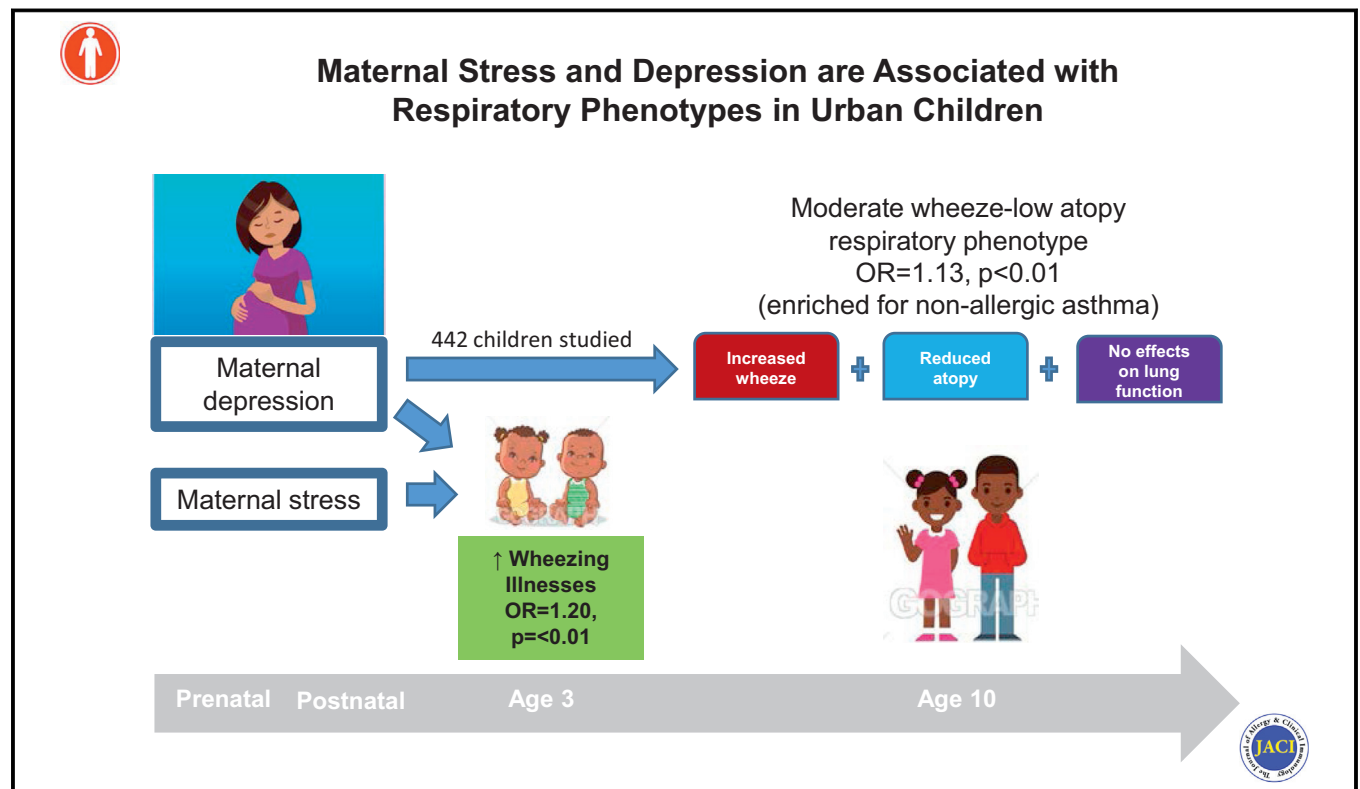


Maternal stress and depression are associated with respiratory phenotypes in urban children

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GRAPHICAL ABSTRACT



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Background: Prenatal and early-life exposure to maternal stress and depression is linked to development of recurrent wheezing in young children.

Objective: We sought to determine whether maternal stress and depression in early life are associated with nonatopic wheezing phenotype in urban children.

Methods: The Urban Environment and Childhood Asthma Study examined a birth cohort of children at high risk for asthma in low-income neighborhoods. Prenatal and postnatal (through age 3 years) maternal stress and depression scores were compared with respiratory phenotypes through age 10 years (multinomial regression), self-reported colds (linear regression), and detection of respiratory viruses (Poisson regression).

