Chronic caregiver stress and IgE expression, allergen-induced proliferation, and cytokine profiles in a birth cohort predisposed to atopy

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Background: Psychologic stress modifies immune function and cytokine production.

Objective: We examined relationships between caregiver stress on the following markers of early childhood immune response: (1) IgE expression (n = 215); (2) mitogen-induced and allergen-specific (Dermatophagoides farinae [Der f 1] and cockroach [Bl a 2]) proliferative response (n = 114); and (3) subsequent cytokine expression (INF-γ, TNF-α, IL-10, and IL-13) in a prospective birth cohort predisposed to atopy.

Methods: Caregiver stress was measured at 2-month intervals for the first 2 years of life and yearly thereafter by using the Perceived Stress Scale. A subsequent blood sample obtained from the children (median age, 2.1 years; range, 18-32 months) was analyzed for total serum IgE level and allergen-induced proliferation quantified as the stimulation index (SI; mean thymidine incorporation of the stimulated sample divided by that of the unstimulated sample). The relationship between stress and the proliferative response (SI >3 vs SI ≤3), and total IgE level (≤100 IU/mL vs >100 IU/mL) was examined by using logistic regression. The relationship between cytokine levels and stress was analyzed by using linear regression.

Results: In adjusted analyses higher caregiver stress in the first 6 months after birth was associated with a Der f 1 SI of greater than 3 (odds ratio [OR], 1.5; 95% CI, 1.0-2.3) and nominally associated with a Bla g 2 SI of greater than 3 (OR, 1.13; 95% CI, 0.7-1.8). Higher stress between ages 6 and 18 months was associated with a Der f 1 SI of greater than 3 (odds ratio [OR], 1.5; 95% CI, 1.0-2.3) and nominally associated with a Bla g 2 SI of greater than 3 (OR, 1.13; 95% CI, 0.7-1.8). Higher stress among ages 6 and 18 months was associated with a high total IgE level (OR, 2.03; 95% CI, 1.1-3.6). Higher stress was significantly associated with increased production of TNF-α, with a suggested trend between higher stress and reduced INF-γ production.

Conclusion: Increased stress in early childhood was associated with an atopic immune profile in these children predisposed to atopy-asthma. (J Allergy Clin Immunol 2004;113:1051-7.)

Key words: Caregiver stress, IgE, lymphocyte proliferation, cytokines, birth cohort

The majority of asthma involves allergen-mediated inflammation, with T-lymphocyte activation central to the allergic asthmatic response. The most common paradigm divides T-helper cells into profiles of differentiated cell function having different patterns of cytokine release on activation (eg, TH1 and TH2). TH1 cells tend to express IL-2 and IFN-γ, and TH2 cells tend to express IL-4, IL-5, and IL-13. Allergy and asthma might also be influenced by cytokines produced through pathways or inflammatory processes not directly related to the TH1/TH2 dichotomy. For example, some proteins are secreted both by TH1 and TH2 cells (eg, TNF-α). Studies suggest that TNF-α, produced by both lymphocytes and macrophages, is involved in the atopic response. Activation of TH2 lymphocytes underlying allergen sensitization is associated with increased IgE production. Seroepidemiologic studies have shown an association between increased total IgE levels and asthma that increases in magnitude and significance over the first 4 to 6 years of life.

Environmental exposures might influence early immune function and cytokine production. Polarization of the immune system into an atopic phenotype likely occurs during early childhood and even before birth. For example, studies suggest that maternal exposure to inhaled allergens can prime fetal T cells toward an atopic phenotype. Our laboratory has demonstrated that allergen exposure at 3 months of age predicts allergen-specific lymphocyte proliferative responses at age 2 years.

Exposure to other environmental factors at critical developmental periods that induce functional changes in neuroendocrine and immune processes might also polarize the immune system toward an atopic phenotype. Dysregulation of homeostatic neuroimmunologic mechanisms can occur in the face of chronic stress that affects cytokine expression, allergic inflammation, and asthma expression. The family is 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.\textsuperscript{15} Growing evidence links caregiver stress to the child’s stress response. Maternal stress influences the hormonal stress response in early childhood and modifies infant neuroendocrine function during development, even beginning prenatally.\textsuperscript{16,17} Investigators have demonstrated an increased cortisol response in children from families that show high stress.\textsuperscript{18}

We examined the influence of caregiver stress beginning in the first 2 to 3 months of the index child’s life on the lymphocyte proliferative response, cytokine production, and total IgE expression in a population predisposed to atopy-asthma. We hypothesized that higher caregiver stress would be associated with an enhanced inflammatory response, including an increased allergen-specific proliferative response and higher levels of IgE expression.

