Children with Both Asthma and Depression Are at Risk for Heightened Inflammation

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Objective To test whether children and adolescents with co-occurring asthma and depression are at risk for elevated inflammation—concurrently and at the next assessment.

Study design Up to 6 yearly assessments per person from the prospective, population-based Great Smoky Mountains Study (N = 1420) were used, covering children in the community aged 10-16 years old. High-sensitivity C-reactive protein (CRP) was assayed from annual bloodspot collections and provided indicators of elevated inflammation at CRP > 1, CRP > 2, and CRP > 3 mg/L. Depression was assessed with the Child and Adolescent Psychiatric Assessment. Asthma was assessed using a form adapted from the Centers for Disease Control and Prevention National Health Interview Survey.

Results Controlling common covariates of CRP, the co-occurrence of asthma and depression predicted heightened CRP—concurrently and at the next assessment. In turn, elevated CRP was relatively stable from one assessment to the next.

Conclusions The co-occurrence of asthma and depression in childhood poses a risk for substantially elevated inflammation concurrently and over time, which could contribute to pathophysiological processes involved in the development of additional chronic diseases and also to asthma-related morbidity and mortality. *(J Pediatr 2013;163:1443-7)*.

The acute phase protein C-reactive protein (CRP) is a marker of systemic inflammation that is used as a nonspecific indicator for cardiovascular and metabolic disease risk in adults. Early identification of risk for chronic disease is crucial for effective prevention and intervention. Elevated CRP is a promising biomarker for this purpose because it is detectable during childhood, when it is already associated with precursors of chronic disease, including obesity and vascular changes.[1-3] But what predicts elevated CRP during the early life course beyond body mass index (BMI)? In adults, inflammatory processes are exacerbated when chronic disease with an inflammatory basis co-occurs with depression.[4,5] And, these exaggerated immune responses may at least partially be responsible for elevated morbidity and mortality rates in adults with comorbid chronic disease and depression. Is a pattern of exacerbated inflammation already observable in children with comorbid physical illness and depression?

In children, inflammatory markers are reliably elevated when inflammatory-based asthma[3,6,7] co-occurs with chronic or acute stressors, including poverty and life events.[8] Such stressors also tend to be associated with depression, which itself can change stress physiology and predict increases in low-grade systemic inflammation over time.[9,10] Notably, no studies of children with asthma have examined whether its co-occurrence with depression accentuates inflammatory processes. Here, we addressed this gap in research and tested whether children who were experiencing both depression and asthma at the same point in time were at risk for exacerbated inflammation—concurrently and at the next assessment, 1 year later.

Methods

The Great Smoky Mountains Study (GSMS) is a longitudinal study of the development of psychiatric disorder in youth.[11,12] A representative sample of 3 cohorts, aged 9-13 at intake was recruited from 11 counties in North Carolina and interviewed yearly to age 16. Potential participants were selected from the population of about 12 000 eligible children using a household equal probability, accelerated cohort design. All children scoring above a predetermined cut point on a screening questionnaire assessing risk for psychopathology,[13] plus a 1-in-10 random sample of the rest were recruited. Of all children recruited, 80% (N = 1420) agreed to participate. About 8% of the area residents are African American. American Indians constituted only about 3% of the population of the study area, but, because they are an understudied group,

BMI	Body mass index
CRP	C-reactive protein
GSMS	Great Smoky Mountains Study

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were oversampled to constitute 25% of the study sample. All statistical analyses used a sampling weight inversely proportional to participants' probability of selection; therefore, results were representative of the population from which the sample was drawn and not biased from the oversampling procedure. Annual participation rates ranged between 74% and 94%.

A parent figure and the child were interviewed separately by trained interviewers. Before the interviews began, parent and child signed informed consent forms approved by the Duke University Medical Center Institutional Review Board. Each parent and child received an honorarium for their participation. Blood spot samples were obtained at the beginning of each in-person assessment, as follows: 2 finger-prick samples (yielding 10 bloodspots total per visit) were applied to standardized collection paper, immediately refrigerated upon drying, and express-shipped (without refrigeration) to the laboratory within 2 weeks of collection.[14] Samples were then stored at −28°C until they were assayed in duplicate. Blood spot samples are a reliable and feasible medium for field collection of biomarker data, including high-sensitivity-CRP.[14,15]

