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I, Maya Nanda M.D., hereby submit this original work as part of the requirements for the degree of Master of Science in Clinical and Translational Research .

It is entitled:

Association of Allergic Diseases with Internalizing Disorders in Early Childhood

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Association of Allergic Diseases with Internalizing Disorders in Early Childhood

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by

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A. Abstract

Background: The association between allergic disease and behavioral symptoms in childhood is not well established.

Objective: To longitudinally examine the relationship of allergic diseases and atopy at age four with validated measures of internalizing, anxiety, and depressive symptoms at age 7 years.

Methods: Children enrolled in the Cincinnati Childhood Allergy and Air Pollution Study (CCAAPS), a birth cohort study, completed skin prick testing (SPT) and clinical examinations at 1, 2, 3, 4, and 7 years of age. At age seven, parents completed the Behavior Assessment System for Children, Second Edition (BASC-2), a validated psychological assessment of internalizing disorders composite scale including subscales anxiety and depression. The associations between rhinitis, persistent wheezing, eczema, and allergic sensitization at age four and internalizing disorders at age seven are examined by logistic and linear regression adjusting for maternal education, gender, parental asthma, BMI, and sleep disturbance.

Results: In a cohort of 546 children with complete information on allergic disease and behavioral symptoms, the prevalence of internalizing disorders was 13.4%, anxiety disorders 15.2%, and depression was 10.8%. Allergic rhinitis at age 4 years was significantly associated with having elevated BASC-2 scores in the clinically 'at risk' range for internalizing disorders, (aOR=3.2 [1.8-5.8]), anxiety disorders (aOR=2.0 [1.2-3.6]), and depressive disorders (aOR=3.2 [1.7-6.5]). Atopic persistent wheeze at age 4 years was significantly associated with BASC-2 'at risk' score for internalizing disorders (aOR=2.7 [1.2-6.3]). Aeroallergen sensitization and food sensitization alone were not associated with BASC-2 'at risk' score for internalizing, anxiety, or depressive disorders. Presence of more than one allergic disease (rhinitis, persistent wheeze, or eczema) was significantly associated with BASC-2 'at risk' score for internalizing disorders (aOR=4.0 [2.0-8.0]), anxiety disorders (aOR=2.5 [1.2-5.0]), and depressive disorders (aOR=3.5 [1.6-7.7]). Presence of rhinitis plus another allergic disease had an even stronger association than rhinitis alone with internalizing disorders (aOR=5.2 [2.6-10.8]), anxiety disorders (aOR=2.5 [1.2-5.4]), and depressive disorders (aOR=4.4 [1.9-10.0]). Multivariate linear regression showed same associations between allergic diseases and BASC-2 continuous outcome.

Conclusions: Children with allergic diseases at age 4, in particular rhinitis, persistent wheeze, are more likely to be at-risk for internalizing disorders including anxiety and depression at 7 years. Furthermore, there was an additive risk of having more than one allergic disease on the subsequent development of an internalization disorder.

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B. Tables and Figure Headings

C. Introduction

Up to one quarter of children under the age of 18 years will develop a mental health disorder.[1-3] Adults with anxiety disorders reported a median age of onset of only 11 years of age; these disorders in childhood have been associated with a 3-fold increased risk of a mental health disorder later in life.[4,5] The prevalence rates at age 9-10 years have been estimated for anxiety disorders to be 2.4% and for depressive disorders to be 0.5%.[5]; however, these rates vary with children ages 6 to 19 years estimated between 3.8% to 4.7% for depressive disorders and for anxiety disorders ranging from 5.5% to 8.1%.[6] This demonstrates that these disorders are some of the most common illnesses in childhood and unfortunately are often unnoticed because of the more subtle and non-typical features—i.e somatic complaints or poor concentration.[7-9] Anxiety and depressive disorders fall under the broader category of internalizing behaviors which refers to symptoms that are internally focused such as withdrawal, anxiety, phobias, and depressive mood. Internalizing disorders in childhood and adolescence have been associated with future mental and behavioral problems,[5,10,11] chronic health problems,[11-13] and high risk health behaviors.[11,14] Many chronic diseases, have been shown to be a risk factor of anxiety and depression in children.[22,23] It is also notable that although allergic diseases[15]—allergic rhinitis,[16,17] asthma,[18,19] food allergy,[20] and atopic dermatitis[21] have been associated with internalizing disorders, none of these studies have rigorously evaluated this relationship prospectively using well-defined allergic phenotypes as well as standardized measures of internalizing disorders. The importance of evaluating this relationship lies in the implications for future outcomes and the increased risk of missed diagnosis in childhood.

Ghandour et al. reported the prevalence of internalizing mental health symptoms among children with allergic disease to be 29.2% and children with asthma to be 21.9% which was

comparable to the rates seen in cystic fibrosis (29.9%) and diabetes mellitus (28.8%).[22] Similar findings have been shown in adults as well.[23] In these other chronic health disorders, the psychological effect of the disease is common knowledge thus routine screening, support, and referral are provided; however, this is not often the case in allergic diseases. This may be due to few studies showing no association between allergic diseases and internalizing disorders,[16,24] the perception among physicians that allergic diseases have low morbidity, and the lack of rigorous studies demonstrating the association between allergic disease and internalizing disorders.