\section*{METHODS}

Participants in the Home Allergen and Asthma Study include infants and their 499 families with a history of asthma or allergy recruited within 48 hours of delivery between September 1994 and July 1996, as previously reported.\textsuperscript{19} The Brigham and Women’s Hospital Human Studies Committee approved the study, and written parental informed consent was obtained.

At the home visit, when the index child was 2 to 3 months old, data were collected on environmental exposures, including dust samples analyzed for Dermatophagoides farinae (Der f 1) and cockroach (Bl a 1 or 2), as previously described.\textsuperscript{19} Quantification of allergen was performed by means of 2-site monoclonal and polyclonal antibody immunoassays.\textsuperscript{20} Der f 1 concentrations were reported as micrograms of allergen per gram of dust, whereas Bl a 1 or 2 concentrations were reported as units per gram of dust. A home maximum was determined on the basis of the highest allergen level obtained from sampling in the index home. Data on sociodemographic factors were also obtained through personal interview questionnaires.

\section*{Standard control variables}

The child was classified as white if both parents were white, black if either parent was black, Hispanic if no parent was black but at least one parent was Hispanic, and Asian if at least one parent was Asian but no parent was black or Hispanic. Annual household income was stratified as unknown, $15,000 or less, $15,000 to $29,000, $30,000 to $49,000, and $50,000 or greater. Analyses were controlled for child’s age and sex and maternal active asthma, as previously defined.\textsuperscript{19}

\textbf{Psychologic stress.} Data on caregiver stress were obtained at the initial home visit. Subsequently, bimonthly telephone questionnaires ascertained changes in caregiver stress for the first 2 years of life and yearly thereafter. The stress questionnaire was administered to the index child’s primary caregiver at each follow-up contact (i.e., the same caregiver responded at each interview). Caregiver stress was ascertained by using the 4-item Perceived Stress Scale (PSS),\textsuperscript{21} a measure of the degree to which respondents believed their lives were unpredictable, uncontrollable, and overwhelming in the preceding 1 month (reliability, 0.85).\textsuperscript{22} The PSS was developed on the basis of Lazarus’s concept of stress appraisal,\textsuperscript{23} which is central to current stress theory. When confronting demands, individuals appraise whether the event is threatening or potentially overwhelming to their existing coping resources.\textsuperscript{24} This perception is presumed to result in negative emotional states (eg, anxiety and depression), which in turn might be accompanied by neuroendocrine and immunologic changes that affect health outcomes. Each item is scored on a 5-point frequency scale, ranging from “never” (0) to “very often,” and scores were obtained by summing the 4 items (maximum, 16). The PSS has been validated in a representative population for measuring stress across age groups, race, sex, and socioeconomic status\textsuperscript{25} and reflects changes in stress over time.\textsuperscript{26} Studies have shown the prospective relationship between the PSS and multiple behaviors, health outcomes, and cytokine expression.\textsuperscript{27-29} The PSS predicts outcomes independently of psychologic symptoms, showing good discriminant validity.\textsuperscript{22}

\textbf{Total serum IgE levels.} Serum samples were analyzed for total IgE antibodies (n = 215), as previously described.\textsuperscript{30} Results are reported in international units of IgE. We defined a high total IgE value as 100 IU/mL or greater, a level that has been associated with sensitization and subsequent childhood asthma risk.\textsuperscript{31}

\textbf{Proliferative response.} A subsample of 114 children was selected for peripheral blood analysis on the basis of home allergen levels\textsuperscript{19} and complete data on covariates. Blood was obtained for lymphocyte proliferation when the children presented for state-mandated lead testing at a median age of 2.1 years (range, 18-32 months). At the blood draw, parents were asked to report whether the child had an upper respiratory infection within the previous week.

