Parental Stress as a Predictor of Wheezing in Infancy
A Prospective Birth-Cohort Study

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The role of stress in the pathogenesis of childhood wheeze remains controversial. Caretaker stress might influence wheeze through stress-induced behavioral changes in caregivers (e.g., smoking, breast-feeding) or biologic processes impacting infant development (e.g., immune response, susceptibility to lower respiratory infections). The influence of caregiver stress on wheeze in infancy was studied in a genetically predisposed prospective birth-cohort (n = 496). Caregiver-perceived stress and wheeze in the children were ascertained bimonthly from the first 2 to 3 mo of life. Greater levels of caregiver-perceived stress at 2 to 3 mo was associated with increased risk of subsequent repeated wheeze among the children during the first 14 mo of life (RR, 1.6; 95% CI, 1.3 to 1.9). Caregiver-perceived stress remained significant (RR, 1.4; 95% CI, 1.1 to 1.9) when controlling for factors potentially associated with both stress and wheeze (parental asthma, socioeconomic status, birth weight, and race/ethnicity) as well as mediators through which stress might influence wheeze (maternal smoking, breast-feeding, indoor allergen exposures, and lower respiratory infections). Furthermore, caregiver stress prospectively predicted wheeze in the infants, whereas wheeze in the children did not predict subsequent caregiver stress. The effect of caregiver stress on early childhood wheeze was independent of caregiver smoking and breast-feeding behaviors, as well as allergen exposure, birth weight, and lower respiratory infections. These findings suggest a more direct mechanism may be operating between stress and wheeze in early childhood. Stress may contribute significantly to the population burden of preventable childhood respiratory illness.

Keywords: caregiver stress; wheeze; infancy; birth cohort

Long-standing clinical observation and evolving research support the hypothesis that psychosocial or emotional factors, particularly stress, may impact disease expression (1). It has long been speculated that psychologic stress can influence wheeze in early life (2). Although a causative link has not yet been clearly established, several lines of research suggest that psychologic stress may be a factor contributing to childhood respiratory illness and wheeze (3).

Increased understanding of the complex cellular and molecular basis of airway obstruction, airway inflammation, and wheezing respiratory illnesses in childhood (4), in parallel with evidence evolved over the last two decades of important interactions among behavioral, neural, endocrine, and immune processes, provide fresh insight into means by which psychosocial stress may influence the development and expression of wheeze in early childhood (5). The behavioral and emotional changes that follow the perception of, and the effort to adapt to, environmental stressors can be accompanied by complex neuroendocrine and immunologic alterations (6, 7). Stress-induced neuroendocrine or immunologic changes, in turn, may affect airway inflammation and reactivity through immunologic (i.e., humoral and cell-mediated) and neural (i.e., sympathetic and parasympathetic) pathways that may lead to wheeze. Stress may contribute to early life lower respiratory infections, which may be predictive of repeated wheeze in infancy. Studies have demonstrated increased susceptibility to viral respiratory infections in children of parents experiencing stress (8, 9) and in adults with increased perceived stress (10, 11). Parental stress may also influence early childhood wheeze through modification of caregiver behaviors that influence wheeze, e.g., smoking, breast-feeding (12), or home cleaning characteristics that may influence allergen level exposure and atopy (13).

Over the last few decades, the prevalence of recurrent wheezing episodes among children has been increasing in industrialized countries (14)—a trend that has not been fully explained by known risk factors suggesting there are as yet unidentified factors contributing (15). The impact of a continued increase in childhood wheezing respiratory illnesses, at or surpassing the current trends, on both childhood and adult respiratory health could result in significant burden on future healthcare resources. Such trends have, in part, led to a paradigm shift that reconsiders the influence of psychosocial factors on both behavioral and biologic processes that may, in turn, play a role in the rising burden of childhood respiratory illness.

There is a growing body of evidence suggesting the influence of psychosocial factors, in particular stress, on chronic airway obstruction and asthma symptomatology in those with existing disease (5, 16). However, epidemiologic data to support a role for stress as a risk factor for the development of early childhood wheeze are sparse and largely cross-sectional or retrospective. Two recent prospective studies have examined the influence of disturbed family interaction as a form of stress on early childhood wheeze with contradictory results: while one study of 150 Colorado families found that parenting difficulties predicted the development of recurrent wheeze (17), a Swedish study of 97 families determined that dysfunctional family interaction was the result, rather than the cause, of wheezing in children (18). These studies were limited by small sample size and the inability to more fully account for other known risk factors that may also be mediators of the relationship between stress and childhood wheeze (e.g., smoking, breast-feeding, birth weight, indoor allergens).

