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Allergic Diseases and Internalizing Behaviors in Early Childhood

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abstract

BACKGROUND AND OBJECTIVES: The relationship between allergic diseases and internalizing disorders has not been well characterized with regard to multiple allergic diseases or longitudinal study. The objective of this study was to examine the association between multiple allergic diseases in early childhood with validated measures of internalizing disorders in the school-age years.

METHODS: Children enrolled in the Cincinnati Childhood Allergy and Air Pollution Study underwent skin testing and examinations at ages 1, 2, 3, 4, and 7 years. At age 7, parents completed the Behavior Assessment System for Children, Second Edition (BASC-2), a validated measure of childhood behavior and emotion. The association between allergic diseases at age 4, including allergic rhinitis, allergic persistent wheezing, atopic dermatitis, and allergic sensitization, and BASC-2 internalizing, anxiety, and depression T scores at age 7 was examined by logistic and linear regression, adjusting for covariates.

RESULTS: The cohort included 546 children with complete information on allergic disease and BASC-2 outcomes. Allergic rhinitis at age 4 was significantly associated with elevated internalizing (adjusted odds ratio [aOR]: 3.2; 95% confidence interval [CI]: 1.8–5.8), anxiety (aOR: 2.0; 95% CI: 1.2–3.6), and depressive scores (aOR: 3.2; 95% CI: 1.7–6.5) at age 7. Allergic persistent wheezing was significantly associated with elevated internalizing scores (aOR: 2.7; 95% CI: 1.2–6.3). The presence of >1 allergic disease (aOR: 3.6; 95% CI: 1.7–7.6) and allergic rhinitis with comorbid allergic disease(s) (aOR: 4.3; 95% CI: 2.0–9.2) at age 4 had dose-dependent associations with internalizing scores.

CONCLUSIONS: Children with allergic rhinitis and allergic persistent wheezing at age 4 are at increased risk of internalizing behaviors at age 7. Furthermore, multiple allergic diseases had a dose-dependent association with elevated internalizing scores.

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Dr Nanda conceptualized and designed the study, performed statistical analysis, drafted the initial manuscript, and made multiple edits to develop the final manuscript as submitted; Drs Ryan and Newman helped conceptualized and design the study and reviewed and revised the manuscript; Drs LeMasters, Bernstein, Khurana-Hershey, and Lockey designed the initial cohort study, coordinated and supervised data collection, and critically reviewed the manuscript; Dr Levin carried out initial statistical analyses, oversaw the analyses conducted by Dr Nanda, and critically reviewed the manuscript; Drs Assa'ad and Rothenberg aided Dr Nanda in design of the study and interpretation of data and critically reviewed the manuscript; and all authors approved the final manuscript as submitted.

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WHAT'S KNOWN ON THIS SUBJECT: Allergic diseases in childhood have been associated with internalizing disorders, including anxiety and depression, but this is not well characterized in longitudinal studies and the effect of multiple allergic diseases on this relationship is unknown.

WHAT THIS STUDY ADDS: Young children with allergic rhinitis or allergic persistent wheezing have significantly higher internalizing behavior scores in the school-age years. There is a dose-dependent relationship between multiple allergic diseases in early childhood with internalizing, anxiety, and depression scores in later years.

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Up to one-quarter of children <18 years will develop a mental health disorder.[1–4] Within the spectrum of mental health disorders, anxiety and depressive disorders are classified under the broader category of internalizing behaviors[5–7] and refer to symptoms that are internally focused including anxiety, phobias, and depressive mood.[8,9] The prevalence of depressive and anxiety disorders in children ages 6 to 19 years has been estimated to range from ~4% to 8%,[10] and these disorders in childhood have been associated with later mental and behavioral problems,[8,11,12] chronic health problems,[8,13,14] and high-risk health behaviors.[4] The association between allergic diseases,[15–17] such as allergic rhinitis,[18,19] asthma,[20,21] food allergy,[22] and atopic dermatitis,[23,24] with internalizing disorders has been shown; however, whereas many of these studies[25] used validated measures, few studies have been able to evaluate the relationship longitudinally. In addition, no previous study has extensively evaluated whether there is a dose-dependent relationship between multiple comorbid allergic diseases and the development of internalizing behaviors.

