with an asterisk. In addition, any cytokine responses that do not show much variability (i.e., most responses are at the limit of detection) are marked with a diagonal white line. The analysis was adjusted for mother's race/ethnicity, prenatal smoking, maternal smoking in the first year of the child's life, maternal asthma, child's birth weight, birth season, number of previous live births, and child's sex. cr = cockroach extract; dm = dust mite extract; mab = CD3/ α CD28 monoclonal antibody; pha = phytohemagglutinin; rv = rhinovirus; rsv = respiratory syncytial virus; tt = tetanus toxoid.

maternal depression had a strong and consistent association with recurrent wheezing. Notably, the magnitude of the positive relationships between recurrent wheeze and maternal depression (OR = 1.54) or the hardship factor (OR = 2.00) were similar to those previously reported for aeroallergen sensitization (OR = 1.53–1.63) (18). Finally, our data indicate that coping skills may partially mediate the relationship between stress and recurrent wheeze.

Stress and depression were not associated with enhanced type 2 responses, and, in fact, there were several significant inverse associations with type 2 cytokine responses. We previously reported that prenatal composite stress was associated with changes in cord blood responses suggestive of Th2 polarization (16) in this birth cohort. However, our results through age 3 years suggest that this effect was transient, and that neither stress nor depression augment allergic sensitization or type 2 cytokine responses at age 3 years. In addition, we previously reported that prenatal composite stress and depression were not positively associated to type 2 cytokine responses in the urban mothers participating in this cohort (32). Taken together, these findings suggest that the relationship between stress, depression, and recurrent wheeze is not mediated by effects on allergic sensitization.

Most preschool wheezing episodes are initiated by viral respiratory infections. However, we did not find evidence that maternal stress or depression during the prenatal period or first 3 years of life inhibited PBMC antiviral responses. Other possible mechanisms underlying the association of maternal stress and depression and recurrent wheeze at age 3 years include stress-induced neuroendocrine effects through the hypothalamic–pituitary–adrenocortical axis and the autonomic nervous system (33, 34), effects on lung development and airway size (35, 36), and interactions between viral infections (37).

This study has a number of strengths, including the prospective design and high rate of study participant retention. The URECA study design includes repeated measures of stress across a number of domains using standardized measures during critical windows of development (pregnancy and annually during the first 3 years of the child's life). This study also

included a fairly comprehensive assessment of cytokine responses to innate, adaptive, and polyclonal stimuli that was performed using standardized reagents and protocols with stringent quality control procedures. We also recognize limitations of the study. The study population consists of urban families, largely minorities, with low socioeconomic status who are at high risk for respiratory illnesses and, ultimately, allergic diseases and asthma. Understanding risk factors for wheeze in these children is thus of great importance,

but the results of this study may not be broadly generalizable to other populations that are not at high risk for atopic disease. In addition, depressed or stressed mothers may perceive their children's respiratory symptoms differently, and this could have resulted in over reporting of wheezing. However, we found that maternal stress and depression are associated with cytokine responses that support the validity of the family-reported outcomes.

In conclusion, we have shown that maternal stress and depression are positively

associated with recurrent wheeze. Neither stress nor depression was associated with allergic sensitization or enhancement of type 2 cytokine responses, or inhibition of antiviral responses. Continued follow up of this prospective birth cohort will allow us to examine whether maternal stress and depression in early life will also influence asthma expression and lung function in these children. ■

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