The Cincinnati Childhood Allergy and Air Pollution Study (CCAAPS) cohort presents an ideal population to examine the association between early allergic disease and internalizing behaviors. CCAAPS is a high-risk birth cohort that followed patients until age 7 years with evaluation of atopy by skin prick testing, allergic symptoms by standardized survey, and mental health with validated assessment. The purpose of this study is to better understand the pathway from allergic disease to developing internalizing disorders and determine the risk of allergic patients for mental health disorders. Herein, we performed the first longitudinal birth cohort study designed to determine if allergic disease impacted the subsequent develop of internalization disorders by 7 years of age.

D. Methods

Study Population

Internalization disorders were assessed in the Cincinnati Childhood Allergy and Air Pollution Study (CCAAPS), a prospective birth cohort of children at-risk for allergic diseases born between 2001 and 2003. The study's objective, design, and methods have been described in detail previously.[26] Briefly, children living less than 400 m or greater than 1500 m from a major

highway or interstate were identified by birth records.[27] Eligible infants included those with 1 or more atopic parent, defined as minimum 1 skin prick test (SPT) positive with asthma or allergy symptoms. Children were evaluated yearly for development of rhinitis, wheezing, and eczema using a modified International Study of Asthma and Allergies in Children (ISAAC) parental questionnaire, physical exam, and SPT to 17 allergens. The allergens tested included dog, cat, dust mite mix (*Dermatophagoides farina and Dermatophagoides pteronyssinus*), pollen (timothy and meadow fescue grass, white oak, maple mix, American elm, red cedar, short ragweed), mold (*Alternaria, Aspergillus fumigatus, Penicillium mix, Cladosporium*), German Cockroach (*Blattela germanica*), cow's milk and egg. SPT to 15 aeroallergens and foods were performed using a bifurcated Accuset device (ALK-Abelló); a positive SPT was defined as a wheal ≥ 3 mm greater than negative saline control after 15 minutes. Parents of children enrolled provided informed consent and the study was approved by the Institutional Review Board at the University of Cincinnati.

Behavioral Outcome Assessment

At age seven, in addition to the clinical evaluation for allergic disease, parents completed the parental rating scale (PRS) 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 atypical behavior in children.[28]The PRS consists of 160 questions with responses of 'never, sometimes, often, always' and 4 composite scales of which internalizing behaviors with the subscales anxiety and depression were the outcomes of interest.[28] The subscale somatization was excluded *a priori* because of questions regarding difficulty breathing i.e. unable to differentiate asthma versus somatization. The anxiety subscale contains 18 items (ex: worries, fearful, nervous, serious) and the depression subscale contains 19 items (ex:

'nobody likes me,' 'I want to die,' sad, seems lonely). BASC-2 PRQ ASSIST^{TM} software was used to obtain a raw score and convert to a T score based on gender and age norms; T score > 59 (1 SD above mean) are considered "at risk" and >70 (2 SD above mean) considered clinically significant. The primary outcome assessed in this analysis for anxiety, depression, and internalizing disorders was a dichotomized T score > 59 which included those "at risk" and those clinically significant. The internal validity scores used to determine accurate parental reporting included: F Index ('Faking Bad') used to detect excessively negative responses, Consistency Index (rater reliability) to detect agreement among highly similar items, and Response Pattern (R) Index to detect number of times response differs from previous items response.[28,29]

Allergic Disease at Age Four

The association between the allergic diseases at ages 4 years with the BASC-2 internalizing composite score, and subscale anxiety and depression scores at age 7 years was examined and the variables of interest included:

- Non-allergic rhinitis defined as negative aeroallergen SPT and positive parental response to modified ISAAC question at age 4 years ("*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 rhinitis defined as one aeroallergen SPT positive and positive parental response to rhinitis question at age 4 years.[30]
- Non-allergic persistent wheeze defined as negative aeroallergen SPT and recurrent wheeze (wheezing 2 or more times in the past 12 months regardless of cold) at age 4 years and one year prior.[31]

- Atopic persistent wheeze is one aeroallergen SPT positive and presence of persistent wheeze at age 4 years.
- Eczema defined as negative aeroallergen SPT and frequent skin scratching for 6 months and one other symptom for 6 months: redness/red spots, raised bumps, or rough dry skin[32] at age 4 years.
- Atopic dermatitis is one aeroallergen SPT positive and presence of eczema at age 4 years.
- Food sensitization defined at age 4 years as one egg or milk SPT positive at age 1, 2, 3, or 4 years.
- Aeroallergen sensitization is one aeroallergen SPT positive at age 4 years.
- Non-atopic diseases include SPT- rhinitis, SPT- persistent wheeze, and SPT-eczema at age 4 years.
- Atopic diseases includes SPT+ rhinitis, SPT+ persistent wheeze, and SPT+ atopic dermatitis at age 4 years.
- All diseases include rhinitis, persistent wheeze, and eczema regardless of SPT results.

Statistical Analysis

Children were eligible for this analysis if they underwent BASC-2 at age 7 years and if responses to the BASC-2 were within normal limits of the 3 internal validity indices—F index, Consistency Index, and R Index. The primary outcomes of interest were the dichotomized BASC-2 composite scale internalizing disorders and its' subscales of anxiety and depression. Descriptive statistics were used to calculate the prevalence of internalizing, anxiety, and depressive disorders among children with rhinitis, wheezing, and eczema, respectively. Bivariate analyses were conducted between the variables of interest and internalizing, anxiety, and depressive disorders, respectively; associations were tested using a χ^2 test of independence.