PBMCs isolated from heparinized blood\textsuperscript{32} were immediately processed and not cryopreserved. Briefly, cells were incubated for 72 hours with media alone, media with PHA (10 µg/mL), or media with Der f 1 (30 µg/mL) and Bl a 2 (30 µg/mL). After 72 hours, tritiated thymidine uptake was determined by means of β-counting. Proliferation was quantified by using the stimulation index (SI), which was defined as the mean thymidine incorporation of the stimulated sample divided by that of the unstimulated sample. The lymphocyte proliferative response was considered as a binary variable indexed as a high (SI >3) or low (SI ≤3) response.

\textbf{Allergen exposure.} Allergen exposure levels were categorized as binary indices for which associations between exposure and either sensitization or development of allergy-related wheeze has been determined.\textsuperscript{13} Der f 1 levels were categorized as follows: high (≥10 µg/g dust), intermediate (2 to <10 µg/g dust), low (<2 µg/g dust), and no dust. Bl a 1 or 2 levels were categorized as high (≥2 U/g dust), intermediate (0.05 to <2 U/g), and no dust. Values of greater than the upper levels of detection for the assay were considered high, and those that were less than the levels of detection were indexed as low.

\textbf{Cytokines.} Supernatants from allergen- and mitogen-stimulated samples were harvested at 24 and 60 hours. On the basis of optimization of the detection of cytokine levels, IL-10 and TNF-α secretion were measured in the 24-hour sample, and IFN-γ and IL-13 secretion were measured in the 60-hour sample (Endogen, Cambridge, Mass).\textsuperscript{12} Cytokines were analyzed by means of ELISA according to the manufacturer’s protocol. Detection limits were typically 1.25 to 2.5 pg/mL.

\section*{Analyses}

Descriptive summaries, including means and proportions, describe the characteristics of the sample stratified by high or low IgE levels and SIs. Differences across groups were examined by using the Fisher exact test and the \(t\) test of equality of the means.
These data have a nonstandard structure in that the caregiver stress covariate is longitudinal for each family (repeated and measured at irregular time points approximately every 2 months), whereas the immune responses (IgE, SI, and cytokines) are measured at a single time point for each child. We were interested in the association between different profiles of caregiver stress over time and the subsequent immune response measures. We analyze these associations in 2 ways, yielding similar conclusions.

First, we treat the stress measurements as responses, stratify the children into 2 groups on the basis of IgE level (or Der f 1 SI or Bla g 2 SI levels in separate analyses), and use covariate adjusted nonparametric smoothing to estimate 2 curves of average stress over the child’s age for the dichotomous outcomes. Smoothing was done with the linear mixed model formulation of penalized splines, with family-specific random intercepts included in the model to allow for within-family correlation.

In this approach differences between the curves at a specific age indicate an association between average stress exposure and different immune responses at that specific age.

The second approach treated the dichotomized immune outcome as the response and used a summary statistic derived from each family’s stress curve as a covariate. The time interval for the stress summary statistics was suggested from the nonoverlapping regions in the spline smooth average stress curves for total IgE and the SI. We tested whether the index children from those family’s having mean stress levels over specific developmental intervals (on the basis of the child’s age) of greater than the population median stress level over the same age interval expressed higher levels of IgE or demonstrated a higher lymphocyte proliferative response (SI >3). The analyses with dichotomized IgE, Der f 1 SI, and Bla g 2 SI as the outcomes were done by using multiple logistic regressions.

Multiple linear regression was used to examine the relationship between caregiver stress and the cytokine outcomes. Logarithmic transformation of the cytokine outcomes was used to symmetrize the residuals.

RESULTS

Table 1 shows the distribution of sociodemographic factors, maternal asthma, and whether the child had a cold within a week of the blood draw relative to total IgE levels and allergen-specific SIs. Fig 1 contains estimates of the stress curves for the families stratified by IgE level (IgE > 100 IU/mL vs IgE ≤ 100 IU/mL) or Der f 1 SI (SI > 3 vs SI ≤ 3). In these data IgE level (mean ± SD, 40.2 ± 95.2 IU/mL; range, 2-1247 IU/mL) and Der f 1 SI (5.5 ± 6.2; range, 0.4-34.0) showed considerable variability. Total IgE and Der f 1 SI levels were dichotomized into distinct subsets to limit the influence of high leverage