Results: Scores for maternal depression, and, to a lesser extent, maternal perceived stress, were positively related to multiple wheezing phenotypes. In particular, cumulative measures of maternal depression in the first 3 years were related to the moderate-wheeze-low-atopy phenotype (odds ratio, 1.13; [1.05, 1.21]; $P < .01$). Considering indicators of respiratory health that were used to identify the phenotypes, there were multiple positive associations between early-life scores for maternal stress and depression and increased wheezing illnesses, but no consistent relationships with lung function and some inverse relationships with allergic sensitization. Cumulative maternal stress and depression scores were associated with cumulative number of respiratory illnesses through age 3 years.

Conclusions: Among high-risk, urban children, maternal stress and depression in early life were positively associated with respiratory illnesses and a moderate-wheeze-low-atopy phenotype. These results suggest that treating stress and depression in expectant and new mothers could reduce viral respiratory illnesses and recurrent wheeze during the preschool years and some forms of childhood asthma. (J Allergy Clin Immunol 2021;■■■:■■■-■■■.)

Key words: Asthma, maternal depression, atopy, wheeze, pediatrics, allergic sensitization

There is increasing evidence from animal models and birth cohort studies linking prenatal and postnatal maternal stress and depression to the development of recurrent wheezing in young children.¹⁻⁸ The URECA (Urban Environment and Childhood Asthma) birth cohort was established to identify which urban exposures in early life, including maternal stress and depression, affect the development of childhood allergies and asthma. We have previously shown that maternal perceived stress and depression in early life are significantly associated with wheezing at age 1 year, recurrent wheeze at age 3 years,^{4,9} and development of asthma at age 7 years.¹⁰ Furthermore, in the same cohort, we performed a cluster analysis of longitudinal trajectories of wheeze, allergic sensitization, and lung function, which identified 5 distinct respiratory phenotypes at age 7 years.¹¹ Scores for maternal perceived stress and maternal depression were both greatest in children who went on to develop a high-wheeze, low-atopy (HW-LA) phenotype.

The phenotypes of respiratory health in the URECA study were recently updated to include trajectories of wheeze, allergen-specific IgE, and lung function data that were prospectively

Abbreviations used

FVC:	Forced vital capacity
HW-HA-LF:	High wheeze, high atopy, low lung function
HW-LA:	High wheeze, low atopy
LW-HA:	Low wheeze, high atopy
LW-LA:	Low wheeze, low atopy
MW-HA:	Moderate wheeze, high atopy
MW-LA:	Moderate wheeze, low atopy
TW-LA:	Transient wheeze, low atopy
URECA:	Urban Environment and Childhood Asthma
XA:	Reactance area

measured from birth until age 10 years. On the basis of our earlier findings in this population, we hypothesized that maternal stress and depression in early life would be associated with nonatopic wheezing phenotype. To define the nature of this relationship, we also tested for associations between maternal stress and depression and factors that were used to identify the respiratory phenotypes, including longitudinal trajectories of wheezing illnesses, allergic sensitization, and lung function development.

METHODS

The design, methods, and study population of the URECA study have been previously reported in detail.¹² Briefly, URECA is a longitudinal birth cohort study in 4 US 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 34 weeks or more. Expectant families were recruited during the prenatal period, and written informed consent was obtained. Between February 2005 and March 2007, a total of 1850 families were screened, 776 met eligibility criteria, and 560 newborns were enrolled at birth.

Study assessments

Maternal depressive symptoms were ascertained prenatally and annually in first 3 years of life using the Edinburgh Postnatal Depression Scale, which has been validated for detecting depression in the prenatal as well as postpartum periods.¹³ Maternal perceived stress was assessed quarterly by the 4-item Perceived Stress Scale, which measures the degree to which respondents believe their lives were unpredictable, uncontrollable, and overwhelming in the preceding month.¹⁴ The quarterly responses were averaged across each year. Perceived Stress Scale is scored from 0 to 16, with a higher score indicating a higher degree of stress. Edinburgh Postnatal Depression Scale is scored from 0 to 30, with scores of at least 10 indicating possible depression and recommending patients should receive further evaluation.^{13,15,16}

Asthma definition and asthma phenotypes

We classified children as having asthma at age 10 years using information about symptoms, lung function, and diagnosis by a health care provider as previously described.¹⁰ Wheezing episodes were determined from caretaker report, during phone calls at time of illnesses, from records of hospitalizations due to respiratory illnesses, and from physical examinations at scheduled study visits. To define the 10-year respiratory phenotypes, we used a process similar to that used to assess phenotypes at age 7 years.¹¹ Using 10 years of data, longitudinal trajectories of wheezing (caretaker report of any wheezing episodes and number of wheezing illnesses), atopy (aeroallergen IgE ratio and skin test ratio), and lung function (FEV₁/forced vital capacity [FVC] ratio from spirometry and reactance area [XA] from impedance oscillometry)