The association between allergic disease at age four and the dichotomized BASC-2 outcomes at age seven was examined by logistic regression adjusting for relevant covariates. As a secondary analysis, we also examined the association between allergic disease and continuous BASC-2 T score using linear regression. A priori we chose to examine the following covariates based on previous work[29,33]: gender, race (African American, not African American), maternal education (≤high school diploma/GED, ≥some college), presence of 1 or more parents with asthma, BMI (≥85th%ile, <85th%ile), sleep disturbance (≤ 9 hours, > 9 hours sleep per night), dog ownership (yes, no), cat ownership (yes, no), and breastfeeding (>5 months or ≤5 months assessed at age 1 year). Maternal education has been shown in this cohort to be significantly associated with income and Medicaid status, therefore was used to represent socio-economic status.[29] Sleep was dichotomized at ≤ 9 hours per night because the mean at age 7 years is 10.7 hours per night with SD of 0.7, therefore a cut off of 2 SD below the mean was chosen. [33,34] Sleep disturbance was defined as sleep ≤ 9 hours or 'a moderate amount' or 'a lot' response to the modified ISAAC question "*How much does rhinitis disturb sleep?*" The final multivariate models were all adjusted for gender, parental asthma, maternal education, BMI, and sleep disturbance. In addition, remaining covariates associated with the BASC-2 outcomes at α=0.2 were included into the multivariate logistic and linear regression models. The primary independent variables which included rhinitis, persistent wheeze, and eczema had three levels in each model (i.e. neither =0, non-allergic rhinitis=1, allergic rhinitis=2). The association between multiple atopic diseases, multiple allergic diseases, and rhinitis plus multiple allergic diseases with the BASC-2 outcomes were assessed in same manner using multivariate logistic and linear regression. SAS 9.4 was used to conduct these analyses.

E. Results

Study Population Characteristics

In total, 546 children with valid BASC-2 data and completed modified ISAAC questionnaires and skin prick testing at age four were included in this analysis. The number of patients included in this study and included in the subgroups are shown in Figure 1. At age 7 years, 562 children with complete age four data had an internalizing BASC-2 score completed; however, internal validity scores with an F Index less than zero (n=1) or greater than six (n=1), consistency index greater than 17 (n= 4), and R Index <66 or >125 (n= 10) were excluded. The mean age was 6.9 (6.4-8.6) years at the 7 year visit in which the BASC-2 was completed. The mean age was 4.04 (3.3-5.6) years at the 4 year visit in which SPT and modified ISAAC questionnaire were performed. The subjects' demographic characteristics are presented in Table 1. Of the 546 children, 114 (21%) were African American, 299 (55%) were male, 127 (23%) had a BMI $\geq 85^{th}$%ile, and 250 (46%) have sleep disturbances. The mean BASC-2 T scores for internalizing disorders is 48.8 (standard deviation [SD]= 9.5), for anxiety disorders is 49.6 (SD=10.4), and for depressive disorders is 49.1 (SD=9.3). Clinically 'at-risk' (> 59) BASC-2 T scores for internalizing, anxiety, and depressive disorders are reported in 73 (13%), 83 (15%), and 59 (11%) of children, respectively. In the internalizing disorder and anxiety disorder groups, there are no significant differences in terms of the subjects' demographic characteristics between those with the disorders versus those without. The depressive disorder group has a significantly greater portion of male children (p=0.03), children with maternal education $\leq$ to a high school degree (p<0.001), children with a BMI $\geq 85^{th}$%ile (p=0.02), and children with sleep disturbance (p=0.03).

Association of allergic diseases at age 4 years with internalizing disorders at age 7 years

The prevalence of internalizing disorders in children with allergic rhinitis was 24%, 31% for those with atopic persistent wheeze, 26% with those with more than one allergic disease and 38% for those with rhinitis plus another allergic disease. Unadjusted associations of allergic diseases with internalizing disorders are shown in Table 2. Allergic diseases at age four were significantly associated with elevated BASC-2 internalizing disorders scores, including allergic rhinitis (odds ratio, (OR) 2.6; 95% CI, 1.6-4.4) and atopic persistent wheezing (OR, 3.2; 95% CI, 1.4-7.3). Eczema and skin test positivity alone to foods or aeroallergens were not significantly associated with abnormal BASC-2 scores for internalizing disorders (Table 2). Similar associations were found between the allergic diseases and the continuous BASC-2 outcomes (Table 4 & 5). The results of the adjusted models are shown in Table 3. After adjusting for gender, parental asthma, maternal education, BMI, and sleep disturbance, both allergic rhinitis (aOR, 3.2; 95% CI, 1.8-5.8), non-allergic rhinitis (aOR, 2.7; 95% CI 1.4-5.3), and atopic persistent wheeze (aOR, 2.7; 95% CI 1.2-6.3) were significantly associated with elevated BASC-2 internalizing disorders scores (Table 3).