We examined caregiver stress beginning in the first 2 to 3 mo of the index child's life as predictors of subsequent wheeze during infancy in a prospective birth-cohort. We also evaluated whether the association between caregiver stress and

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subsequent wheeze in infancy could be explained by factors that might be influenced by stress: increased susceptibility to lower respiratory illness, less breast-feeding, maternal smoking, or elevated allergen levels. Bimonthly measurements of perceived stress enabled us to further evaluate the temporal influence of caregiver stress on subsequent infant wheeze.

METHODS

Infants and their 499 families with a history of asthma or allergy were recruited within 48 h of delivery from a Boston hospital between September 1994 and July 1996. Details of the cohort have been reported previously (19). The Brigham & Women's Hospital Human Studies Committee approved the study, and written informed consent was obtained from each participant.

At an initial home visit, when each child was 2 to 3 mo of age, data were collected on home environmental exposures (e.g., smoking and indoor allergens), sociodemographics, and caregiver stress through personal-interview questionnaires. Subsequently, six bimonthly telephone questionnaires ascertained changes in caregiver stress, maternal smoking, infant feeding, and the occurrence of respiratory illnesses in the children.

Wheeze Surveillance

At each bimonthly follow-up interview, the caretaker was asked: "Since we last spoke with you on (date), has your child had symptoms of wheeze"?

Psychologic Stress

Caregiver stress was ascertained at each bimonthly interview using the four-item Perceived Stress Scale (PSS4) (20), a measure of the degree to which respondents felt their lives were unpredictable, uncontrollable, and overwhelming in the preceding 1 mo (reliability, $\alpha = 0.85$) (21). Each item is scored on a 5-point scale, ranging from "never" (0) to "very often" (4), and scores were obtained by summing the four items (maximum = 16). Higher scores indicate greater stress.

Covariates

A series of control variables was assessed to see if characteristics of the children or caretakers that might correlate with caretaker stress could account for why children of stressed parents would be at higher risk for recurrent wheeze. These included: child's race, household income, caregiver education, maternal age, marital status, child's birth weight, and whether either parent had active asthma as defined previously (19).

We also assessed potential pathways (mediators) through which stress might contribute to increased risk of wheeze. We thought that caregiver stress might influence whether the mother smoked or was able to keep the house clean (cockroach allergen exposure) and whether she breast-fed after the birth of the child. Finally, we thought that a stressful family environment might influence the child's host resistance to infections. Maternal smoking was defined as any smoking during pregnancy and/or the first year of the child's life. Lower respiratory illnesses (LRIs) were defined as doctor-diagnosed croup, bronchitis, bronchiolitis, or pneumonia reported at any of the follow-ups. Breast-feeding was coded as whether or not the mother reported any breast-feeding more than half-time at the bimonthly follow-ups. Dust samples collected at the home visit were assayed for cockroach antigen (*Bla g* 1 or 2) (22), with exposure levels categorized as defined earlier (19).

Statistical Analysis

All analyses used SAS statistical software version 6.12 (SAS Institute, Inc., Cary, NC). Relationships among caregiver stress and covariates were examined using Wilcoxon's rank-sum test and the Kruskal-Wallis one-way analysis of variance to test differences in mean PSS4 scores for two or more groups, respectively. Wilcoxon's rank-sum testing was conducted for each two-group pairing within multigroup comparisons.

Two approaches were used to examine the relationship between caregiver stress and wheeze in the children. The first was a traditional prospective between-subjects analysis. In simple terms, this analysis asks whether children whose parents report higher stress at the 2- to 3-mo assessment (baseline) were at greater risk for multiple wheeze episodes during the subsequent year than were children whose parents report lower levels of stress. Nine of the 505 children (six sets of twins) were dropped from these analyses because they were missing data from Months 10, 12, and 14 during follow-up and had fewer than two reports of wheeze prior to 10 mo or they had two episodes of wheeze reported prior to 2 to 3 mo of age (leaving a final 496 children and 490 caregivers).

In these analyses, logistic regression was used to predict the dichotomous outcome "multiple wheeze episodes" defined as two or more reports of wheeze compared with fewer than two. We began by fitting a univariate model that included only baseline-perceived stress. We then fit a multivariate model in which we added the standard control variables to ascertain whether associations we found might be spurious. Finally, we added the hypothesized mediating pathway variables. In this final analysis, a substantial decrease in the effect size of the association between stress and wheeze would be consistent with the operation of one or more of the pathways.