Cluster Name	wheeze	Atopy	Lung Function	N
LW-LA	Low	Low	NI	95 (21.5%)
TW-LA	Transient	Low	NI	75 (17.0%)
MW-LA	Medium	Low	NI	76 (17.2%)
LW-HA	Low	High	NI	86 (19.5%)
MW-HA	Medium	High	NI	54 (12.2%)
HW-HA-LF	High	High	Obstructed	56 (12.7%)

FIG 1. Summary of the 6 respiratory phenotypes identified by cluster analysis. Each row describes a specific respiratory phenotype.

were identified from prospective measurements through age 10 years (see Fig E1 in this article's Online Repository at www.jacionline.org) (Altman M, et al, unpublished data, 2021). Six respiratory phenotypes were identified (Fig 1): (1) low wheeze-low atopy (LW-LA), low to minimal wheezing and low to minimal allergic sensitization; (2) low wheeze-high atopy (LW-HA), intermediate allergic sensitization that increased over time and little or no wheezing; (3) transient wheeze-low atopy (TW-LA), wheezing in early life that resolved early and with minimal allergic sensitization; (4) moderate wheeze-low atopy (MW-LA), wheezing that diminished over time and little or no allergic sensitization; (5) moderate wheeze-high atopy (MW-HA), wheezing that diminished over time with allergic sensitization; and (6) high wheeze-high atopy-low lung function (HW-HA-LF), high rate of wheezing illnesses with allergic sensitization and airway obstruction. See Table E1 in this article's Online Repository at www.jacionline.org for other characteristics associated with the 6 phenotypes. See the Results section in this article's Online Repository at www.jacionline.org for a comparison between the respiratory phenotypes at age 7 years and at age 10 years.

Statistical analysis

Demographic comparisons between children across phenotypes were tested using Wilcoxon tests or ANOVA for continuous data and chi-square tests for categorical data. Multivariable multinomial logistic regression was performed to determine the association of perceived stress score and depression score, measured prenatally, and years 1, 2, and 3 of the child's life, and a 3-year cumulative variable summed over the first 3 years of life, with respiratory phenotypes through age 10 years. In all multivariable models, LW-LA was the basis of comparison for all remaining 5 phenotypes. Similarly, multivariable multinomial and logistic models were also used on the 6 variables that were responsible for the derivation of the 10-year phenotypes. 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 in the association of 10-year phenotype but were found to be nonsignificant. Maternal race/ethnicity, 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 were identified as being related to psychological stress and the clinical domains for asthma phenotype generation (atopy, wheeze, and lung function), and therefore were treated as a full confounder set in all models (unpublished observations).

The relationships of early exposure to maternal stress/depression to self-reported colds and number of wheezing illnesses in the first 3 years of life were assessed using linear regression. Nasal mucus samples during the first 3 years were collected during moderate or severe respiratory illnesses as described in the Methods section in this article's Online Repository at www.jacionline.org. Next, we assessed associations between stress and depression and viral detection rates using a Poisson regression model. Viral detection rates were calculated as the number of specimens that tested positive for a respiratory virus divided by the total number of samples in the entire study.¹⁰

Statistical analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC), and the R system for statistical computing (version 3.4.6). Significance was set at an alpha value of .05 (probability < 0.05) in all models.

RESULTS

Study population

Of the 560 enrolled infants, 442 (79%) were followed to the age of 10 years. Children in the 6 respiratory phenotypes were similar in terms of race, income, and maternal education status (Table E1). A history of maternal asthma was most frequent in the MW-LA phenotype and least frequent in the LW-HA phenotype. The rates of childhood asthma at age 10 years were highest in the MW-LA (54.3%), MW-HA (48.1%), and