The prevalence of allergic diseases varies based on the population studied; in American children, asthma prevalence has increased to 9.5%,[26] food allergy prevalence has increased to 8%,[27] allergic rhinitis affects up to 20% of children,[28] and atopic dermatitis affects 10% to 20% of children.[29] In a German high-risk birth cohort, the prevalence of children with 3 allergic diseases (asthma, eczema, and allergic rhinitis) was 12.2%,[30] although the worldwide prevalence for having all 3 allergic diseases was only 1.2%.[31] Risk factors for allergic diseases and multiple allergic diseases include male gender, parental history of allergies, and socioeconomic status. The increased rates of anxiety and depression in children with allergic diseases have been hypothesized to be due to behavioral modification, meaning that the child's attitude toward his or her allergies may affect his or her psychological adjustment as seen in other chronic diseases.[22,32] Other hypotheses for the increased rates include an underlying biological mechanism that relates to hypersensitivity responses activating cortisol release versus direct effect of T helper 2 cytokines, both of which may alter serotonin release in the prefrontal cortex.[33–35]

The objective of this study was to investigate the association between well-defined allergic disease phenotypes in childhood and validated measures of internalizing behaviors. Our primary a priori hypothesis was that children with allergic disease at age 4 years, including allergic rhinitis, allergic persistent wheezing, and atopic dermatitis, are at significantly increased risk of internalizing behaviors, including anxiety and depression, at age 7 years. We also a priori hypothesized children with multiple allergic diseases at age 4 years will have increased risk of internalizing behaviors at age 7 years. As exploratory analyses, we determined whether food or aeroallergen sensitization without symptoms in early childhood is significantly associated with internalizing behaviors at age 7 years.

METHODS

Study Population

Allergic diseases and internalizing behaviors were assessed in the Cincinnati Childhood Allergy and Air Pollution Study (CCAAPS), a prospective birth cohort of children born between 2001 and 2003 at risk of developing allergic diseases. The study's objective, design, and recruitment methodology have been described in detail previously.[36] Briefly, children living <400 m or >1500 m from a major highway or interstate were identified by birth records.[37] Eligible infants included those with ≥1 allergic parent, defined as a parent reporting symptoms of asthma or allergy, and who were positive to at least 1 of 15 aeroallergens by skin-prick test (SPT). Children were evaluated yearly from ages 1 to 4 and at age 7 for development of rhinitis, wheezing, and dermatitis with the use of a modified International Study of Asthma and Allergies in Children (ISAAC) parental questionnaire,[38,39] physical examination, and SPT to 17 allergens. The allergens tested included dog, cat, dust mite mix (*Dermatophagoides farina*, *Dermatophagoides pteronyssinus*), pollen (timothy and meadow fescue grass, white oak, maple mix, American elm, red cedar, short ragweed), mold (*Alternaria, Aspergillus fumigatus, Penicillium, Cladosporium*), German cockroach (*Blattela germanica*), cow's milk, and egg. SPTs were performed by using a bifurcated Accuset device (ALK-Abelló, Round Rock, TX); a positive SPT was defined as a wheal ≥3 mm greater than a negative saline control after 15 minutes. Parents of children enrolled provided informed consent, and the Institutional Review Board at the University of Cincinnati approved the study.

Behavioral Outcome Measures

At the age 7 visit, parents completed the parent rating scale of the Behavior Assessment System for Children, Second Edition (BASC-2; child version, ages 6–11 years), a validated screening assessment of externalizing, internalizing, and adaptive behavior in children.[40] The parent rating scale consists of 160 questions with response options of "never," "sometimes," "often," and "always"; results are divided into 4 composite scales, of which internalizing behaviors with the

anxiety and depression subscales were the outcomes of interest for this analysis.[40] The somatization subscale was excluded a priori because of questions regarding difficulty breathing. The anxiety subscale is composed of 18 items (eg, "worries," "fearful," "nervous") and the depression subscale contains 19 items (eg, "nobody likes me," "I want to die," "sad"). BASC-2 PRQ ASSIST software (Pearson, San Antonio, TX) was used to obtain a raw score and convert itto a T score with a mean of 50 and standard deviation (SD) of 10 on the basis of gender and age norms. A T score of >59 is considered "at risk," and scores >69 are considered clinically significant.[40] The internal validity scores used to determine accurate parental reporting included the following: F Index ("Faking Bad"), used to detect excessively negative responses; Consistency Index (rater reliability), used to detect agreement among highly similar items; and Response Pattern (R) Index, used to detect the number of times a response differs from the previous item's response.[40,41]