Association of allergic diseases at age 4 years with anxiety disorders at age 7 years

Anxiety disorders are present in 21%, 24%, 23%, and 23% of children with allergic rhinitis, atopic persistent wheeze, more than one allergic disease, and with rhinitis plus another allergic disease, respectively. Unadjusted associations of allergic diseases with anxiety disorders are shown in Table 2. Allergic diseases were significantly associated with elevated BASC-2 anxiety scores including allergic rhinitis (OR, 1.7; 95% CI, 1.0-2.8). Eczema and skin test positivity alone to foods or aeroallergens were not significantly associated with abnormal BASC-

2 scores for anxiety disorders (Table 2). Similar associations were found between the allergic diseases and the abnormal BASC-2 scores using linear regression (Table 4 & 5). Multivariate logistic regression models are shown in Table 3. Allergic rhinitis (aOR, 2.0; 95% CI, 1.2-3.6) and non-allergic rhinitis (aOR, 2.2; 95% 1.2-4.2) were also significantly associated with elevated BASC-2 anxiety disorders scores (Table 3).

Association of allergic diseases at age 4 years with depressive disorders at age 7 years

The prevalence of depressive disorders in children with allergic rhinitis was 19%, 24% for those with persistent atopic wheeze, 21% for those with more than one allergic diseases, and 27% for those with rhinitis plus another allergic disease. Unadjusted associations of allergic disease predictors association with depressive disorders are shown in Table 2. Allergic diseases significantly associated with abnormal BASC-2 depressive disorders scores included allergic rhinitis (OR, 2.4; 95% CI, 1.4-4.2), non-allergic rhinitis (OR, 2.1; 95% CI, 1.1-3.9), and atopic persistent wheezing (OR, 2.8; 95% CI, 1.2-7.0). Eczema and skin test positivity alone to foods or aeroallergens were not significantly associated with abnormal BASC-2 scores for depressive disorders (Table 2). There were few differences found using the BASC-2 continuous outcome variable; no significant association between atopic persistent wheeze and depressive disorders (Table 4 & 5). The final multivariate logistic regression models are shown in Table 3. A significant association was found between allergic rhinitis (aOR 3.2; 95% CI, 1.7-6.5) and non-allergic rhinitis (aOR, 3.5; 95% CI, 1.7-7.3) with elevated BASC-2 depressive disorder scores (Table 3).

Linear relationship between number of allergic diseases at age 4 years and risk of internalizing disorders at 7 years

The unadjusted association of more than one allergic or atopic disease with BASC-2 outcomes are shown in Table 2. Presence of more than one atopic disease (SPT+) or more than one allergic (SPT ±) disease was significantly associated with elevated BASC-2 scores for internalizing, anxiety, and depressive disorders. The adjusted associations are shown in Table 3. After adjusting for gender, parental asthma, maternal education, BMI, and sleep disturbance, it is notable that the presence of more than one atopic disease (SPT+) is significantly associated with abnormal BASC-2 scores for internalizing disorders (OR, 3.6; 95% CI, 1.7-7.6) and anxiety disorders (OR, 2.2; 95% CI, 1.0-4.7). When adjusting for the same covariates, the presence of more than one allergic disease (SPT ±) is significantly associated with abnormal BASC-2 scores for internalizing disorders (OR 4.0; 95% CI 2.0-8.0), anxiety disorders (OR 2.5; 95% CI 1.2-5.0), and depressive disorders (OR 3.5; 95% CI 1.6-7.7). When this increasing number of allergic diseases association was examined further, rhinitis plus another allergic disease had the strongest association with internalizing disorders (aOR 5.2; 95% CI, 2.6-10.8), anxiety disorders (aOR 2.5; 95% CI 1.2-5.4), and depressive disorders (aOR 4.4; 95% CI 1.9-10.0) (Table 3). Similar associations were found using linear regression (Table 4 & 5).

F. Discussion

We performed a longitudinal association between allergic rhinitis, non-allergic rhinitis, and atopic persistent wheeze in early childhood with elevated internalizing BASC-2 scores at age 7 years. In particular, rhinitis in early childhood was associated with elevated internalizing, anxiety, and depressive scores at age 7 years. To the best of our knowledge this is the first study to demonstrate this association longitudinally using standardized measures of allergy and

validated measures of internalizing disorders; the findings are indeed consistent with less controlled studies.[15,16] Xi et al demonstrated adults with allergic rhinitis and concomitant asthma were at significant risk for anxiety[17]; however, no studies have looked at the association of more than one allergic disease or rhinitis with another allergic disease with internalizing disorders in children. We observed a 4-fold increase in risk of internalizing disorders in children with more than one allergic disease and more than a 5-fold increase in risk of internalizing disorders in children with rhinitis plus another allergic disease.