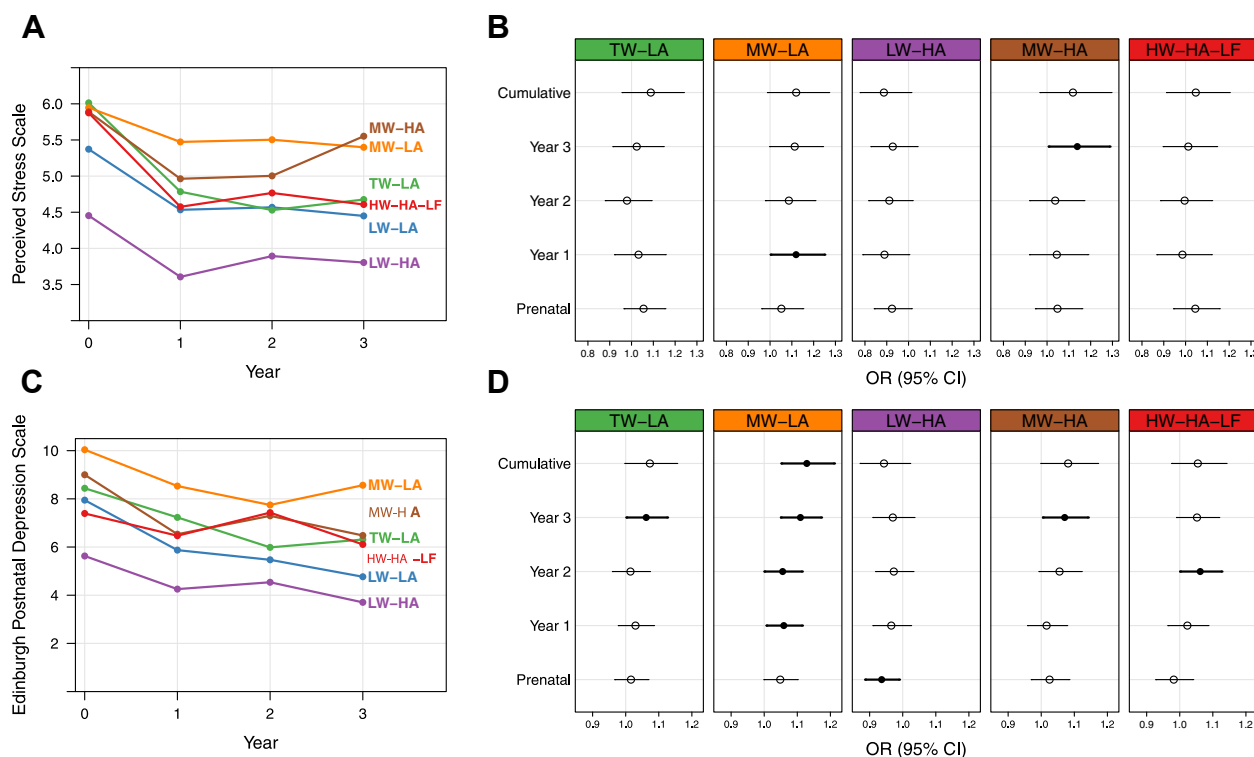


FIG 2. Association of maternal stress and depression scores with respiratory phenotypes at age 10 years. Scores for maternal stress (A) and depression (C) obtained during the prenatal period and at intervals until year 3 were plotted for the 6 respiratory phenotypes. Odds ratios (ORs) were calculated as an estimate for the relationships between scores for stress (B) and depression (D) for the respiratory phenotypes. The LW-LA phenotype was used as the reference group. Closed circle indicates $P < .05$.

HW-HA-LF (81.5%) phenotypes. The population was mostly minority (72.2% black, 19.8% Hispanic), low income, and at high risk for developing asthma on the basis of parental histories (Table E1).

Relationships of maternal stress and depression to respiratory phenotypes and asthma

We tested for differences in maternal stress and depression during the prenatal period and the first 3 years of life across the 6 respiratory phenotypes through age 10 years. Overall, scores for maternal stress and depression were lowest in the LW-HA group and highest in the MW-LA group (Fig 2, A and C). We next tested for associations of maternal stress and depression scores with the respiratory phenotypes using the LW-LA group as the reference group. Maternal stress scores during the first 3 years were positively associated with the moderate wheezing phenotypes, but these relationships were not consistent (Fig 2, B). Cumulative stress scores (prenatal through year 3) were not significantly related to respiratory phenotypes. Maternal depression scores during the postnatal period were positively and consistently associated with the MW-LA phenotype, as was the cumulative depression score (odds ratio, 1.13 [1.05, 1.21]; $P < .01$, Fig 2, D). Maternal depression scores at some ages were also positively associated with other wheeze phenotypes (TW-LA, MW-HA, HW-HA-LF), but these relationships were not consistent across time. In contrast, prenatal maternal

depression scores were inversely related to the LW-HA (odds ratio, 0.94 [0.89, 0.99]; $P = .018$) phenotype (Fig 2, D), with similar trends during the postnatal period.