The second approach to analysis was a within-subject (repeated measures) comparison that collapses across the seven bimonthly assessments of caregiver stress. In the simplest terms, these analyses ask for each child whether he or she has a higher risk for wheeze during periods his or her caretaker is under high stress in comparison with periods when the caretaker is experiencing less stress. These associations are aggregated across children, resulting in an overall estimate of relative risk. Because high stress periods are compared with low stress periods in the same subjects, individual differences that might play a role in selecting people into high or low stressed conditions in the between-subject analyses (standard control variables) are not an issue in these within-subject analyses. We asked three questions. Was caregiver stress associated with reports of wheeze collected at the same assessments (cross-sectional), with wheeze reported 2 mo later (prospective), or with wheeze reported 2 mo earlier (retrospective)? A separate model was fit to address each question using generalized estimating equations (GEE) for the logistic case (PROC GENMOD) specifying exchangeable correlation matrices (23), which accounts for correlations between repeated measures that are relatively close in time.

We hypothesized a prospective relationship. That is, caregiver stress as reported at each assessment would predict the child's risk of wheeze over the subsequent 2-mo periods. We predicted the 2-mo lag between increased caregiver stress and the child's increased risk of wheeze because we thought that the wheeze would occur in response to stress-elicited changes in parent behavior and/or child biologic response that might take time before they influenced wheeze risk. This analysis technique allowed us to test (using covariates that were also reported at 2-mo intervals and could potentially change) whether changes in parental behaviors (caregiver smoking, breast-feeding practices) or child biologic response (occurrence of LRIs) were viable pathways through which stress might influence subsequent wheeze risk. To do this the mediators measured at each assessment were covaried out of the relationship of stress assessed at the same time as wheeze risk. If the mediators were playing a role, including them in the analyses would be expected to result in a decreased relative risk associated with caregiver stress. Finally, this analysis allowed us to clarify the direction of causality by testing whether stress reported prior to a report of wheeze would be more strongly associated with subsequent wheeze than stress reported after the wheeze episode. In other words, is stress a better predictor of wheeze than wheeze is of stress? This analysis actually predicts wheeze reports at the previous assessment from stress at the current one. We also address this issue by using linear regression analysis. In this case, we examine the occurrence of wheeze in the child as a predictor of caregiver stress in the next 2-mo follow-up interval.

RESULTS

A total of 496 children (263 male, 233 female, six sets of twins) and their caregivers were considered in these analyses. The primary caregivers were mothers in 473 (96.6%) of the 490 families. The mean maternal age was 32.8 ± 4.7 yr. The majority of caregivers were married, of relatively higher socioeconomic status, and > 30 yr of age.

Wheeze Experience

Of the 496 index children, 287 (57.9%) never wheezed, 116 (23.4%) had one reported episode of wheeze, 47 (9.5%), 28 (5.6%), and 18 (3.6%) had 2, 3, and 4 reports of wheeze up to 14 mo of age, respectively.

Associations Between the Covariates and Baseline Stress

For a covariate (whether a control variable or proposed mediator variable) to provide an alternative causal explanation for the relationship between stress and wheeze, it must be associated with stress. As apparent from Table 1, whites reported lower levels of stress than did Hispanics ($p < 0.03$) or Asians ($p < 0.004$) and marginally lower levels than did blacks ($p < 0.07$). Perceived stress decreased as household income increased. Divorced and single caretakers had higher stress than did those who were married. There was also a trend toward decreasing mean PSS scores with increasing education level. Caregiver's perceived stress was marginally associated with active maternal asthma. Unexpectedly, the highest stress scores were reported by caregivers with children in either the bottom or the top quartile of birth weight. Maternal age was not associated with stress in these data.

The relationship between stress at baseline and the pathways through which we hypothesized that psychologic stress might contribute to increased risk of wheeze is shown in Table 2. Caregiver's perceived stress was marginally associated with greater risk of lower respiratory illnesses ($p < 0.06$) but not with maternal smoking, breast-feeding, or presence of cockroach antigen.

TABLE 1. MEAN PERCEIVED STRESS SCORES BY STANDARD CONTROL VARIABLES AMONG CAREGIVER RESPONDENTS (n = 490)

