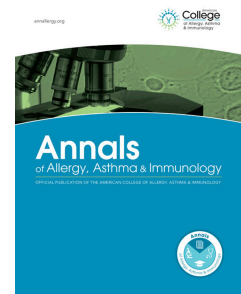


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Food Allergy in At- Risk Adolescents with Asthma: A Key Area for Focus

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Keywords: asthma, food allergy, adolescents, school based care, low income, minority health

Abbreviations: FEV1; forced expiratory volume in one second; FeNo; fractional excretion of nitric oxide;

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Background : Asthma affects more than 6.2 million children in the United States and is a major source of chronic disease burden. Concurrent food allergy may be a risk factor for worse asthma outcomes.

Objective: To estimate the prevalence of food allergy among a cohort of adolescents with persistent asthma and assess whether food allergy is an independent risk factor for asthma morbidity.

Methods: We included 342 adolescents aged 12 – 16 years with persistent asthma from the Rochester City School District, who were participants in the School Based Asthma Care for Teens (SB-ACT) trial between 2014 and 2018. Multivariable models were used to estimate the association between food allergy and asthma morbidity. **Results:** Overall, 29% of asthmatic adolescents reported having food allergy. While there were no statistically significant differences in daytime asthma symptoms, teens with food allergy had higher FeNO (47.5 vs 33.9 p=0.002) and reported more days with activity limitation due to asthma (3.1 vs 2.3 days/2 weeks, p=0.032) compared to teens without food allergy. Less than half (42%) of adolescents with food allergy had an epinephrine auto-injector.

Conclusion: Food allergy is common among this cohort of asthmatic adolescents. While food allergy was not related to asthma symptom severity, food allergic adolescents had higher FeNo and more activity limitation, and the majority did not have epinephrine auto-injectors. A history of food allergy and lack of epinephrine autoinjector may increase near fatal outcomes in adolescents with asthma. Preventive measures in addition to standard asthma treatments are warranted for these teens.

1 Introduction

2 Asthma is the most common chronic disease of childhood and is a persistent public health
3 problem. In the United States, asthma affects 8.6% of children.¹ Childhood asthma is associated
4 with significant morbidity and high rates of school absenteeism, particularly in minority children
5 and those of low socioeconomic status.² Food allergy (FA) is also a serious, potentially life
6 threatening disease with increasing prevalence presently estimated at approximately 8%.³ A
7 study using data from the National Health and Nutrition Examination Survey (NHANES) to
8 derive US population-based estimates of clinical FA reported an increased odds of FA among
9 Black people, males, and children. This investigation also highlighted that FA could be an under-
10 recognized risk factor for persistent and severe asthma.⁴ Of particular concern is the increased
11 morbidity and risk of mortality in adolescents both for asthma and FA individually, and
12 specifically in food allergic individuals with co-morbid asthma.

13 Adolescence is a period marked by cognitive, social, and behavioral change, with
14 increasing independence and responsibility. It is also a time when adherence to chronic illness
15 treatment may decrease, and adolescents with asthma are at particularly high risk for decreased
16 adherence to preventive medications.⁵ Adolescents are also at risk for severe food allergic
17 reactions. In a study assessing the prevalence of FA in the US, Gupta et al reported that the odds
18 of severe FA increased with increasing age in childhood.³ Importantly, adolescents have been
19 shown to be at increased risk of food-induced anaphylaxis if they delay administration of
20 epinephrine and/or have a diagnosis of asthma.^{6,7} Similarly, fatal food induced anaphylaxis is
21 most common among adolescents and young adults, and in a review of fatal food analysis
22 reported to the National Food Allergy Death Registry, the average age of patients was 18.⁷

FA and asthma are co-existent atopic conditions with potentially overlapping mechanisms. These conditions are associated with environmental and genetic factors, and risks for development are similar (parent or family history of allergy, atopic dermatitis, and allergic rhinitis). There have been a number of attempts to elucidate the biologic commonalities between FA and asthma. In a small study of risk factors of life-threatening asthma, more than half of children requiring intubation for asthma had food sensitization compared with other hospitalized children with non - life -threatening asthma.⁸ Asthma is also a risk factor for anaphylaxis and is associated with poor outcomes in children with FA.⁹ Interestingly, a study utilizing methacholine challenges before and after double-blind placebo-controlled food challenges reports that food-induced allergic reactions can increase airway reactivity, without inducing acute asthma.¹⁰ Results from these studies reinforce the hypothesis that FA and asthma may be more than co-existent atopic conditions and they may share similar pathogenic mechanisms.