In contrast to the associations with respiratory phenotypes, there were no significant differences in maternal depression and stress measures at age 3 years according to the child's asthma status at age 10 years (mean Edinburgh Postnatal Depression Scale score, 6.6 vs 5.5 for asthmatic children vs nonasthmatic; $P = .11$; mean Perceived Stress Scale score, 4.9 vs 4.6; $P = .36$).

Maternal stress and depression by wheezing, atopy, and lung function trajectories

We tested whether maternal stress and depression scores in early life were associated with differences in the trajectories for wheezing, atopy, and lung function that were used to identify the respiratory phenotypes. For these comparisons, we used the trajectories with the least wheeze or atopy and best lung function (highest FEV₁/FVC ratio or lowest XA) as the reference groups for calculating odds ratios.

Wheezing. There were multiple positive associations between scores for maternal stress and depression and trajectories of any wheeze and number of wheezing illnesses (both assessed annually). For any wheeze, maternal stress scores were most consistently associated with medium and transient wheeze trajectories from the prenatal period through year 3 (Fig 3, A;

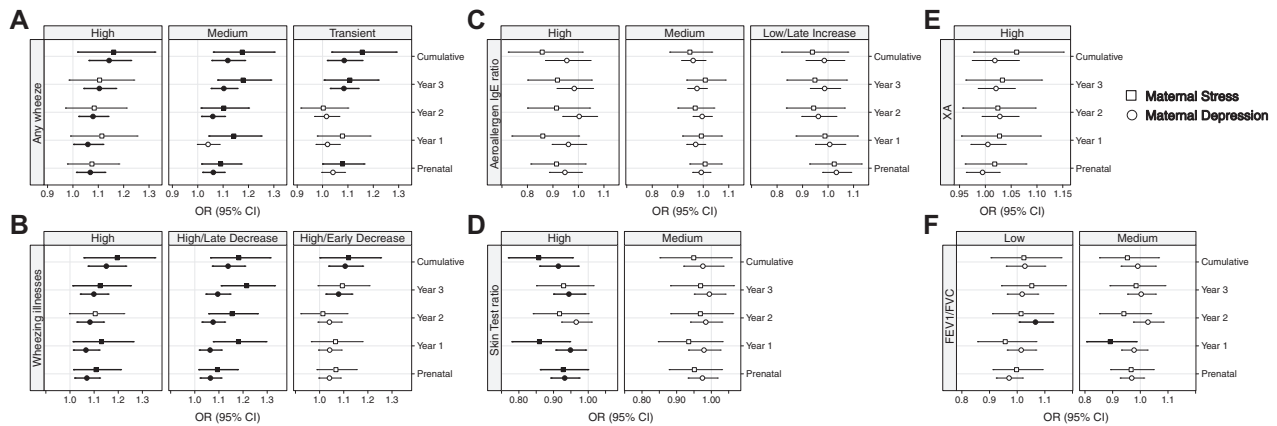


FIG 3. Associations between maternal stress and depression scores and trajectories of wheeze, atopy, and lung function over 10 years. Maternal stress and depression scores during the prenatal period, years 1 to 3, and cumulative scores were compared with the odds ratio (OR) for trajectories of (A) any wheeze, (B) number of wheezing illnesses, (C) aeroallergen-specific IgE ratios, (D) skin prick testing, (E) impulse oscillometry XA, and (F) FEV₁/FVC. Closed circle indicates $P < .05$.

see Table E2 in this article's Online Repository at www.jacionline.org). Maternal depression was positively and consistently associated with high and medium wheeze trajectories (Fig 3, A; see Table E2). Notably, both cumulative (prenatal through year 3) maternal stress and maternal depression scores were positively associated with the high, medium, and transient wheeze trajectories (Fig 3, A; see Table E2).

There were similar relationships between maternal stress and depression scores and the number of wheezing illnesses. Maternal stress was positively and consistently associated with the high and high/late decrease trajectories (Fig 3, B; see Table E2). Likewise, there were significant associations for depression scores over time for the high and high/late decrease wheeze trajectories. Finally, cumulative measures of stress and depression were positively associated with all wheezing illness trajectory groups (Fig 3, B; see Table E2).