Characteristics, n (%)	PSS4* (mean ± SD)	p Value†
Maternal asthma		
No asthma, 341 (69.6)	3.9 ± 2.7	
Active, 103 (21.0)	4.3 ± 2.7	
Inactive, 46 (9.4)	4.2 ± 3.2	p = 0.06
Paternal asthma		
No asthma, 368 (76.5)	4.0 ± 2.8	
Active, 77 (16.0)	4.0 ± 2.5	
Inactive, 36 (7.5)	3.9 ± 2.6	p = 0.16
Maternal age, yr		
18–29, 115 (23.7)	4.4 ± 3.0	
30–39, 347 (70.6)	3.9 ± 2.7	
40–50, 28 (5.7)	4.5 ± 2.7	p = 0.28
Marital status		
Married, 447 (91.2)	4.0 ± 2.7	
Single, 39 (8.0)	4.3 ± 3.6	
Divorced, 4 (0.8)	8.0 ± 0.8	p = 0.02
Maternal race		
White, 397 (80.8)	3.8 ± 2.6	
Black, 46 (9.6)	4.9 ± 3.6	
Hispanic, 26 (5.3)	4.9 ± 2.8	
Asian, 17 (3.5)	5.5 ± 2.1	
Other, 4 (0.8)	3.8 ± 2.1	p = 0.003
Household income		
> $50,000, 347 (71.4)	3.8 ± 2.6	
$30,000–$49,999, 85 (18.0)	4.7 ± 3.1	
< $30,000, 43 (8.9)	4.8 ± 2.8	
Unknown, 8 (1.7)	4.1 ± 2.7	p = 0.02
Education level		
Some HS/HS graduate, 35 (7.2)	5.3 ± 3.2	
Some post-HS, 66 (13.5)	4.3 ± 3.1	
College graduate, 158 (32.4)	3.9 ± 2.6	
Some postcollege, 229 (46.9)	3.9 ± 2.6	p = 0.09
Birth weight, kg		
3.79 to < 4.91, 125 (25.2)	4.3 ± 3.1	
3.46 to < 3.79, 119 (24.0)	3.8 ± 2.8	
3.19 to < 3.46, 127 (25.6)	3.7 ± 2.3	
1.84 to < 3.18, 125 (25.2)	4.4 ± 2.7	p = 0.03

* Baseline perceived stress scale (PSS4) score (appraisal of perceived stress in the preceding month) ascertained when the index child was 2 to 3 mo of age.
† For difference between multigroup comparisons.

TABLE 2. MEAN CAREGIVER PERCEIVED STRESS SCORES: RELATION TO POTENTIAL MEDIATING PATHWAY COVARIATES AMONG CAREGIVER RESPONDENTS (n = 490)

Characteristics, n (%)	PSS4* (mean ± SD)	p Value†
Maternal smoking		
No, 449 (91.6)	3.9 ± 2.7	
Yes, 41 (8.4)	4.6 ± 3.1	p = 0.3
Breast-feeding		
No, 158 (32.2)	4.4 ± 3.0	
Yes, 332 (67.8)	3.8 ± 2.6	p = 0.10
Lower respiratory illness‡		
No, 343 (69.2)	3.9 ± 2.7	
Yes, 153 (31.2)	4.2 ± 2.9	p = 0.06
Bla g 1 or 2 (family room, U/g)		
< 0.05, 355 (72.9)	4.0 ± 2.8	
⩾ 0.05, 106 (21.8)	4.1 ± 2.5	
No dust, 26 (5.3)	3.8 ± 3.2	p = 0.6

* Baseline PSS4 score (appraisal of perceived stress in the preceding month) ascertained when the index child was 2 to 3 mo of age.
† For difference between multi-group comparisons.
‡ Croup, bronchitis, bronchiolitis, or pneumonia.

Associations Between Multiple Wheeze and Covariates

The relationship between caregiver stress and the other covariates and multiple wheeze episodes among the index children is shown in Table 3. As reported elsewhere (19), there were also associations between some of the standard control variables and wheeze. Children were more likely to wheeze if they had mothers (but not fathers) with active asthma (RR = 1.7, 95%CI = 1.2 to 2.5), their parents had lower annual incomes (RR = 1.9, 95%CI = 1.1 to 3.2 for < $30,000; RR = 1.4, 95%CI = 0.9 to 2.2 for $30,000 to < $50,000; RR = 1.8, 95%CI = 0.8 to 4.2 if income unknown), and their parents were black (RR = 1.7, 95%CI = 1.1 to 2.7) or other race (RR = 1.6, 95%CI = 0.6 to 5.4). Higher birth weight predicted a decreased risk of repeated wheeze. The remaining control variables (maternal age, marital status, and education) were not associated with wheeze (data not shown).

On the other hand, all of the proposed mediators predicted multiple wheeze in the expected directions. Repeated wheeze was associated with reported lower respiratory illness (OR = 3.2, 95%CI = 2.3 to 4.5) and with the presence of higher levels of cockroach antigen in the home (OR = 1.6, CI = 1.1 to 2.4). Risk for wheeze also increased with maternal smoking, but the association was marginal (OR = 1.6, CI = 0.9 to 3.0).