Allergic Diseases Measures

The associations between the allergic diseases present at age 4 years and the BASC-2 T scores for the internalizing behaviors at age 7 years were investigated. Disease variables of interest were defined as follows:

Allergic rhinitis: ≥1 aeroallergen SPT positive and positive parental response to modified ISAAC question at age 4 years[42] ("In the past 12 months, has your child ever had a problem with sneezing, or a runny or a blocked nose when he/she did not have a cold or flu?").

Allergic persistent wheezing: ≥1 aeroallergen SPT positive and recurrent wheezing (wheezing ≥2 times in the past 12 months regardless of presence or absence of a cold) at ages 3 and 4 years.

Atopic dermatitis: ≥1 aeroallergen SPT positive and frequent skin scratching for 6 months and 1 other symptom for 6 months (redness/red spots, raised bumps, or rough dry skin)[38,43,44] at age 4 years.

Food sensitization: 1 positive egg or milk SPT at age 1, 2, 3, or 4 years; this age range was chosen due to the limited (n = 21) number of children positive at age 4 years.

Aeroallergen sensitization: 1 positive aeroallergen SPT at age 4 years.

Multiple allergic diseases: >1 allergic disease (allergic rhinitis, allergic persistent wheezing, atopic dermatitis) at age 4 years.

Allergic rhinitis plus allergic disease(s): allergic rhinitis plus allergic persistent wheezing and/or atopic dermatitis at age 4 years.

Sensitization refers to positive allergen SPT regardless of symptoms.

Statistical Analysis

Children were excluded from the initial cohort if they were <37 weeks' gestational age and/or if their parent lacked a positive aeroallergen SPT. Children were eligible for this study if the parent completed the BASC-2 at age 7 years and if responses to the BASC-2 were within normal limits of the 3 internal validity indices. The primary outcome variable was the dichotomized BASC-2 T score >59 for the internalizing, anxiety, and depression scales.

Bivariate analyses were conducted between the allergic variables of interest and the dichotomized BASC-2 outcomes; associations were tested by using a χ^2 test of independence. The association between allergic diseases at age 4 and the dichotomized BASC-2 outcomes at age 7 was examined by logistic regression, adjusting for covariates. As a secondary analysis, we examined the association between allergic disease and continuous BASC-2 T score with the use of linear regression. A priori, we chose to examine the following covariates on the basis of previous work[41,45]: gender, race, maternal education, presence of ≥1 parents with asthma, BMI, sleep disturbance, dog ownership, cat ownership, and breastfeeding. These variables were examined because they are potential risk factors for the outcome of interest in this study, internalizing disorders.[41,45–48] Maternal education has been shown in this cohort to be significantly associated with income and Medicaid status; therefore, maternal education was used to represent socioeconomic status.[41] Sleep disturbance was defined if either of the following conditions were met: (1) parents reported that their child sleeps ≤9 hours at night or (2) their child's sleep was reported as disturbed due to rhinitis, wheezing, and/or eczema "a moderate or a lot" or >1 night per week. Sleep was dichotomized at ≤9 hours per night, which is 2 SDs below the mean reported hours of sleep at age 7.[45,49] The final multivariate models were adjusted for covariates significant at $\alpha < 0.2$: gender, parental asthma, maternal education, BMI, and sleep disturbance.

Multiple-comparison adjustment was not performed because we a priori hypothesized that allergic diseases and multiple allergic diseases are associated with elevated internalizing, anxiety, and depressive BASC-2 T scores. SAS version 9.4 (SAS Institute, Cary, NC) was used to conduct all analyses.