Atopy. We next tested whether stress and depression were associated with patterns of allergic sensitization, as measured by longitudinal trajectories of aeroallergen-specific IgE (serum testing and skin prick tests) through age 10 years. Maternal stress scores at year 1 were weakly inversely related to the high specific IgE trajectory (Fig 3, C; see Table E2). There were no significant relationships with maternal depression or stress at any other year for the high, medium, or low/late increasing serum-specific IgE trajectories. For skin test results, there were significant inverse relationships between maternal stress and depression scores at prenatal and postnatal time points and the high trajectory (Fig 3, D; see Table E2). Cumulative measures of maternal stress and depression were both inversely related to the high skin prick test trajectory (Fig 3, D; see Table E2). Neither maternal depression nor stress was associated with the medium skin prick test ratio trajectory (Fig 3, D).

Lung function. In comparison to the low impulse oscillometry XA trajectory (normal), there was no association between maternal depression and stress and high impulse oscillometry XA trajectory (Fig 3, E; see Table E2). In comparison to the high FEV₁/FVC trajectory, there was significantly lower maternal stress in the medium trajectory at year 1 and there was significantly higher maternal depression in

the low trajectory at year 2 (Fig 3, E; see Table E2). However, these relationships were not present at other time points, or with cumulative measures of stress or depression.

Associations of cumulative maternal stress and depression and number of colds and respiratory viral recovery rates

The positive associations between wheezing trajectories and maternal scores for stress and depression suggest that these factors in early life could increase susceptibility to respiratory illnesses. To test this hypothesis, we compared cumulative stress and depression scores to prospectively collected data on the number of respiratory illnesses ("colds") and the number of wheezing illnesses in the first 3 years of life. There was a positive relationship between cumulative maternal stress and the cumulative number of colds (Fig 4, A). Similarly, cumulative maternal depression scores were positively related to children with a higher cumulative number of colds (Fig 4, B).

We next considered the possibility that higher levels of stress or depression could lead to overreporting of respiratory symptoms, which could be reflected in lower viral recovery rates during illnesses. Coordinators collected nasal mucus samples during moderate or severe illnesses in the first 3 years, which were tested for common respiratory viruses as previously described.¹⁷ Viral recovery rate was consistent among all quartiles of cumulative scores for stress ($P = .16$) (Fig 5, A), and for all quartiles of cumulative scores for depression ($P = .42$) (Fig 5, B).

DISCUSSION

Identification of a wide range of asthma phenotypes in several different cohort and cross-sectional studies implies that there may be unique relationships between specific phenotypes of asthma and environmental exposures in early life. In URECA, we evaluated how environmental exposures in early life are associated with respiratory phenotypes in children at high risk for asthma and allergies living in 4 economically disadvantaged urban neighborhoods. We had previously identified 5 respiratory

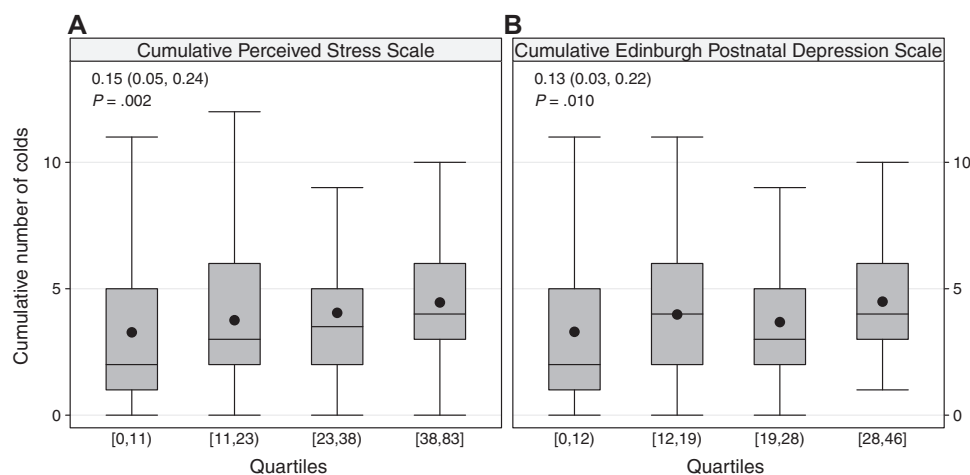


FIG 4. Relationship of maternal stress and depression quartiles to respiratory illnesses. Quartiles of cumulative scores (prenatal through year 3) for maternal stress (**A**) and depression (**B**) were compared with the total number of colds reported for the children during the first 3 years of life. The lines represent the means, and box plots represent the medians and 95% CI, respectively. Solid horizontal line and filled circle within a box represent the median and mean, respectively, the box margins are the interquartile range (50% of the observations), and whisker lines extend for 1.5 times the interquartile range.

phenotypes that were mainly differentiated by patterns of wheezing and allergic sensitization using 7 years of data.¹¹ After updating the analysis to include 10 years of data, children were clustered into 6 respiratory phenotypes, including 1 (HW-HA-LF) with airway obstruction. In this study, we prospectively measured exposure to early-life maternal stress and depression and tested for associations with the 6 respiratory phenotypes. Maternal depression in early life was positively associated with wheezing phenotypes, and these relationships were strongest for the MW-LA group.