<table>
<thead>
<tr>
<th>Predictor</th>
<th>IgE =100 IU/mL, N (%)</th>
<th>IgE &gt;100 IU/mL, N (%)</th>
<th>Der f 1 SI ≤3, N (%)</th>
<th>Der f 1 SI &gt;3, N (%)</th>
<th>Bla g 1 or 2 SI ≤3, N (%)</th>
<th>Bla g 1 or 2 SI &gt;3, N (%)</th>
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<td>Sex</td>
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<td></td>
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<tr>
<td>Male</td>
<td>113 (57.4)</td>
<td>12 (67)</td>
<td>33 (66)</td>
<td>37 (58)</td>
<td>20 (66.7)</td>
<td>50 (60.2)</td>
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<td>Female</td>
<td>84 (42.6)</td>
<td>6 (33)</td>
<td>17 (34)</td>
<td>27 (42)</td>
<td>10 (33.3)</td>
<td>33 (39.8)</td>
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<td>White</td>
<td>149 (75.6)</td>
<td>14 (78)</td>
<td>34 (68)</td>
<td>50 (78.1)</td>
<td>24 (80)</td>
<td>59 (71.1)</td>
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<td>Black</td>
<td>22 (11.2)</td>
<td>3 (17)</td>
<td>4 (8)</td>
<td>7 (10.9)</td>
<td>3 (10)</td>
<td>8 (9.6)</td>
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<td>Other</td>
<td>26 (13.2)</td>
<td>1 (5)</td>
<td>12 (24)</td>
<td>7 (10.9)</td>
<td>3 (10)</td>
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<td>10 (56)</td>
<td>34 (68)</td>
<td>45 (71.4)</td>
<td>22 (73.3)</td>
<td>56 (68.3)</td>
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<td>&lt;$30,000</td>
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<td>6 (12)</td>
<td>9 (15.9)</td>
<td>4 (13.3)</td>
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<td>Maternal asthma</td>
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<td>No</td>
<td>156 (79.2)</td>
<td>13 (72)</td>
<td>37 (74)</td>
<td>53 (82.8)</td>
<td>23 (76.7)</td>
<td>66 (79.5)</td>
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<td>Yes</td>
<td>41 (20.8)</td>
<td>5 (28)</td>
<td>13 (26)</td>
<td>11 (17.2)</td>
<td>7 (23.3)</td>
<td>17 (20.5)</td>
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<td>Cold status</td>
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<td>No</td>
<td>148 (75.9)</td>
<td>12 (66.7)</td>
<td>32 (67)</td>
<td>53 (84.0)</td>
<td>17 (59)</td>
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<td>Yes</td>
<td>47 (24.1)</td>
<td>6 (33.3)</td>
<td>16 (33)</td>
<td>10 (16.0)</td>
<td>12 (41)</td>
<td>14 (17)</td>
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<td>Age at blood draw, mean ± SE</td>
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<td>Household</td>
<td>2.40 ± 0.04</td>
<td>2.22 ± 0.11</td>
<td>2.28 ± 0.07</td>
<td>2.51 ± 0.07</td>
<td>2.47 ± 0.10</td>
<td>2.39 ± 0.06</td>
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<td>Der f 1 SI</td>
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<tr>
<td>Low (&lt; 2 µg/g dust)</td>
<td>67 (34)</td>
<td>7 (38.9)</td>
<td>17 (34)</td>
<td>26 (40.6)</td>
<td>16 (53.3)</td>
<td>27 (32.5)</td>
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<td>Medium (2-10 µg/g dust)</td>
<td>48 (24.1)</td>
<td>5 (27.8)</td>
<td>15 (30)</td>
<td>10 (15.6)</td>
<td>12 (41)</td>
<td>14 (17)</td>
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<tr>
<td>High (10 µg/g dust)</td>
<td>82 (41.6)</td>
<td>6 (33.3)</td>
<td>18 (36)</td>
<td>28 (43.8)</td>
<td></td>
<td></td>
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<tr>
<td>Bla g 1 or 2 SI</td>
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<tr>
<td>Low (&lt; 0.05 U/g)</td>
<td>76 (38.6)</td>
<td>6 (33.3)</td>
<td></td>
<td></td>
<td>16 (53.3)</td>
<td>27 (32.5)</td>
</tr>
<tr>
<td>Medium (0.05 to &lt;2 U/g)</td>
<td>96 (48.7)</td>
<td>9 (50)</td>
<td></td>
<td></td>
<td>12 (40)</td>
<td>42 (50.6)</td>
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<tr>
<td>High (2 U/g)</td>
<td>25 (12.7)</td>
<td>3 (16.7)</td>
<td></td>
<td></td>
<td>2 (6.7)</td>
<td>14 (16.9)</td>
</tr>
</tbody>
</table>