RESULTS

Study Population

A total of 762 children were enrolled in the CCAAPS cohort and completed at least 1 study visit through age 4. Of these, 562 children hadSPT and Questionnaire data at age 4 and BASC-2 data at age 7 collected; however, 16 children were excluded

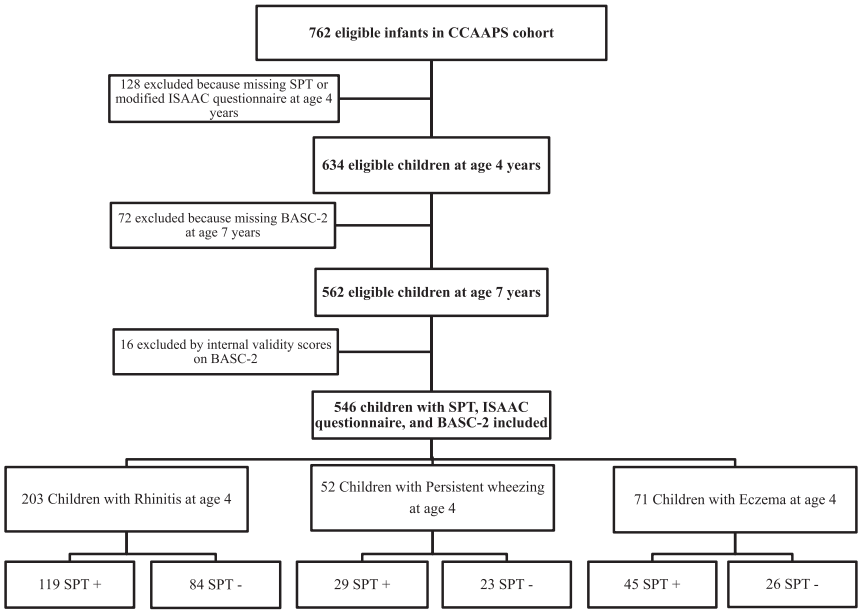

FIGURE 1
Study population grouping. Recruitment was population based; 7352 families were sent a letter requesting participation. Of the respondent and eligible families, 762 infants completed at least 1 study visit.

due to abnormal internal validity scores. Therefore, a total of 546 children were included in our analyses (Fig 1). There was no significant difference in age, race, gender, BMI, and parental asthma between the overall CCAAPS cohort and the subset of children (n = 546) included in the current analyses. The mean (SD) ages of children at the time of their age 4 and 7 clinical examinations were 4.0 (0.24) and 6.9 (0.29) years, respectively. Of the 546 children in this analysis, 114 (21%) were African American, 299 (55%) were male, 126 (23%) had a BMI ≥85th percentile, and 264 (48%) reported sleep disturbances (Table 1).

Mean BASC-2 T scores and percentages of elevated T scores in this cohort are presented in Table 2. There were no significant differences

TABLE 1 Subject Demographic Characteristics and Risk Factors for Elevated Internalizing Symptoms, Anxiety, and Depression BASC-2 T Scores at Age 7 Years

Variable	Total (N = 546)	Internalizing T Score		P	Anxiety T Score		P	Depression T Score		P
		Elevated[a] (n = 73)	Normal (n = 473)		Elevated[b] (n = 83)	Normal (n = 463)		Elevated[c] (n = 59)	Normal (n = 487)	
Breastfeeding ≥4 months[d]	295 (54)	35 (48)	260 (55)	.3	42 (51)	253 (55)	.5	26 (44)	269 (55)	.1
Maternal education (high school degree or less)[e]	109 (21)	20 (28)	89 (19)	.09	21 (26)	88 (20)	.2	23 (40)	86 (18)	<.01*
One or more parent with asthma	227 (42)	37 (51)	190 (40)	.09	42 (51)	185 (40)	.07	31 (53)	196 (40)	.07
Male	299 (55)	39 (53)	260 (55)	.8	42 (51)	257 (56)	.4	40 (68)	259 (53)	.03*
African American[f]	114 (21)	14 (19)	100 (21)	.7	15 (18)	99 (21)	.5	14 (24)	100 (21)	.6
BMI at age 7 years ≥85th percentile[g]	126 (23)	21 (29)	105 (22)	.2	23 (28)	103 (22)	.3	20 (34)	106 (22)	.04*
Sleep disturbance	264 (48)	40 (54)	224 (47)	.2	40 (48)	224 (48)	.9	36 (61)	228 (47)	.04*
Cat ownership[h]	125 (24)	19 (26)	106 (23)	.6	19 (23)	106 (24)	.98	12 (20)	113 (24)	.5
Dog ownership[i]	188 (36)	30 (42)	158 (35)	.2	30 (37)	158 (35)	.8	21 (36)	167 (36)	.99