We then tested whether the relationships were specifically related to the trajectories of wheezing, atopy, and lung function over 10 years that were used to identify the respiratory phenotypes. Early-life maternal stress and depression were each consistently related to wheezing trajectories, whereas there were no consistent relationships with lung function trajectories. Interestingly, there were some significant inverse relationships between maternal stress and depression and early onset of aeroallergen-specific skin tests (“high” skin test trajectory), but no significant relationships with trajectories of serum IgE. Finally, stress and depression were positively related to respiratory illnesses in early life. We previously reported that maternal stress and depression measures in early life were significantly associated with asthma at age 7 years.¹⁰ Although there was a similar nonsignificant trend at age 10 years in the current analysis, the relationship between depression (and to a lesser extent stress) and a low atopy wheezing phenotype is quite consistent. These findings suggest that maternal depression may predispose to a particular phenotype of nonallergic asthma.

In URECA, maternal perceived stress and depression in early life have been consistently associated with wheezing, including assessments of wheeze at age 1 year and recurrent wheeze at age 3 years,^{4,9} as well as wheezing trajectories. Notably, the cumulative measure of depression across the first 3 years had the strongest relationship to risk of the MW-LA phenotype, suggesting that chronic depression may connote a particular risk.

A meta-analysis of 10 observational studies confirmed that prenatal psychological stress is associated with an increased risk of childhood wheezing and asthma.¹⁸ Alton et al¹⁹ have shown that wheeze at age 3 years was almost 5 times more likely in girls of mothers who experienced postpartum depression.¹⁹ Thus, the association between early exposure to maternal stress and depression and childhood wheezing has been consistently demonstrated in observational studies.

In light of the positive associations of maternal stress and depression with trajectories of wheezing in our study, we tested whether exposure to maternal stress or depression was associated with respiratory illnesses in general. In fact, cumulative maternal stress and depression scores were associated with greater numbers of childhood colds during the first 3 years of life. We next considered the possibility that mothers with higher stress and depression scores might overreport respiratory symptoms in their children. If this were true, we would have expected that stress and depression would be associated with a lower viral detection rate during “illnesses.” However, stress and depression scores were not related to the rate of virus detection, providing evidence that stress or depression did not influence the mother’s assessment of respiratory illnesses. Previous studies have linked psychological stress to increased susceptibility and severity of the common cold in healthy volunteers following experimental inoculation with a strain of rhinovirus.²⁰ In addition, viral respiratory tract infections in infancy and preschool-age children have been linked to the development of asthma later in childhood and young adulthood.^{21–25}

Remarkably, in this study, there were some inverse relationships between cumulative measures of stress and depression and trajectories of allergic sensitization, and these findings are consistent with previous observations in this cohort. For example, we previously reported that early exposures to maternal stress or depression were not associated with increased atopy in URECA children through age 3 years, and in fact there were several significant inverse associations with type 2 cytokine responses