These results support the hypothesis that the pathway between allergic rhinitis and association with internalizing disorders later in childhood is through both behavioral modification and an underlying biologic mechanism. Two potential pathways by which allergic disease may result in developing internalizing disorders have been proposed— (1) behavioral modification due to parental stress/anxiety, clinical manifestations and treatment of disease acting as a stressors[20,21] and (2) altered serotonin release by cortisol release from activation of the hypothalamic-pituitary-adrenal (HPA) axis by hypersensitivity response.[25] In this study, atopy alone and allergic symptoms alone were not sufficient to put patients at risk of internalizing behaviors; both symptoms and specific IgE were required to put patients at risk. This demonstrates that likely both behavior modification from chronic symptoms and an underlying biologic mechanism from atopy are required to develop internalizing disorders. Behavioral modification is attributed to the stress associated with the symptoms and treatment of a chronic disease, the parental stress and anxiety, and the changes to the home environment due to these factors[35]. The morbidity of allergic rhinitis is maybe thought to be insignificant; however, there are numerous studies demonstrating the low quality of life measures in patients with allergic rhinitis.[36,37] The biologic mechanism proposed is that hypersensitivity reactions lead to IL-1β

release[38] which activates the HPA axis stimulating the release of cortisol[39] which modifies serotonin release[40]. However, some mouse models have proposed a direct relationship, independent of cortisol release, between antigen exposure and altered brain function leading to increases anxiety[25]. Tonelli et al demonstrated amplified T_H2 cytokines production, IL-4, IL-5, IL-13 in the pre-frontal cortex and olfactory bulbs of mouse and rats with tree pollen and OVA-induced allergic rhinitis[25] which supports the hypothesis that mediators of allergic inflammation directly influence the centers of the brain involved in emotions and socialization.

Some of the limitations of this study include lack of family psychiatric history and lack of home chaos measures which may contribute to the development of internalizing disorders. We attempted to adjust for the influence of the home and parental environment by adjusting for socio-demographic factors, BMI and sleep disturbance. Furthermore, the strengths of this study which include assessing the association longitudinally, adjusting for many relevant variables, and using standardized, validated measures of independent and outcome measures, contribute to the value of the association found between allergic diseases and future internalizing disorders. Future studies that examine the relationship between food allergy in a similar manner and re-examining this relationship again at age 12 years would be invaluable.

This finding of a significant association between early childhood allergic rhinitis, atopic persistent wheeze, and increasing number of allergic diseases with internalizing disorders at age 7 years has substantial clinical implications. Physicians who care for allergic patients should be aware of the significant risk for developing internalizing disorders, especially in those with more than one allergic disease since this risk is additive. Our findings call for improved screening and psychiatry referral of allergic children, particularly those with allergic rhinitis alone or with another allergic disease. Atopy appears to play a role in developing internalizing disorders;

however, the role of treatment of allergic diseases in prevention of mental health diseases is unclear and requires further studies. The impact of mental health disorders on the patient and society is substantial, therefore screening at-risk patients and work towards prevention is key. A high clinical suspicion is vital for early diagnosis of internalizing disorders in children in hopes of prevention of poor mental health, behavioral, and chronic disease outcomes.

G. Tables

Table 1. Subjects' Demographics and Risk Factors for Elevated Anxiety, Depressive, and Internalizing Disorders BASC-2 Score at Age 7.

Variable	Total (n=546)	Internalizing Disorders ǂ (n=73)	No Internalizing Disorders (n=473)		Anxiety Disorder¶ (n=83)	No Anxiety Disorders (n=463)		Depressive Disorders§ (n=59)	No Depressive Disorders (n=487)	
	No. (%)	**No. (%)**	**No. (%)**	**p value**	**No. (%)**	**No. (%)**	**p value**	**No. (%)**	**No. (%)**	**p value**
Breastfeeding ≥ 4 Months*	295 (54)	35 (48)	260 (55)	0.3	42 (51)	253 (55)	0.5	26 (44)	269 (55)	0.1
Maternal Education (≦ High School Degree)**	109 (21)	20 (28)	89 (19)	0.09	21 (26)	88 (20)	0.19	23 (40)	86 (18)	**<0.001**
≧ 1 Parent With Asthma	227 (42)	37 (51)	190 (40)	0.09	42 (51)	185 (40)	0.07	31 (53)	196 (40)	0.07
Male	299 (55)	39 (53)	260 (55)	0.8	42 (51)	257 (56)	0.4	40 (68)	259 (53)	**0.03**
African American	114 (21)	14 (19)	100 (21)	0.7	15 (18)	99 (21)	0.5	14 (24)	100 (21)	0.6
BMI At Age 7 Years ≥ 85th%ile***	127 (23)	22 (30)	105 (22)	0.14	24 (29)	103 (22)	0.2	21 (36)	106 (22)	**0.02**
Sleep ≤9 Hours/Night*	250 (46)	39 (53)	211 (45)	0.16	39 (47)	211 (46)	0.8	35 (59)	215 (44)	**0.03**
Cat Ownership#	125 (24)	19 (26)	106 (23)	0.6	19 (23)	106 (24)	0.98	12 (20)	113 (24)	0.5
Dog Ownership##	188 (36)	30 (42)	158 (35)	0.2	30 (37)	158 (35)	0.8	21 (36)	167 (36)	0.99

*Missing 1 subject **Missing 16 ***Missing 3 #Missing 15 ##Missing 17

ǂ Internalizing Disorders: Internalizing Problems Composite Scale BASC-2 T score > 59

¶ Anxiety Disorders: Anxiety Subscale BASC-2 T score > 59

§ Depressive Disorders: Depression Subscale BASC-2 T score > 59

Note: P values were calculated using Pearson's χ^2

Table 2. Unadjusted Association of Allergic Disease Predictors with Elevated Anxiety, Depressive, and Internalizing Disorders BASC-2 Score at Age 7 Years. SPT+, Skin Prick Test Positive; SPT-, Skin Prick Test Negative; OR, Odds Ratio; CI, Confidence Interval.