Data are presented as n (%). P values were calculated by using Pearson's χ^2. *p < .05.
[a] Internalizing composite scale BASC-2 T score >59.
[b] Anxiety subscale BASC-2 T score >59.
[c] Depression subscale BASC-2 T score >59.
[d] Data not available for 1 subject, who was excluded from analysis.
[e] Data not available for 16 subjects, who were excluded from analysis.
[f] Races in this cohort were African American and white.
[g] Data not available for 3 subjects, who were excluded from analysis.
[h] Data not available for 15 subjects, who were excluded from analysis.
[i] Data not available for 17 subjects, who were excluded from analysis.

in the demographic characteristics between children with at-risk scores for internalizing and anxiety behaviors versus those without (Table 1). Children were more likely to have elevated depression scores if they were male ($P = .03$), had a mother with an educational level of high school or less ($P < .01$), had sleep disturbance ($P = .04$), or had a BMI ≥85th percentile ($P = .04$).

Internalizing Behavior Scores

The prevalence of elevated internalizing behavior scores was 24% among children with allergic rhinitis, 31% for those with allergic persistent wheezing, 32% with multiple allergic diseases, and 36% for those with allergic rhinitis plus another allergic disease(s). The unadjusted analyses showed allergic rhinitis (odds ratio [OR]: 2.6; 95% confidence interval [CI]: 1.6–4.4) and allergic persistent wheezing at age 4 years (OR: 3.2; 95% CI: 1.4–7.3) were significantly associated with elevated internalizing behavior scores (Table 3). In contrast, atopic dermatitis and sensitization to foods and aeroallergens were not significantly associated with elevated internalizing T scores (Table 3). Similar results were found between allergic diseases and the continuous BASC-2 internalizing behavior outcome (Supplemental Tables 5 and 6). After adjusting for covariates, both allergic rhinitis (adjusted OR [aOR]: 3.2; 95% CI: 1.8–5.8) and allergic persistent wheezing (aOR: 2.7; 95% CI: 1.2–6.3) were significantly associated with elevated internalizing behavior scores (Table 4).

Anxiety Scores

Elevated anxiety scores were present in 21%, 24%, 27%, and 28% of children with allergic rhinitis, allergic persistent wheezing, multiple allergic diseases, and with allergic rhinitis plus another allergic disease(s), respectively. Allergic rhinitis was significantly associated with elevated anxiety scores, whereas atopic dermatitis and sensitization

TABLE 2 Mean Scores and Percentages of Elevated Internalizing, Anxiety, and Depressive BASC-2 T Scores

BASC-2	Mean (SD) T Score	Combined Group (T Score >59), *n* (%)	At Risk (T Score 59–69), *n* (%)	Clinical (T Score >69), *n* (%)
Internalizing	48.8 (9.5)	73 (13)	58 (11)	15 (3)
Anxiety	49.6 (10.4)	83 (15)	61 (11)	22 (4)
Depression	49.1 (9.3)	59 (11)	35 (6)	24 (4)

TABLE 3 Unadjusted Associations of Allergic Disease Predictors with Elevated Internalizing Symptoms, Anxiety, and Depression BASC-2 T Scores at Age 7 Years

Predictor Variables	Elevated Internalizing Symptoms T Score[a] (*n* = 73)		Elevated Anxiety T Score[b] (*n* = 83)		Elevated Depression T Score[c] (*n* = 59)	
	OR	95% CI	OR	95% CI	OR	95% CI
Rhinitis[d] (*n* =203)						
Allergic SPT+ (*n* = 119)	2.6#	1.6–4.4	1.7*	1.0–2.8	2.4**	1.4–4.2
Persistent wheezing[d] (*n* = 52)						
Allergic SPT+ (*n* = 29)	3.2**	1.4–7.3	1.8	0.8–4.5	2.8*	1.2–7.0
Dermatitis[d] (*n* = 71)						
Atopic SPT+ (*n* = 45)	1.2	0.5–2.8	1.4	0.7–3.1	0.6	0.2–1.9
Sensitization[e] (*n* = 312)						
Food allergen SPT+ (*n* = 108)	1.4	0.8–2.5	1.2	0.7–2.0	1.3	0.7–2.5
Aeroallergen SPT+ (*n* = 274)	1.2	0.8–2.0	1.1	0.7–1.7	1.1	0.7–1.9
Multiple allergic diseases[f] (SPT+; *n* = 147)						
One allergic disease (*n* = 106)	1.3	0.7–2.4	1.1	0.6–2.0	1.5	0.8–2.9
Two or three allergic diseases (*n* = 41)	3.7#	1.8–7.6	2.2*	1.1–4.7	2.4*	1.0–5.5
Allergic rhinitis plus allergic disease(s)[g] (SPT+; *n* = 119)						
Allergic rhinitis alone (*n* = 83)	1.7	0.9–3.3	1.4	0.7–2.5	2.0*	1.0–3.9
Allergic rhinitis plus 1 or 2 allergic diseases (*n* = 36)	4.5#	2.1–9.4	2.4*	1.1–5.2	2.8**	1.2–6.6