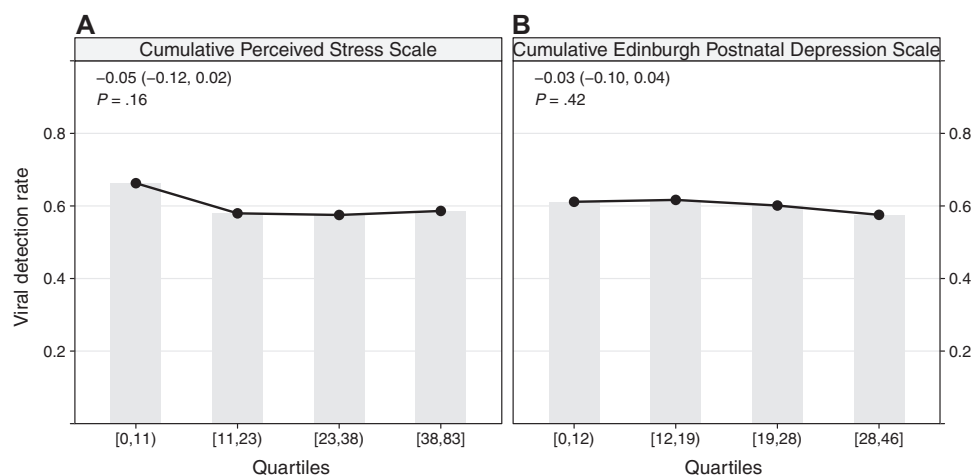


FIG 5. Relationships between maternal stress and depression scores and diagnostic virology. Quartiles of cumulative maternal stress (**A**) and depression (**B**) were compared with the rates of virus detection from nasal mucus specimens obtained in the first 3 years of life. Annotations are Pearson correlations (95% CI) and *P* value assuming a continuous distribution for each variable.

(IL-4, IL-5, and IL-13) of stimulated PBMCs of children at age 3 years.⁴ Furthermore, we reported that depression scores in URECA mothers were associated with reduced maternal PBMC cytokine responses to house dust mite, a common perennial allergen.²⁶ When considered together, results from analyses in the URECA birth cohort suggest that maternal stress or depression could dampen allergic sensitization in mothers and children. One potential mechanism to explain this inverse association could be that stress and depression can alter the hypothalamic-pituitary-adrenal axis, resulting in increased glucocorticosteroid production.²⁷⁻²⁹ Glucocorticoids can inhibit both type 2 inflammatory responses^{30,31} and antiviral responses,^{32,33} and therefore this potential mechanism would fit with observations in URECA that depression was associated with reduced allergic sensitization but increased viral respiratory illnesses. Other studies of stress, depression, and allergy have reported variable results; however, comparisons are difficult due to differences in study design and outcomes assessments, and several previous studies lack objective measures of atopic disease.³⁴

Other mechanisms that could potentially link early-life maternal depression to wheezing in the child could include detrimental effects of depression on airway development or lung maturation or altered airway tone (through autonomic nervous system pathways). However, we did not find any consistent associations between early-life exposure to maternal stress and depression and childhood lung function trajectories (FEV₁/FVC and impulse oscillometry) over 10 years.

These findings suggest that prevention or treatment of perinatal depression could reduce the rates of nonallergic forms of asthma. Perinatal depression is the most common, and underdiagnosed, obstetric complication in the United States.³⁵ Up to 50% of low-income women in the United States may experience perinatal depression.³⁵ Although guidelines for perinatal and postnatal care recommend that obstetricians and pediatricians screen expectant and new mothers for depression and anxiety symptoms,³⁶ screening is inconsistent.³⁷ In addition, low-income women may have poor access to mental health services.³⁸ Although

screening alone is associated with some clinical benefits, it is most effective when coupled with confirmatory diagnostic assessment and access to treatment.³⁹

This study has a number of strengths, including high rate of study participant retention and the prospective design with validated measures of maternal stress and depression repeated annually. One novel aspect of this study is the analysis of associations between exposure to early-life maternal stress and depression and childhood respiratory phenotypes. Frequent assessments of wheeze and objective measurements of allergic sensitization, lung function, and viral illnesses allowed for detailed analysis of associations between stress, depression, and the component predictors that were used to identify asthma and respiratory phenotypes. We also acknowledge the limitations of this study. The URECA cohort consists of children who are minorities with low socioeconomic status and are at high risk for the development of allergic disease and asthma, so the results of this study may not be broadly generalizable to all populations. Causality cannot be determined in observational studies, and it is possible that childhood wheezing could partially account for increased maternal stress and/or depression. However, the temporal relationships suggest that maternal stress and depression preceded the increased wheezing (and reduced rates of allergic sensitization). Finally, there could be unmeasured confounders that are related to both stress/depression and respiratory outcomes.

Conclusions

Our findings suggest that maternal perceived stress and depression could promote wheezing episodes and nonallergic asthma, perhaps by increasing susceptibility to respiratory illnesses in early life. These findings suggest that interventions to improve screening for depression and accessibility of mental health support during pregnancy and the early postnatal period among low-income mothers could help to reduce recurrent wheeze and perhaps nonallergic childhood asthma.

Clinical implications: Stress and depression in expectant and new mothers are risk factors for more respiratory illnesses in early life, and maternal depression is related to nonallergic asthma by age 10 years.

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