*Dermatophagoides farinae (Der f 1) dust mite antigen.
†Cockroach (Bla g 1 or Bla g 2).
‡Fisher exact test of homogeneity of proportions, P < .05.
§t Test of equality of the means, P < .01.
and outlying observations. From shortly after birth (ie, age 2–3 months) onward, the mean of repeated measures of caregiver stress was persistently higher among children who had a higher Der f 1 SI and among those who expressed higher levels of IgE. Findings were similar for the lymphocyte proliferative response to Bla g 2, with higher-level stress related to a high SI, although the curves overlapped and are not shown.

In the second approach using logistic regression analyses to estimate the relationship between caregiver PSS scores and the probability that the child would have a higher lymphocyte proliferative response to antigen at age 2 to 3 years (SI >3 vs SI ≤3), higher caregiver stress averaged over time was associated with the higher-level response to Der f 1. In regression analyses predicting total serum IgE levels (IgE >100 IU/mL vs IgE ≤100 IU/mL), higher mean caregiver stress averaged over time was also associated with higher IgE levels. In the multiple logistic regression analyses predicting IgE, increased stress between ages of 6 and 18 months was associated with increased caregiver stress (mean stress of greater than the study population median averaged over the first 2 years of the child’s life) for allergen-specific and mitogen-induced lymphocyte proliferation. In addition, higher stress predicted lower levels of IFN-γ in the mitogen-induced response. Associations between higher stress and lower

2.29) and nominally associated with a Bla g 2 SI of greater than 3 (OR, 1.13; 95% CI, 0.72–1.78). These analyses are adjusted for age, maternal asthma, sex, cold status, household allergen exposure at age 2 to 3 months, and race-ethnicity.

Finally, we examined the relationship between caregiver stress and cytokine production. Fig 2 shows the distribution of IFN-γ and TNF-α expression in supernatants from allergen-stimulated (dust mite [Der f 1] and cockroach [Bla g]) and mitogen-stimulated (PHA) PBMCs stratified by caregiver stress levels. Stress was categorized as greater than (High) or less than (Low) the study population median averaged over the first 2 years of the child’s life. The upper and lower bounds on the boxes represent the first and third quartiles (25th and 75th percentile of the sample, respectively), the line within the box denotes the median, the whiskers represent values within 1.5 × quartile 3 (top) or quartile 1 (bottom), and the dots show values outlying this range. The y-axis represents actual values that are log spaced.
IFN-γ levels were suggested for allergen-induced responses, but these did not reach statistical significance. Models were adjusted for race, age at blood draw, sex, household allergen exposure, maternal asthma, and whether the child had a cold in the week preceding the blood draw.

**DISCUSSION**

These data demonstrate that higher early-life chronic caregiver stress was associated with increased total IgE expression and an enhanced allergen-specific proliferative response at age 2 to 3 years. Moreover, higher-level stress was associated with increased TNF-α levels by stimulated PBMCs and reduced IFN-γ levels. Exposure to stress in early development might result in functional changes in immune reactivity in susceptible children, potentiating the inflammatory response.

Serial measurement of IgE is an indicator of whether an atopic phenotype is developing in a child. Increased IgE levels might occur during the period of T-cell maturation, when an individual’s phenotype is being determined not only by exposure to allergens but also by a variety of environmental influences. These data suggest that early life stress might be an additional factor influencing this process, given the significant relationship between higher mean caregiver stress and high IgE levels (>100 IU/mL). Given the small number of subjects in the high-IgE group, reproduction of these findings in other studies with larger sample size would increase certainty about their generalizability.