[a] Internalizing composite scale BASC-2 T score >59.
[b] Anxiety subscale BASC-2 T score >59.
[c] Depression subscale BASC-2 T score >59.
[d] Allergic rhinitis, allergic persistent wheezing, and atopic dermatitis as defined in Methods.
[e] Seventy children with aeroallergen and food SPT positive results; thus, total does not equal the sum of the 2.
[f] More than 1 of the following: SPT+ allergic rhinitis, SPT+ allergic persistent wheezing, and SPT+ atopic dermatitis at age 4 years.
[g] Allergic rhinitis plus allergic persistent wheezing and/or atopic dermatitis.
* $P < .05$, ** $P < .01$, # $P < .001$. SPT, skin prick test

TABLE 4 Adjusted Associations of Allergic Disease Predictors and Elevated Anxiety, Depressive, and Internalizing Disorder BASC-2 Scores at Age 7 Years

Predictor Variables	Elevated Internalizing Symptoms T Score[a] (*n* = 73)		Elevated Anxiety T Score[b] (*n* = 83)		Elevated Depression T Score[c] (*n* = 59)	
	OR	95% CI	OR	95% CI	OR	95% CI
Rhinitis[d] (*n* = 203)						
Allergic SPT+ (*n* = 119)	3.2#	1.8–5.8	2.0*	1.2–3.6	3.2#	1.7–6.5
Persistent wheezing[d] (*n* = 52)						
Allergic SPT+ (*n* = 29)	2.7*	1.2–6.3	—[e]	—[e]	2.3	0.9–5.8
Multiple allergic diseases[f] (SPT+; *n* = 147)						
One allergic disease (*n* = 106)	1.2	0.6–2.3	1.1	0.6–2.1	1.5	0.7–2.9
Two or three allergic diseases (*n* = 41)	3.6#	1.7–7.6	2.2*	1.0–4.7	2.3	0.97–5.6
Allergic rhinitis plus allergic disease(s)[g] (SPT+; *n* = 119)						
Allergic rhinitis alone (*n* = 83)	1.6	0.8–3.1	1.4	0.7–2.6	1.9	0.96–3.9
Allergic rhinitis plus 1 or 2 allergic diseases (*n* = 36)	4.3#	2.0–9.2	2.2*	1.0–4.9	2.7*	1.1–6.6

Covariates include gender, parental asthma, maternal education, BMI, and sleep disturbance. *$P < .05$, #$P < .001$. SPT, skin prick test.

[a] Internalizing composite scale BASC-2 T score >59.

[b] Anxiety subscale BASC-2 T score >59.

[c] Depression subscale BASC-2 T score >59.

[d] Allergic rhinitis, allergic persistent wheezing, and atopic dermatitis as defined in Methods.

[e] Multiple regression analyses not performed because association was not significant in unadjusted models.

[f] More than 1 of the following: SPT+ allergic rhinitis, SPT+ allergic persistent wheezing, and SPT+ atopic dermatitis at age 4 years.

[g] Allergic rhinitis plus allergic persistent wheezing and/or atopic dermatitis.

to foods and aeroallergens were not significantly associated with elevated anxiety scores (Table 3). Similar results were found between allergic diseases and the continuous BASC-2 anxiety scores with the use of linear regression (Supplemental Tables 5 and 6). The adjusted analyses showed that allergic rhinitis at age 4 years (aOR: 2.0; 95% CI: 1.2–3.6) was significantly associated with elevated anxiety scores at age 7 years (Table 4).