Our high-sensitivity assay for CRP in whole-blood spots was a biotin–streptavidin-based immunofluorometric system that improved on a previously published method.[15] Streptavidin A-coated microtiter plates bind a biotinylated capture antibody to CRP, clone C2. A second Europium-labeled antibody then binds to the streptavidin A biotin-C2-CRP complex; fluorescence of the resultant complex is directly proportional to the CRP concentration in each well. Detail regarding our CRP assays, and the calculation of serum equivalents have been previously published.[10,14,15] The blood spot method has good precision and reliability.[10]

CRP < 10 mg/L in the analytic sample ranged from 0.01-9.71 (mean = 0.77, SD = 1.41). Fifty-seven cases (1.2%; all percentages reported are weighted) were in the CRP > 10 mg/L range. CRP > 3 mg/L is a useful cutoff for disease risk in adults, but children typically have lower CRP.[16] Consistent with previous research,[3] we examined several dichotomous elevated CRP variables (>1 [19.1%], >2 [11.2%], >3 [7.8%]). These cutoffs resulted in reasonably-sized groups and are not sample-specific. Given our focus on exacerbated inflammation and research indicating that very high CRP is a powerful predictor of later disease risk,[17] cases with CRP > 10 mg/L were included. Children with asthma and depression were more likely to have very high CRP (OR = 4.15, 1.88-9.14; $P < .004$ and OR = 13.48, 3.41-52.83; $P < .001$, respectively). Thus, excluding these cases would have biased the analytic sample toward excluding the cases of most interest.

Physical health problems were assessed from parents with a survey adapted from the Centers for Disease Control and Prevention National Health Interview Survey Child Supplement (1988). A dichotomous variable indicated whether asthma, respiratory allergies, or hay fever were present in the past year. Additional dichotomous variables indicated the presence of infections (eg, tonsillitis, ear infection, urinary tract infections), other atopic diseases (eg, eczema), other chronic diseases (eg, diabetes, cancer, arthritis, chronic heart disease), and injuries in the past year. An additional variable summed the number of all illnesses experienced during the past year.

Depression was also measured at each assessment, using the Child and Adolescent Psychiatric Assessment, a structured interview.[18] The time frame for ascertaining the presence of most behaviors was the past 3 months to minimize forgetting and recall biases. A symptom was counted as present if reported by either parent or child. Information about the date of onset, duration, and intensity of each symptom was used to create diagnostic variables consistent with the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*.[19] Depressive disorders included major depression, dysthymia, and depressive disorder not otherwise specified. Two-week test-retest reliability of diagnoses is comparable with that of other highly-structured child psychiatric interviews.[20] For a discussion of the prevalence rate of psychiatric disorders in the GSMS during childhood.[12]

Controls included age, sex, race, and low socioeconomic status (≥2 of the following conditions: income below federal poverty level, low parental education, or occupational status). BMI was calculated from weight and height, measured at each assessment. Substance use (ie, current nicotine, alcohol, and illicit drug use) was assessed in the Child and Adolescent Psychiatric Assessment. Medication use in the past 12 months was assessed using the Child and Adolescent Services Assessment.[21]

Asthma was first assessed at Assessment 2 (ages 10+ years); thus, analyses focused on ages 10-16. During these ages, interviews with the 1420 participants in the longitudinal study resulted in a total of 5231 observations. During 3900 (74.6%) of these interviews, blood spots were collected. Bloodspots were unavailable when subjects refused or completed interviews by phone. Of 3900 bloodspots obtained, 3854 (97.3%) were successfully assayed for high-sensitivity-CRP. Of these cases, N = 3664 also had data on asthma and BMI. The mean number of CRP samples per person was 3.14 (SD = 1.59, range = 1-6). Cases included vs excluded from the analyses did not differ in terms of asthma and depression (OR = 0.93, 0.70-1.24; $P = .61$ and OR = 1.21, 0.62-2.40; $P = .57$, respectively), but were more likely to be American Indian and to be younger (OR = 1.71, 1.37-2.14; $P < .001$ and OR = 0.88, 0.83-0.93; $P < .001$, respectively). Thus, there were 1420 participants in the GSMS; between ages 10-16, the repeated interviews resulted in 3664 observations from these participants with complete CRP and health information. When conducting longitudinal analyses requiring the simultaneous use of at least 2 waves of data, we used 2194 observations.

Results

Weighted logistic regression models were implemented in a generalized estimating equations framework by SAS PROC GENMOD, specifying an exchangeable covariance matrix. The robust variance (sandwich type) estimates derived