These results corroborate others, suggesting that chronic stress might influence cytokine production, although data in early childhood are sparse. The association between stress and decreased ability of peripheral blood lymphocytes to synthesize IFN-γ when stimulated *in vitro* has been reported. The suggestion that IFN-γ production is reduced in the context of higher stress is interesting in light of prospective seroepidemiologic evidence demonstrating that decreased IFN-γ and IL-2 production by stimulated lymphocytes in infancy predicts later development of atopy. IFN-γ levels tended to be lower in children whose caregivers reported more stress for both mitogen-induced and allergen-specific stimulation. Other analyses of these data have demonstrated decreased expression of IFN-γ for both Der f 1 and Bla g 2 stimulation among children with both atopic disease (ie, eczema) and wheeze when compared with those with no atopic disease and no history of wheeze.

Sample size did not allow further stratification by these disease categories to test whether the relationship between increased caregiver stress and reduced IFN-γ production might also be stronger among children expressing atopy.

Catecholamines, glucocorticoids, and proinflammatory cytokines (including TNF-α) are considered the principal messengers between the nervous system and immune system in the stress response. Increased TNF-α levels can activate the HPA axis and have been associated with increased cortisol levels. Cortisol has been shown to shift T cells toward a Th2 phenotype. Others have demonstrated a relationship between stressor-induced cortisol and increased IgE production. In chronic stress more persistently increased TNF-α levels might result in dysregulation of the HPA axis, which might in turn play a role in the development of childhood asthma.

Notably, the most consistent finding in these analyses suggests that chronic stress enhances the production of TNF-α. This is interesting in light of evidence that TNF-α, produced by both lymphocytes and macrophages, is involved in the atopic immune response. TNF-α also participates in the recruitment and activation of many inflammatory cell types and stimulates the synthesis of nitric oxide and other inflammatory mediators that drive chronic delayed-type inflammatory responses.

Although we identify associations between stress and cytokine expression (eg, increased TNF-α) in these epidemiologic data, at this stage it is not clear whether stress preceded the increase of TNF-α production or whether TNF-α is a mediator of the effect of stress on allergic or airway disease expression. Future epidemiologic studies...
are needed to explore this further. Similarly, complemental
ary studies informed through these epidemiologic
findings might explore suggested mechanisms, as dis-
royed below.

Although we had only a single measure of the immune
response at age 2 to 3 years, it is interesting to speculate on
the potential influence of stress-induced increased TNF-α
levels during earlier development. That is, during early
maturation of the infant’s immune system, TNF-α might
be produced by antigen-presenting cells, such as mono-
cytes-macrophages, dendritic cells, and mast cells,
playing an important role in the interactions between
innate and adaptive immunity. Innate immune cytokines,
such as TNF-α, are likely involved in priming the adaptive
immune-humoral responses, but it is not known whether,
in some children, this priming results in an increased
predisposition to allergy and allergic disease. Notably,
recent evidence has linked TNF-α to the development of
allergic rhinitis in mice. The influence of stress on the
innate immune response warrants further study.

Moreover, many effects of TNF-α are mediated by the
induction of a cellular state consistent with oxida-
tive stress. Oxidative stress has been implicated in
asthma and allergy. Overlapping research suggests that
psychological stress might augment oxidative toxic-
ity. Emotionally stressed rats have increased levels of
8-deoxyhydroxy-guanosine (8-OHdG), a biomarker of
oxidative stress. Similarly, staying awake all night
increased the levels of thiobarbituric acid–reactive
substances in human subjects. Irie et al used classical
conditioning to illustrate the role of chronic stress and
oxidative damage.

In summary, chronic stress in early childhood might
influence the immune response manifested by an
enhanced allergen-specific response, increased production
of TNF-α, reduced production of IFN-α, and increased
serum IgE expression. Although the TH1/TH2 paradigm
remains an important functional dichotomy to consider
when interpreting quantitative differences in cytokine
expression in response to environmental stimuli like
stress, examination of other mechanisms (eg, oxidative
stress pathways or innate immune factors) or a broader
range of cytokines produced by cells both within and
outside the immune system might better delineate the true
complexity of the underlying mechanisms linking stress to
allergic sensitization and asthma. Moreover, research
linking caregiver stress to atopic sensitization might
change how we think about preventative strategies.
These findings suggest that future interventions should
include clinical approaches and, more broadly, public
policies designed to strengthen families and reduce
parenting stress.

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