Depression Scores

The prevalence of elevated depression scores in children with allergic rhinitis was 19%, 22% for those with allergic persistent wheezing, 20% for those with multiple allergic diseases, and 27% for those with allergic rhinitis plus another allergic disease(s). Unadjusted analysis showed a significant association between allergic rhinitis (OR: 2.4; 95% CI: 1.4–4.2) and allergic persistent wheezing (OR: 2.8; 95% CI: 1.2–7.0) with elevated depression T scores (Table 3). There were few differences found with the use of the BASC-2 depression continuous outcome; no significant association was shown between allergic persistent wheezing and depressive symptoms (Supplemental Tables 5 and 6). Adjusted analysis showed a significant association between allergic rhinitis (aOR: 3.2; 95% CI: 1.7–6.5) and elevated depression scores (Table 4).

Multiple Allergic Diseases

There was a dose-dependent relationship between increasing number of allergic diseases and elevated BASC-2 internalizing, anxiety, and depressive scores, particularly in children with allergic rhinitis plus a comorbid allergic disease(s) (Tables 3 and 4). In the adjusted model, multiple allergic diseases were significantly associated with elevated T scores for internalizing behaviors (OR: 3.6; 95% CI: 1.7–7.6) and anxiety (OR: 2.2; 95% CI: 1.0–4.7). Given the strength of the association found between allergic rhinitis at age 4 years with internalizing, anxiety, and depression BASC-2 T scores, the additive effect of multiple, simultaneous allergic disease associations was examined further in children with allergic rhinitis plus another allergic disease(s). Children with allergic rhinitis in the presence of another allergic disease(s) had the strongest association with elevated T scores for internalizing behaviors (aOR: 4.3; 95% CI: 2.0–9.2) (Table 4). Similar associations were found when examining the continuous T scores (Supplemental Tables 5 and 6).

Sensitivity Analysis

As a sensitivity analysis, a history of parental anxiety, depression, and/or attention-deficit/hyperactivity disorder (ADHD) was collected from a subset of participants (*n* = 187) who completed the currently ongoing CCAAPS age 12 clinical examination. Parental self-report via questionnaire 5 to 6 years after completion of the age 7 clinical examination was obtained. This variable was used to adjust the analyses described above in the subset of children with data available. In this sensitivity analysis, history of parental anxiety, depression, or ADHD was not significantly associated with the primary independent variables. In this subset of patients, the parental history was significantly associated

with the internalizing and depressive BASC-2 T scores ($P < .001$), but the addition of parental mental history to the models did not change the strength of the resulted associations presented above.

DISCUSSION

In the CCAAPS cohort, children with allergic diseases during early childhood, including allergic rhinitis and allergic persistent wheezing, were significantly more likely to have elevated internalizing BASC-2 T scores at age 7 compared with children without allergic disease. This study adds to the growing evidence that children with allergic diseases are at increased risk of developing internalizing behaviors.[15,18] Previous studies have shown that adults with allergic rhinitis and concomitant asthma were at significant risk of anxiety[19]; however, no studies have shown the dose-dependent relationship between multiple allergic diseases with internalizing disorders in children. We observed a threefold increased odds of internalizing BASC-2 T scores in children with multiple allergic diseases and a more than fourfold increase in risk of elevated internalizing T scores in children with allergic rhinitis plus another allergic disease(s).

There are 2 potential pathways by which allergic disease may lead to the development of internalizing disorders, as follows: (1) behavioral modification[22,24] and (2) underlying biologic mechanism related to immunoglobulin E, such as altered serotonin release by cortisol release from activation of the hypothalamic-pituitary-adrenal axis by hypersensitivity response.[33] In this study, both symptoms and sensitization were required to observe an increased risk of internalizing behaviors in children. These findings lend support to the notion that both behavioral modification from chronic symptoms and an underlying biological mechanism related to IgE may be required. Behavioral modification may be attributed to the long-term stress associated with the symptoms and treatment of a chronic disease, particularly allergic rhinitis. Despite the perception that the morbidity of allergic rhinitis is low, poor quality of life in patients with allergic rhinitis has been repeatedly reported.[50,51]

Potential biological mechanisms for this association between allergic diseases and internalizing disorders proposed include the release of interleukin-1β in hypersensitivity reactions,[34] which activates the hypothalamic-pituitary-adrenal axis stimulating the release of cortisol[52] and which modifies serotonin release leading to mood disturbances.[35] However, mouse models have proposed a direct relationship between antigen exposure and altered brain function leading to increased anxiety.[33] T helper 2 cytokines production in the prefrontal cortex and olfactory bulbs of rats with tree pollen– and ovalbumin-induced allergic rhinitis has been demonstrated.[33] These findings support the hypothesis that mediators of allergic inflammation may directly influence the centers of the brain involved in emotions and socialization.