Caregiver Stress at Baseline and Repeated Wheeze up to 14 Mo of Age: Between-Subject Analysis

In order to obtain a relative risk, we modeled the interquartile change for caregiver stress. In unadjusted analyses (Table 3), children whose caregiver reported higher levels of stress at 2 to 3 mo had an increased risk of subsequent repeated wheeze up to 14 mo of age compared with children of caregivers with lower perceived stress in this early period (RR = 1.6, 95%CI = 1.3 to 1.9). Consideration of caregiver-perceived stress as a categorical variable (tertiles) suggested a dose response relationship (12.9, 16.1, and 27.0% with multiple wheeze, respectively; RR = 2.1, 95%CI = 1.3 to 3.4 for highest tertile relative to the lowest tertile).

Notably, caregiver-perceived stress remained a significant predictor of wheeze (RR = 1.5, 95%CI = 1.2 to 1.9) even when

TABLE 3. BASELINE CAREGIVER STRESS AS A PREDICTOR OF TWO OR MORE REPORTS OF WHEEZE IN THE FIRST 14 MO OF LIFE OF THE INDEX CHILDREN (BETWEEN-SUBJECT ANALYSES) (n = 496)

			Univariate	Multivariate†	
Predictor Variable	Subjects (*n*)	Percent with ⩾ 2 Wheeze Reports	RR (95% CI)*	RR (95% CI) Model 1	RR (95% CI) Model 2
Perceived stress scale (PSS4) (Tertiles)					
Low, 1.1 ± 0.8 (mean ± SD)	171	12.9	–		
Intermediate, 4.1 ± 0.8 (mean ± SD)	172	16.1	1.4 (0.8–2.2)		
High, 7.4 ± 1.7 (mean ± SD)	145	27.0	2.1 (1.3–3.4)		
PSS4‡			1.6 (1.3–1.9)	1.5 (1.2–1.9)	1.4 (1.1–1.9)
Maternal asthma§					
No	390	16.4	–	–	–
Active	105	27.6	1.7 (1.2–2.5)	1.6 (1.1–2.4)	1.5 (0.96–2.2)
Maternal smoking§					
No	455	17.8	–		–
Yes	41	29.3	1.6 (0.9–3.0)		1.3 (0.7–2.5)
Birth weight (IQ change, increase)‖			0.8 (0.6–0.9)	0.8 (0.7–1.01)	0.8 (0.7–1.03)
Breast-feeding					
No	156	22.5	–		–
Yes	332	16.9	0.8 (0.5–1.09)		0.9 (0.6–1.4)
Lower respiratory illness (croup, bronchitis or pneumonia)					
No	343	25.6	–		–
Yes	153	53.8	3.2 (2.3–4.5)		2.3 (1.6–2.5)
Annual household income					
>$50,000	351	16.0	–	–	–
$30,000 to < $50,000	88	22.7	1.4 (0.9–2.2)	1.2 (0.8–2.0)	1.2 (0.7–2.0)
< $30,000	43	30.2	1.9 (1.1–3.2)	1.6 (0.9–2.9)	1.3 (0.6–2.6)
Unknown	9	22.2	1.8 (0.8–4.2)	2.0 (0.8–4.6)	1.7 (0.6–4.4)
Race/ethnicity					
White	375	17.3	–	–	–
Black	57	29.8	1.7 (1.1–2.7)	1.0 (0.5–1.6)	1.2 (0.6–2.2)
Hispanic	29	20.7	1.2 (0.6–2.5)	0.9 (0.4–2.0)	0.9 (0.4–2.0)
Asian	28	10.7	0.6 (0.2–1.8)	0.5 (0.2–1.4)	0.6 (0.2–2.1)
Other	7	28.6	1.6 (0.6–5.4)	1.4 (0.4–4.6)	1.7 (0.5–5.7)
Bla g 1 or 2, family room, U/g					
< 0.05	359	16.1	–		–
⩾ 0.05	108	27.0	1.6 (1.1–2.4)		1.5 (0.9–2.4)

* Relative risk and 95% confidence intervals.
† Models 1 and 2 show the relative risk for caregiver-perceived stress when adjusting for all standard control variables and potential mediators, respectively.
‡ Estimated for an interquartile increase (4 units) in the baseline PSS4 score ascertained when the index child was 2 to 3 mo of age.
§ No = reference category unless otherwise stated.
‖ Estimated for an interquartile increase (0.61 kg) in birth weight.

adjusting for the standard control variables (Table 3, Model 1). This indicates that caregiver stress was not simply a marker of these other factors associated with wheeze. Moreover, the size of the association between caregiver-perceived stress and wheeze was only slightly reduced and remained significant after further adjusting for potential mediators including: maternal smoking, breast-feeding, LRIs, and cockroach antigen exposure (RR = 1.4, 95%CI = 1.1 to 1.9) (Table 3, Model 2).