The objectives of this study are to determine the prevalence of FA in a cohort of high-risk urban adolescents with persistent asthma participating in a school-based asthma trial, and to examine whether there is increased asthma morbidity among this cohort of adolescents with reported FA and asthma. We were particularly interested in exploring the experiences with FA in this cohort, as there are few studies including historically under-represented minorities in this age group. We hypothesized that in a cohort of adolescents with persistent asthma, FA may be an independent risk factor for asthma morbidity. In addition, we hypothesized that there may be modifiable risk factors, such as lack of epinephrine auto-injector for FA, which could lead to poor outcomes.

Methods:

Settings and participants

The School Based Asthma Care for Teens (SB-ACT) study is an ongoing randomized controlled trial (RCT) being conducted in Rochester, NY (ClinicalTrials.gov Identifier: NCT0220601). The study is designed to assess school-based directly observed therapy (DOT) of preventive asthma medications, including inhaled corticosteroids and combined inhaled corticosteroids and long acting beta agonists, paired with motivational interviewing, to promote medication adherence among young, Rochester city adolescents with persistent asthma. This study builds upon a previous study in younger children (age 3 -10) that demonstrated decreased asthma morbidity with directly observed preventative asthma medication monitoring in school.¹¹ Through collaboration with the Rochester City School District, adolescents 12-16 years of age were identified for initial eligibility screening through school medical alert forms. Inclusion criteria were physician-diagnosed asthma with persistent symptoms or poor control according to National Heart, Lung and Blood Institute Expert Panel (NHLBI) guidelines¹² and primary care physician agreement. Adolescents were excluded if they had a significant medical condition that could interfere with the assessment of asthma related measures (e.g., cystic fibrosis, congenital heart disease), if there was an inability to speak or understand English, and if the family had no access to a working phone. Randomization was stratified by school and preventive medication use at baseline. Adherence to controller medications was assured by the nurse on the days that the adolescents attend school, and encouraged on the days that the adolescents did not attend school. A FA questionnaire was added to the baseline study visit of the RCT, making this a cross sectional questionnaire study. The current analysis of the FA questionnaire included data from participants enrolled in the trial from November 2014 to August 2018. Analysis from the parent study has not been performed as it is ongoing. The parent randomized trial was approved by the

University of Rochester Institutional Review Board. Written informed consent was obtained from primary caregivers and assent was obtained from adolescents.

Data collection

After eligibility screening and informed consent were completed, an extensive baseline survey assessment was conducted in participant's homes. Baseline assessments included questions about asthma symptoms, family and health history variables, health care utilization, environmental exposures, and presence of reported FA. Standard variables known to influence asthma outcomes were also collected via study questionnaire, including self-reported demographic variables (adolescent and caregiver race, gender, ethnicity, insurance, caregiver's age and education level).

Food allergy questionnaire

At the baseline visit, an 18-item FA questionnaire was administered to participants and their caregivers (see supplement). FA questions were adapted from NHANES and other FA prevalence studies.^{3,13} The questionnaire assessed whether there was a history of physician-diagnosed FA, whether the allergy was current, which food(s) was implicated, and what symptoms were experienced upon ingestion of the food. The prevalence of self/caregiver reported FA was assessed by the question, 'Do you have any food allergies.' Research staff were trained and prompted participants in symptoms consistent with IgE – mediated FA reaction including the following: skin rash, hives, difficulty breathing, wheezing, swelling, itching of the eyes, mouth, throat, and skin. The research staff were also prompted to assess for current FA symptoms rather than remote symptoms. If the adolescents or caregivers answered 'yes' they were asked 'what foods are you currently allergic to?' with options to choose from common

allergens of cow's milk, eggs, wheat, peanut, tree nut, fish, shellfish, and other. Symptoms assessed were consistent with IgE-mediated food allergy, and included wheezing, hives, vomiting, diarrhea, trouble breathing, coughing, eczema, itching of the mouth, tongue, skin, anaphylaxis and low blood pressure. The questionnaire also asked whether blood tests, skin tests or challenge to the food were performed to diagnose FA. Unlike the NHANES evaluation of the prevalence of FA, although epinephrine use and history of serum specific IgE or skin prick testing were elicited, no formal records were obtained.

Adolescents and caregivers were asked about allergic rhinitis status with the question, 'does your teen have history of hay fever or allergies?' They were also asked about history of atopic dermatitis with the question 'do you/your teen have a history of eczema?'

Asthma symptoms

The primary outcome for the parent study was the mean number of asthma symptom free days over 2 weeks. This outcome measure has been widely used for symptoms monitoring in multiple asthma trials.¹⁴⁻¹⁷ Structured interviews provided information about the number of days with no asthma symptoms (including no coughing, wheezing, or shortness of breath) over the past two weeks. Adolescents and caregivers were also asked to identify the number of days the adolescent had any daytime symptoms, nighttime asthma symptoms, and rescue medication use to relieve symptoms over the past two weeks.