There are some limitations to this study; in particular, measures of home environment and data from all children on family history of mental health diseases were not collected. A family history of internalizing disorders and allergic diseases are known risk factors[53] for subsequent internalizing and allergic disorders, respectively. We attempted to control for parental history of anxiety, depression, and/or ADHD; however, these data were only available in a subset of subjects. This sensitivity analysis in a subset of children revealed no change in the strength of associations found when adjusting for a parental history of mental health disorders. It is also important to note that although our findings suggest that children with allergic diseases are at increased risk of internalizing symptoms, this is not necessarily synonymous with a clinical diagnosis of anxiety or depression. Given that this cohort was recruited on the basis of distance from a major highway or interstate, this population is more likely to represent urban dwellers; thus, results may not be generalizable to other environments. Previous studies in this cohort have shown associations between traffic-related air exposure early in life and hyperactivity BASC-2 scores at age 7 years; thus, further study is warranted to understand the influence of traffic-related air pollution on the associations found in this study.[41] Responder bias is another concern because both the ISAAC modified questionnaire and the validated BASC-2 rely on parental report; we attempted to minimize this bias by excluding those with abnormal internal validity indices on the BASC-2 and performing a sensitivity analysis to control for parental anxiety. We attempted to control for the influence of the home and by adjusting for sociodemographic factors, BMI, and sleep disturbance.

In addition, for unclear reasons, we did not observe an association between atopic dermatitis at age 4 and internalizing symptoms at age 7. Previous work on this relationship is conflicting,[54,55] and controlling for sleep in this study may have affected our findings because previous work suggests that infants with eczema and sleeping problems are at increased risk of emotional and conduct problems.[56] Sleep disturbances were reported in 48% of the children in this study, which may be due to the strict definition used for normal sleep, uncontrolled allergic symptoms, underlying

sleep disorder, possible urban environment, or other reasons. Sleep disturbance may be seen in chronic diseases due to poorly controlled symptoms as well as in internalizing disorders and may be considered a potential confounder, and was thus adjusted for in the analyses presented in this study. In addition, we were unable to assess the risk of children with food allergy due to the small sample size at age 4 years; in addition, only 2 food allergens were tested in this cohort because the focus of the initial cohort was on aeroallergen sensitization and diesel exposure, although this would be an important area for future study.

There are, however, numerous strengths of this study including the longitudinal assessment of allergic symptoms, the availability of multiple covariates, and the use of standardized, validated measures of both independent and dependent variables. These strengths contribute to the significance of the association found between allergic diseases and future internalizing behaviors. Current follow-up of the CCAAPS cohort includes additional measures of allergic disease and internalizing behaviors in preadolescence, which will contribute to our understanding of this relationship during the transition to adolescence and adulthood.

CONCLUSIONS

The finding of a significant association between early childhood allergic rhinitis, allergic persistent wheezing, and the increasing number of allergic diseases with internalizing behaviors at age 7 years has substantial clinical implications. Physicians who care for high-risk children, especially those born to allergic parents, should be aware of the two- to fourfold increased risk of developing internalizing behaviors, especially in children with multiple allergic diseases. Our findings call for improved screening and referral of allergic children, particularly those with multiple allergic diseases. However, the treatment of allergic diseases in the prevention of mental health diseases is unclear and requires further consideration. The impact of mental health disorders on the patient and society is substantial; therefore, screening at-risk patients, including children with allergic disease, and implementing primary prevention activities may be warranted.

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ABBREVIATIONS

ADHD: attention-deficit/hyperactivity disorder
aOR: adjusted odds ratio
BASC-2: Behavioral Assessment System for Children, Second Edition
CCAAPS: Cincinnati Childhood Allergy and Air Pollution Study
CI: confidence interval
ISAAC: International Study of Asthma and Allergies in Childhood
OR: odds ratio
SPT: skin-prick test

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