Predictor variables	Internalizing Disorders‡ (n=73)		Anxiety Disorders¶ (n=83)		Depressive Disorders§ (n=59)	
	OR	95% CI	OR	95% CI	OR	95% CI
Rhinitis‖ (n=203)						
SPT + (n=119)	**2.6#**	**1.6, 4.4**	**1.7***	**1.0, 2.8**	**2.4****	**1.4, 4.2**
SPT - (n=84)	1.7	0.9, 3.1	1.7	0.9, 3.0	**2.1***	**1.1, 3.9**
Persistent Wheeze‖ (n=52)						
SPT + (n=29)	**3.2****	**1.4, 7.3**	1.8	0.8, 4.5	**2.8***	**1.2, 7.0**
SPT - (n=23)	0.97	0.3, 3.4	0.8	0.2, 2.9	1.3	0.4, 4.3
Eczema£ (n=71)						
SPT + (n=45)	1.2	0.5, 2.8	1.4	0.7, 3.1	0.6	0.2, 1.9
SPT - (n=26)	0.8	0.3, 2.9	1.4	0.5, 3.7	1.5	0.5, 4.6
SPT (n=341)						
Food SPT+ (n=67)	1.5	0.8, 2.9	1.7	0.9, 3.3	1.1	0.5, 2.5
Aeroallergen SPT + (n=274)	1.2	0.8, 2.0	1.1	0.7, 1.7	1.1	0.7, 1.9
Atopic Diseases¥ (SPT +; n=147)						
1 Atopic Disease (n=106)	1.3	0.7, 2.4	1.1	0.6, 2.0	1.5	0.8, 2.9
2 or 3 Atopic Diseases (n=41)	**3.7#**	**1.8, 7.6**	**2.2***	**1.1, 4.7**	**2.4***	**1.0, 5.5**
All diseasesǂ (SPT ±; n=264)						
1 Allergic Disease (n=207)	1.4	0.8, 2.4	1.4	0.9, 2.4	**1.9**	**1.0, 3.5**
2 or 3 Allergic Diseases (n=57)	**4.2#**	**2.1, 8.3**	**2.6****	**1.3, 5.2**	**3.9#**	**1.8, 8.3**
Rhinitis Combination (SPT ±; n=203)						
Rhinitis Alone (n=155)	**1.8***	**1.0, 3.2**	**1.8***	**1.0, 3.0**	**2.4****	**1.3, 4.5**
Rhinitis Plus 1 or 2 Allergic Diseases (n=48)	**5.4#**	**2.7, 11.0**	**2.7****	**1.3, 5.6**	**4.9#**	**2.2, 10.6**

‡ Internalizing Disorders: Internalizing Problems Composite Scale BASC-2 T score > 59

¶ Anxiety Disorders: Anxiety Subscale BASC-2 T score > 59

§ Depressive Disorders: Depression Subscale BASC-2 T score > 59

‖Rhinitis: positive parental response to modified ISAAC question at age 4 years ("*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?*")

‖Persistent Wheeze: recurrent wheeze (wheezing 2 or more times in the past 12 months regardless of cold) at age 4 years and one year prior
£Eczema: at age 4 years as frequent skin scratching for 6 months and one other symptom for 6 months: redness/red spots, raised bumps, or rough dry skin
¥Atopic Diseases: includes SPT+ rhinitis, SPT+ persistent wheeze, and SPT+ dermatitis at age 4 years
łAll diseases: rhinitis, persistent wheeze, and eczema regardless of SPT results
*P<0.05 **P<0.01 #P<0.001

Table 3. Adjusted Associations of Allergic Disease Predictors and Elevated Anxiety, Depressive, and Internalizing Disorders BASC-2 Scores At Age 7 Years. SPT+, Skin Prick Test Positive; SPT-, Skin Prick Test Negative; OR, Odds Ratio; CI, Confidence Interval.

Predictor Variables	Internalizing Disorders‡ (n=73)		Anxiety Disorders¶ (n=83)		Depressive Disorders§ (n=59)	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Rhinitis| (n=203)						
SPT + (n=119)	**3.2#**	**1.8, 5.8**	**2.0***	**1.2, 3.6**	**3.2#**	**1.7, 6.5**
SPT - (n=84)	**2.7****	**1.4, 5.3**	**2.2***	**1.2, 4.2**	**3.5#**	**1.7, 7.3**
Persistent Wheeze‖ (n=52)						
SPT + (n=29)	**2.7***	**1.2, 6.3**	-	-	2.3	0.9, 5.8
SPT - (n=23)	0.9	0.2, 3.0	-	-	0.9	0.2, 3.2
Atopic Diseases¥ (SPT+; n=147)						
1 Atopic Disease (n=106)	1.2	0.6, 2.3	1.1	0.6, 2.1	1.5	0.7, 2.9
2 or 3 Atopic Diseases (n=41)	**3.6#**	**1.7, 7.6**	**2.2***	**1.0, 4.7**	2.3	0.97, 5.6
All diseasesł (SPT ±; n=264)						
1 Allergic Disease (n=207)	1.4	0.8, 2.4	1.5	0.9, 2.6	**1.9***	**1.0, 3.6**
2 or 3 Allergic Diseases (n=57)	**4.0#**	**2.0, 8.0**	**2.5***	**1.2, 5.0**	**3.5****	**1.6, 7.7**
Rhinitis Combination (SPT ±; n=203)						
Rhinitis Alone (n=155)	**1.8***	**1.0, 3.3**	**1.9***	**1.1, 3.2**	**2.5****	**1.3, 4.9**
Rhinitis Plus 1 or 2 Allergic Diseases (n=48)	**5.2#**	**2.6, 10.8**	**2.5***	**1.2, 5.4**	**4.4#**	**1.9, 10.0**