Short-Term Effects of Caregiver Stress on Wheeze: Within-Subject Analysis

In the cross-sectional analysis we found that increased caregiver stress was associated with an increased risk of the child wheezing when both were measured during the same assessment periods (i.e., the same 2-mo interval) (RR = 1.28, 95%CI = 1.1 to 1.6) (Table 4). We found similar results in the prospective analysis. Caregiver stress (over last month) was associated with increased risk of wheezing during the subsequent 2-mo period (RR = 1.33, 95%CI = 1.1 to 1.6). Finally, to assess whether wheeze could be causing caretaker stress, we asked whether wheeze at the previous assessment (2 mo earlier) predicted current caretaker-perceived stress. This relationship was not significant using either the logistic model (RR = 1.1, 95%CI = 0.9 to 1.3) or linear regression analysis (p = 0.8).

Earlier, we proposed that the short-term influences of caretaker stress on the child's risk of wheezing over the following 2-mo (prospective effect), might be attributable to stress-elicited changes in maternal smoking, breast-feeding, or lower respiratory infections (all measured at each 2-mo assessment as well). However, adding these three variables to the prospective repeated measures model did not alter the association between stress and wheeze (RR = 1.3, 95%CI = 1.1 to 1.6) (Table 4).

DISCUSSION

These prospective data suggest that caregiver stress in early life may influence the risk of wheeze during infancy. Greater levels of caregiver-perceived stress at 2 to 3 mo of age was associated with subsequent risk of recurrent wheeze (two or more) episodes in these children. Higher levels of caregiver-perceived stress remained an independent predictor of early childhood wheeze in these analyses even when controlling for standard control variables that may have been related to stress (i.e., birth weight, parental asthma, race/ethnicity, and socioeconomic status) indicating that caregiver stress was not simply a marker of these other factors. Moreover, higher levels of caregiver stress predicted an increased risk of wheeze in the index children even after adjusting for potential mediators (i.e., maternal smoking, LRI, allergen levels, and breast-feeding), suggesting that the relation between stress and early childhood wheeze may not be primarily mediated through these caregiver behaviors or susceptibility to lower respiratory

TABLE 4. RELATIONSHIP OF SHORT-TERM TEMPORAL CHANGES IN CAREGIVER STRESS TO WHEEZE: REPEATED MEASURES ANALYSIS

	Univariate Relative Risk	Multivariate Relative Risk
Predictor Variable	RR (95% CI)*	RR (95% CI)*
Perceived stress scale (PSS4) 2-mo lag†	1.3 (1.1–1.6)	1.3 (1.1–1.6)
Maternal smoking‡		
No	—	—
Yes	1.6 (0.9–3.0)	1.3 (0.7–2.5)
Breast-feeding (≥ half time)§		
No	—	—
Yes	0.8 (0.6– > 1.0)	0.7 (0.6–1.03)
Lower respiratory illness (croup, bronchitis, bronchiolitis, or pneumonia)‖		
No	—	—
Yes	11.9 (8.9–15.8)	12.6 (9.4–17.0)

* 95% confidence intervals.
† Calculated for an interquartile increase in the PSS4 score ascertained at the 2-mo follow-up interval preceding the interval in which wheeze is reported.
‡ Caregiver smoking status (yes/no) reported at each 2-mo follow-up interval in which wheeze was ascertained.
§ Infant feeding practices (≥ half time) reported at each 2-mo follow-up interval in which wheeze was ascertained.
‖ Occurrence of lower respiratory illness reported at each 2-mo follow-up interval in which wheeze was ascertained.

infections. A plausible alternative hypothesis may be that there is a more direct effect on airway inflammation through influences on the immune system, which may promote airway obstruction and wheeze (5).

Perhaps the strongest evidence from the current literature would suggest that psychologic stress may influence the pathophysiology of wheeze during infancy by increasing the risk of respiratory infections (5). The hypothesis that stress may suppress host resistence to infectious diseases is supported by prospective evidence in adults demonstrating associations between perceived stress and susceptibility to influenza A (24) and the common cold (25). Studies have also demonstrated increased susceptibility to viral respiratory infections in children of parents experiencing stress (8, 9). Early life viral lower respiratory infections may be associated with an increased risk of developing persistent wheeze and asthma (26); however, this too remains an area of considerable debate. Recent evidence supports a more complex pathogenetic role for viral infections—in some cases, viral infections may be protective against the development of asthma (27). Newer evidence suggests that the effects of infection may depend on which pathogen infects the host early in immune development. In this context, it is somewhat surprising that we did not find that lower respiratory illnesses did not more fully account for the association between stress and wheeze. A noted limitation of this study is the absence of viral surveillance data to more objectively document both infection and the pathogens involved, which would have been difficult to obtain in the current study design. It is also possible that the relationship between stress and repeated wheeze was mediated through susceptibility to upper respiratory viral infections that triggered symptoms of wheeze in these children.