In addition, measurement of pulmonary function (using the PiKo-1 device for forced expiratory volume in 1 second (FEV1)), and fractionated exhaled nitric oxide was performed at baseline.

Health care utilization

Adolescents and caregivers were asked about health care utilization over the prior year. They were asked to identify visits to a doctor, subspecialists, emergency room, and hospital for any reason and also specifically due to asthma. Preventive (controller) and rescue asthma medication use was also assessed.

Statistical analysis

Frequency analyses were used to provide descriptive data on the population and to determine the prevalence of FA, allergic rhinitis, and atopic dermatitis within the sample. Unadjusted parametric tests were performed to assess differences between those with and without FA. Subsequently, linear and logistic regression analyses estimated the association between participant demographics and asthma symptoms and FA status. We included several adolescent and caregiver demographics, including adolescent age (continuous), sex (male/female), race (Black, white, other), ethnicity (Hispanic vs. non-Hispanic), insurance type (Medicaid or public insurance vs. other), and caregiver education ($\leq$ high school or $>$ high school). We also explored covariates that have previously been found to be associated with asthma and FA including history of atopic dermatitis and allergic rhinitis.¹⁸⁻²⁰ Finally, the association between FA status and asthma outcomes was assessed, adjusting for age, race, ethnicity, sex, caregiver marital status, income, insurance status, and exposure to environmental tobacco smoke.

Results

Characteristics of study participants

Descriptive statistics of participants are presented in **Table 1**. Overall, 387 adolescents were enrolled from November 2014 to August 2018 (participation rate 79%). For these analyses, we included 342 adolescents who completed questions about FA status (88% of the sample). A majority of the participants were male (55%), Black (55%), and were covered by Medicaid insurance (85%). Approximately 1/3 of the participants were Hispanic, more than half lived in a home with a smoker (55%), and 44% had a primary caregiver with a high school education or greater.

The prevalence of FA was 29% (95% CI 24.7-34.4). In comparing adolescents with and without reported FA, there were no differences in demographic characteristics except that those with reported FA were less likely to report Hispanic ethnicity than those without FA (22.8% vs. 34.4%, $p=.03$). Among adolescents with reported FA, 87.1% reported a history of allergic rhinitis compared to 70.5% without FA ($p = 0.001$), and 77.2% of adolescents with FA reported a history of eczema compared to 46.5% without FA ($p < 0.001$). **Table 1.**

Food allergy characteristics

Of the 101 adolescents with reported FA, shellfish allergy (38%) was the most prevalent, followed by peanut (34%), tree nut (30%), and fin fish (20%). Adolescents had the opportunity to describe other foods not listed, and the majority of responses included fruits, soy, and seeds. The most commonly reported symptoms of FA were hives (13%), swelling (13%), difficulty breathing (10%), wheezing (7%), coughing (4 %), vomiting (4 %) and diarrhea (2%). Anaphylaxis secondary to food ingestion was reported in 3% of adolescents. The majority of 'other' symptoms included itching and flushing. In subgroup analysis, the majority (85%) of adolescents with self – reported FA described ≥ 1 'convincing'³ FA symptoms including anaphylaxis, wheezing, trouble breathing, vomiting, hives, swelling, or low blood pressure.

Further, of the 101 adolescents with self - report of food allergy 62 % had a reported 'confirmed'³ FA with either physician ordered blood, skin prick test, or food challenge. A majority of the participants with reported FA did not have an epinephrine auto-injector (58%). There were few adolescents that reported carrying their epinephrine auto-injectors daily (13%), and (18%) reported that the school nurse had their epinephrine auto-injectors.

Food Allergy and Asthma Morbidity

Table 2 summarizes the primary outcomes in asthmatics reporting FA compared with those without FA. Overall, estimates of the odds of asthma morbidity in relation to FA were consistent with the null hypothesis. There was no statistically significant difference the primary outcome, mean symptom free days, among those with and without FA. Further, there was no difference in number of days with day or night time symptoms, or rescue medication use between the asthmatics with or without FA. Adolescents with FA did experience more days with activity limitation due to asthma within the prior two weeks compared to those without FA (3.1 vs 2.3 days/2 weeks, $p=0.032$) (**Table 2**). Although both groups had elevated levels, fractional excretion of nitric oxide was higher among those with FA (47.5 vs 33.9 $p=0.002$).