Covariates include gender, parental asthma, maternal education, BMI, sleep disturbance.
‡ Internalizing Disorders: Internalizing Problems Composite Scale BASC-2 T score > 59
¶ Anxiety Disorders: Anxiety Subscale BASC-2 T score > 59
§ Depressive Disorders: Depression Subscale BASC-2 T score > 59
|Rhinitis: positive parental response to modified ISAAC question at age 4 years ("*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?*")
‖Persistent Wheeze: recurrent wheeze (wheezing 2 or more times in the past 12 months regardless of cold) at age 4 years and one year prior
¥Atopic Diseases: includes SPT+ rhinitis, SPT+ persistent wheeze, and SPT+ dermatitis at age 4 years
łAll diseases: rhinitis, persistent wheeze, and eczema regardless of SPT results
*P<0.05 **P<0.01 #P<0.001

Table 4. Unadjusted Association between Allergic Disease Predictors and Elevated Internalizing, Anxiety, and Depressive Disorders Continuous BASC-2 T-Scores at Age 7 Years. SPT+, Skin Prick Test Positive; SPT-, Skin Prick Test Negative.

Predictor Variables	Internalizing Disorders‡ (n=73)		Anxiety Disorders¶ (n=83)		Depressive Disorders§ (n=59)	
	β	p value	β	p value	β	p value
Rhinitis| (n=203)						
SPT + (n=119)	**2.8**	**0.006**	**2.7**	**0.01**	**2.4**	**0.01**
SPT - (n=84)	**2.9**	**0.01**	2.1	0.08	**2.8**	**0.01**
Persistent Wheeze‖ (n=52)						
SPT + (n=29)	**4.3**	**0.02**	2.0	0.3	3.4	0.06
SPT - (n=23)	2.8	0.18	0.5	0.8	0.9	0.6
Eczema£ (n=71)						
SPT + (n=45)	0.04	0.9	1.5	0.4	-1.3	0.4
SPT - (n=26)	-1.0	0.6	-1.8	0.4	1.2	0.5
SPT (n=341)						
Food SPT + (n=67)	1.4	0.3	1.7	0.2	1.4	0.3
Aeroallergen SPT + (n=274)	-0.03	0.9	-0.02	0.97	-0.1	0.9
>1 Atopic Disease¥ (SPT +; n=147)	**1.6**	**0.02**	**1.6**	**0.02**	1.1	0.09
> 1 Allergic Diseaseł (SPT ±; n=264)	**2.4**	**0.0002**	**1.9**	**0.005**	**1.9**	**0.001**
Rhinitis Plus 1 or 2 Allergic Diseases (SPT ±; n=203)	**3.2**	**<0.0001**	**2.6**	**0.0003**	**2.7**	**<0.0001**

‡ Internalizing Disorders: Internalizing Problems Composite Scale BASC-2 T score > 59

¶ Anxiety Disorders: Anxiety Subscale BASC-2 T score > 59

§ Depressive Disorders: Depression Subscale BASC-2 T score > 59

|Rhinitis: positive parental response to modified ISAAC question at age 4 years ("*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?*")

‖Persistent Wheeze: recurrent wheeze (wheezing 2 or more times in the past 12 months regardless of cold) at age 4 years and one year prior

£Eczema: at age 4 years as frequent skin scratching for 6 months and one other symptom for 6 months: redness/red spots, raised bumps, or rough dry skin

¥Atopic Diseases: includes SPT+ rhinitis, SPT+ persistent wheeze, and SPT+ dermatitis at age 4 years

łAllergic diseases: rhinitis, persistent wheeze, and eczema regardless of SPT results