Thus, while these findings do not rule out that the underlying mechanism operating between stress and wheeze may be, at least in part, predisposition to viral respiratory infections, they do suggest that additional mechanisms need to be considered. Although wheezing disorders of early childhood may be, by and large, precipitated by acute viral lower respiratory infections (28), many other proposed genetic, anatomic, physiologic, and environmental causes may predispose to airway obstruction and wheezing in infancy (29). These include early life environmental exposures that have the potential to influence immune mechanisms and lead to bronchial inflammation through nonallergenic and allergenic mechanisms (30, 31).

Environmental factors potentially affecting maturation of the immune system during childhood may set the stage for the inflammatory processes and altered reactivity to stimuli that are characteristic of airway obstruction and recurrent wheeze (32). It has even been speculated that, during early childhood, stress may trigger hormones, which may influence polarization toward a T-cell-immune response potentiating airway inflammation in genetically predisposed individuals (i.e., T helper (Th)-2 cell predominance), perhaps through a direct influence of stress hormones on the production of cytokines that are thought to modulate the direction of differentiation. Existing evidence suggesting that (*1*) polarization of the immune system into an atopic phenotype likely occurs during early childhood (33), (*2*) immune response regulation in early life may be influenced by stress (34), and (*3*) early caregiver stress may impact infant stress response (35), support the biologic plausibility of the hypothesis that family stress can lead to increased risk of wheeze in infants through alteration in their immune development.

Evidence suggests that for most children who become allergic or asthmatic, the polarization of their immune system into an atopic phenotype likely begins before birth (36–38). Studies suggest that characteristics of the *in utero* environment influence fetal immunologic development along with genetic susceptibility. Gestational exposures to maternal stress have been shown to alter the development of humoral immunocompetence in offspring as well as their hormonal and immunologic responses to postnatal stress (39–41). Recent evidence in rhesus monkeys finds that stress experienced during pregnancy impacts the infant monkeys response to antigens at birth (42). Genetic factors *in utero* and postnatal environmental factors, and the timing of exposures to these factors, are likely to play a role in the differentiation of the immune response. Maternal stress may be an important factor potentially affecting maturation of the immune system during childhood, setting the stage for the inflammatory processes and altered reactivity to stimuli that are characteristic of airway obstruction and recurrent wheeze.

Evolving research underscores the important link between stress and the health of children. Moreover, the speculation that caregiver stress may impact the health of their children is supported by several lines of evidence. When addressing early childhood risks, the family is viewed as the most important social context influencing the health and development of children with family functioning and interactions with a primary caregiver being important sources of stress (43). Growing evidence links caregiver stress to the stress response in their off-

spring. Indeed, both animal and human studies support the idea that caregiver stress may influence the stress response of the child and modify infant neuroendocrine function during early development (44–47). For example, the stress response in infancy is influenced by family factors (families that show high stress also have children with high cortisol response) (48). In humans, maturation of an infant's neuroendocrine stress response begins as early as 2 to 3 mo of age and remains fairly consistent, at least over the 4- to 18-mo period (49). Stress-induced neuroendocrine or immunologic changes, in turn, may affect airway inflammation and reactivity through immunologic and neural pathways, which may lead to wheeze.

Prenatal maternal stress may also influence childhood wheeze through its documented relationship to low birth weight (50). It has been hypothesized that children with anatomically smaller airways may be intrinsically at greater risk for wheezing lower respiratory tract illnesses in early life. It is also possible that life stress may influence health beliefs and behaviors (i.e., cigarette smoking, breast-feeding practices), which may subsequently impact wheeze risk. Because we did not measure maternal stress during pregnancy, we could not examine associations between maternal stress and maternal smoking during pregnancy or the impact on birth weight. However, we could examine the prospective relationship of caregiver stress levels, which may potentially alter postnatal caregiver behaviors, including smoking and breast-feeding, on subsequent wheeze in their children during early infancy. In our repeated-measures analysis, adjusting for caregiver behaviors, including smoking behaviors and breast-feeding practices, in each follow-up interval did not explain the increased risk of wheeze associated with higher stress levels in the home. However, it may be that allowing for only a 2-mo lag in these analyses was not sufficient (i.e., in order to see the impact of a caregiver behavior change, it may need to occur and be sustained for longer than a 2-mo period).