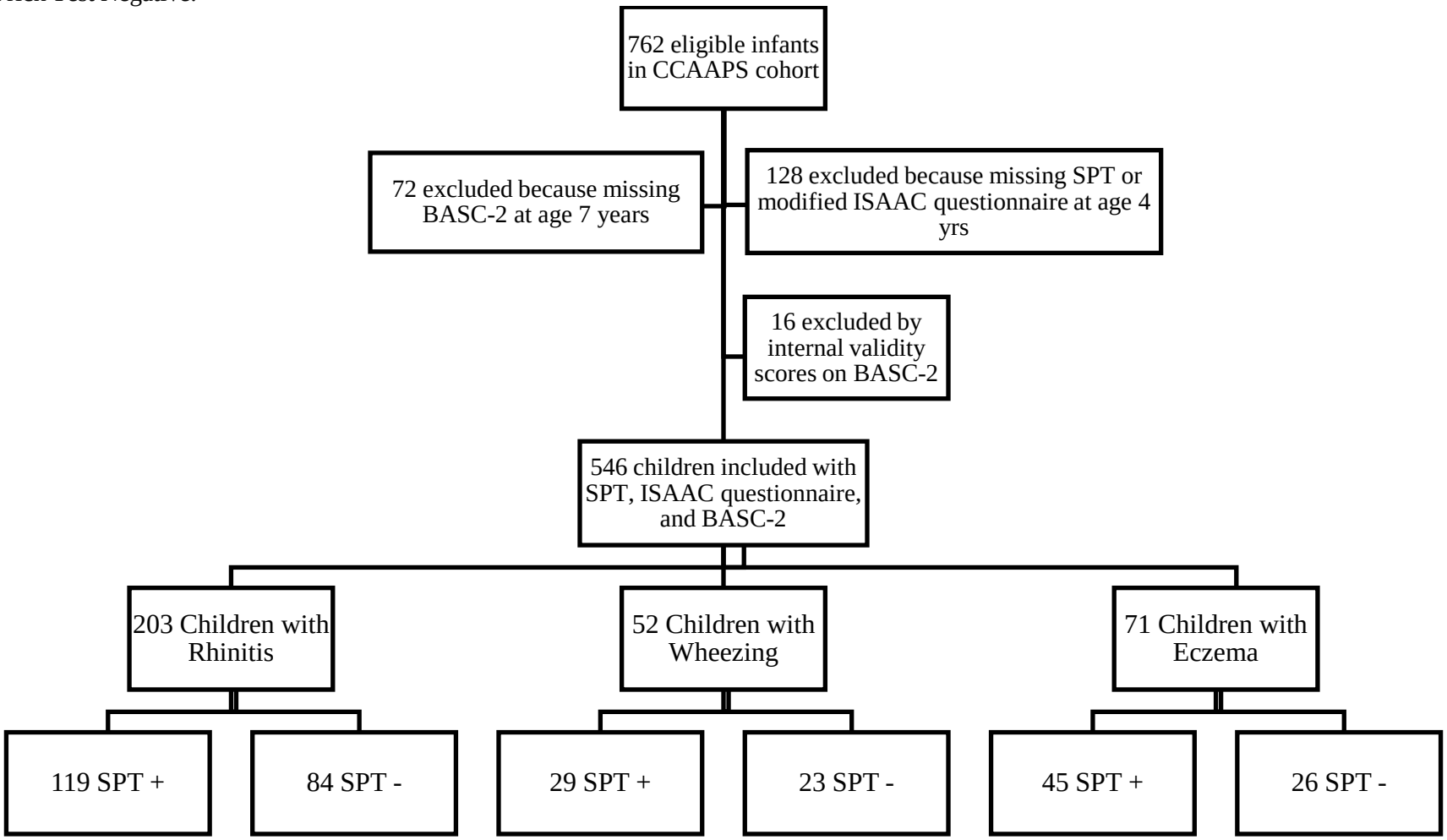
Table 5. Adjusted Associations Between Allergic Disease Predictors and Elevated Internalizing, Anxiety, and Depressive Disorders Continuous BASC-2 T-Scores At Age 7 Years. SPT+, Skin Prick Test Positive; SPT-, Skin Prick Test Negative.

Predictor Variables	Internalizing Disorders‡ (n=73)		Anxiety Disorders¶ (n=83)		Depressive Disorders§ (n=59)	
	β	p value	β	p value	β	p value
Rhinitis| (n=203)						
SPT + (n=119)	**2.7**	**0.01**	**2.7**	**0.01**	**2.1**	**0.03**
SPT - (n=84)	**3.3**	**0.007**	**-**	**-**	**3.1**	**0.005**
Persistent Wheeze‖ (n=52)						
SPT + (n=29)	**3.6**	**0.06**	**-**	**-**	**-**	**-**
SPT - (n=23)	**-**	**-**	**-**	**-**	**-**	**-**
>1 Atopic Disease¥ (SPT +; n=147)	**1.7**	**0.02**	**1.7**	**0.02**	**-**	**-**
> 1 Allergic Diseaseł (SPT ±; n=264)	**2.3**	**0.0003**	**2**	**0.004**	**1.8**	**0.003**
Rhinitis Plus 1 or 2 Allergic Diseases (SPT ±; n=203)	**3.2**	**<0.0001**	**2.6**	**0.0005**	**2.6**	**<0.0001**

Covariates include gender, parental asthma, maternal education, BMI, sleep disturbance.
‡ Internalizing Disorders: Internalizing Problems Composite Scale BASC-2 T score > 59
¶ Anxiety Disorders: Anxiety Subscale BASC-2 T score > 59
§ Depressive Disorders: Depression Subscale BASC-2 T score > 59
|Rhinitis: positive parental response to modified ISAAC question at age 4 years ("*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?*")
‖Persistent Wheeze: recurrent wheeze (wheezing 2 or more times in the past 12 months regardless of cold) at age 4 years and one year prior
¥Atopic Diseases: includes SPT+ rhinitis, SPT+ persistent wheeze, and SPT+ dermatitis at age 4 years
łAllergic diseases: rhinitis, persistent wheeze, and eczema regardless of SPT results

H. Figure

Figure 1. Study Population Grouping. CCAAPS, Cincinnati Childhood Allergy and Air Pollution Study; BASC-2, Behavioral Assessment System for Children 2nd edition; ISAAC, International Study of Asthma and Allergies in Childhood; SPT+, Skin Prick Test Positive; SPT-, Skin Prick Test Negative.



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