In contrast to our finding that parental stress predicted childhood wheeze in a cohort of 490 families, a Swedish study of 97 families suggested that wheezing illnesses in infants precipitated dysfunctional family interaction (18). A prospective study of 150 genetically predisposed children in which 14 children developed asthma found that parental difficulties measured at 3 wk of age predicted an increased risk of asthma onset by 3 yr of age after controlling for frequent illness and 6-mo IgE level (17). However, these investigators did not concurrently account for factors that are potentially related to both caregiver stress and risk of wheeze in early childhood (i.e., cigarette smoking, breast-feeding, and lower socioeconomic status). Our data convincingly support a prospective relationship between caregiver stress and wheeze in these infants that persisted when simultaneously accounting for known potential confounders and mediators. Although the outcome in this study was parent-report of wheeze in their children, questionnaire report of wheeze has been validated through a number of studies correlating the relationship of persistent wheeze to subsequent diagnosis of asthma, lung function, and airway hyperresponsiveness (51).

The magnitude of the increased risk of wheeze in these infants associated with higher levels of caregiver stress was relatively small in our study which might raise the question of whether the relationship would be clinically significant. Although studies of stress and illness have consistently found significant relationships, these have been universally modest in magnitude (52). Although in part genetically determined, differences in social supports, developed coping skills, attitudes, beliefs, and personality characteristics may render some persons more susceptible to stress-induced illness (53). It is likely that many factors not measured in the present study may have influenced the stress experience across the individual families and index children. For example, Priel and colleagues (54) have suggested that an infant's temperament may modulate maternal-child interactions and the infant's physiologic stress response, which may in turn influence wheeze in early infancy. Specific characteristics of the stressors may also be important to understand (55). A better understanding of a possible role for stress in the inception of wheeze may emerge from continued study of both the types of stressors individuals experience and how an individual's affective response, as well as his or her biologic and behavioral reactivity to stress, modify these relationships (i.e., identification of susceptible subgroups).

Furthermore, although the observed effect may be modest at the individual level, there still may be significant implications at the population level. Early childhood wheezing has become one of the leading reasons for consultation in clinical pediatric practice associated with significant healthcare expenditures (29). Our contemporary understanding of wheezing illnesses in infancy is that of a heterogeneous disorder influenced by complex genetic and environmental interactions that remain poorly understood. This coupled with our current understanding of the stress response that involves complex psychoneuroimmunologic processes may in part explain why the magnitude of main effects of caregiver stress on childhood wheeze may be modest at the individual level in epidemiologic studies. However, stress may contribute significantly to the population burden of preventable childhood respiratory illness given that it is such a pervasive exposure.

In conclusion, greater reported caregiver stress, examined prospectively, may increase risk of multiple wheeze episodes during early childhood. The role of caregiver stress in early childhood wheeze was independent of caregiver smoking and breast-feeding behaviors, as well as allergen exposure, birth weight, and lower respiratory infections. These findings suggest other mechanisms may be operating between stress and wheeze in early childhood. Continued follow-up of this cohort will also determine whether early-life experience of greater caregiver stress predicts the persistence of wheeze and the development of later doctor-diagnosed childhood asthma. Although the relationship of wheeze in early childhood to subsequent asthma has not been completely elucidated, repeated or persistent wheeze is the chief symptom leading to doctor-diagnosed asthma in early childhood (56). Also, the knowledge that the phenotypic expression of wheezing respiratory illnesses in early childhood are so varied (57) makes the study of the underlying mechanisms linking stress to wheeze more challenging.

These data buttress a growing body of evidence that suggests that family stress and the health of children are linked. These findings have broad implications regarding the future development of strategies toward increasing our understanding of the determinants of childhood respiratory morbidity that will facilitate the design of effective intervention strategies. Future research must focus on elucidation of the possible mechanisms linking stress to wheezing respiratory illnesses of childhood. Further epidemiologic investigations are needed to determine whether early-life stress relates to early atopic airway sensitization, transient wheezy syndromes of early childhood mediated through nonallergen pathways (e.g., neurogenic, increased susceptibility to viral respiratory illnesses), or both. For example, investigations on the relationship of early-life stress to lymphocyte proliferation, T-cell cytokine production patterns, and other markers of airway inflammation are likely to be informative. We need to explore how early-life stress predicts the development of atopy and sensitization to

indoor allergens. Future interventions might also include clinical approaches and public policies that are designed to strengthen families and reduce parenting stress (58).

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