We used multivariable models to assess the independent association between FA and asthma morbidity outcomes. In a linear regression model adjusted for age of adolescent and caregiver, sex, race, ethnicity, smoke exposure, insurance status, caregiver marital status and household poverty, adolescents with reported FA had 0.97 ($p=0.02$) more days of activity limitation in a two week period due to asthma compared to those without FA. Further, those with reported FA had 1.64 times the odds of missing school due to asthma compared to those without FA (95 % CI 1.0 – 2.6) (Table 2).

Discussion

Asthma is the most common chronic disease in childhood and minorities are disproportionately affected.²¹⁻²³ This study assessed the relationship of reported FA and asthma morbidity among a diverse school-based cohort of adolescents with persistent asthma. We found a prevalence of 29% for self - reported FA in this group. In addition to asthma, those adolescents with FA also reported a very high rate of reported history of allergic rhinitis (87%) and atopic dermatitis (77%). While previous research has shown that having one atopic disease can predispose to another, this study prevalence of FA is higher than the often reported 3.5 – 8% worldwide prevalence of FA. Similar to the increased prevalence of reported FA in this cohort, other studies have also shown an increased prevalence of up to 45% of asthmatics having concurrent FA.²⁴ Having a diagnosis of both asthma and FA has been associated with disease severity,²⁵ yet the way that these entities interact and influence each other have yet to be fully elucidated. This study suggests that these adolescents with asthma are a highly atopic population with not only FA but several allergic comorbidities.

Previous studies of asthmatic school children have reported increased asthma morbidity among children with concomitant FA.²⁶ In this adolescent cohort, there was not a significant difference in reported asthma symptoms among those with FA compared with those without FA as per our primary outcome measure. However, we did find that those with FA and asthma had more missed school days and more activity limitation due to asthma compared to those without FA. We also found that those with FA had higher FeNO levels, which is similar to previous findings.²⁷ These results suggest increased burden from concomitant FA, allergic rhinitis and eczema, and this may have implications for overall poor asthma control in this population.

One explanation may include the possibility of under-reported or estimation of daily/nightly asthma symptoms. Friedlander et al reported increased daytime symptoms, decreased FEV1 and increased hospital admissions in inner-city elementary school children with both FA and asthma.²⁸ In a study of food sensitization of inner-city children with asthma enrolled in the National Cooperative Inner City Asthma Study (NCICAS), asthmatics with at least one food sensitization had increased corticosteroid use, ED visits and hospital admissions for asthma.⁴ The authors make the point that on the basis of their data, screening patients for FA should be considered in patients with moderate to severe asthma whose disease is not well controlled with standard asthma medications.⁴ This paper also concludes, as do we, that those with possible FA and reported IgE mediated FA symptoms may be at increased risk, and we should take this into consideration in those with moderate to severe asthma. In comparison to similar studies examining asthma morbidity among those with FA compared with those without FA, our study only included adolescents with persistent asthma, which may have limited our ability to find more differences in symptoms between groups.

Our findings regarding type of food allergies were consistent with those identified in prior inner-city cohorts. Shellfish and peanut were the most common reported allergens. In a study examining the differences in FA phenotype and health care utilization, peanut was the most common allergen reported among white, Black people and Hispanics, while Black people had higher rates of allergy to shellfish, fish, and corn.²⁹ Gupta et al reported the most common allergens to be peanut, followed by milk and shell fish in a prevalence study of FA among children within the US.³ Interestingly, in this report the odds of FA was higher among Asian and Black children, yet odds of confirmed FA lower among Asian, Black and Hispanic children versus white children.³ Mahdavinia and colleagues also reported that African Americans with FA

had significantly higher prevalence of comorbid asthma compared with whites, and the odds of atopic dermatitis were higher for both African American and Hispanic children.²⁹ Further exploration of this cohort showed that compared to whites, African Americans and Hispanics had higher rates of FA related anaphylaxis and emergency department visits.²⁹

As with other studies of FA, one major limitation is our use of self-report to ascertain FA status. The gold standard diagnosis of confirmation of FA is oral food challenge. In studies which utilize this resource, the general estimate of FA is often lower than self-reported rate or rates based on IgE sensitization.³⁰ We did perform sub-analysis given the limitations of self-report of FA, and found that the majority of adolescents had ‘convincing’ symptoms based on other prevalence studies.³ Nevertheless, in this study, FA may be over-estimated and non-differential misclassification of FA may have attenuated our estimate of FA and asthma morbidity outcomes. Other limitations of this study include possible recall and selection bias. Asthma outcome measures were also assessed via self-report of adolescents and caregivers. There is the possibility that both adolescents and caregivers either under or overestimate the burden of symptomatic disease. In addition, this study population, while similar in demographics to other inner city asthma cohorts, comprises only one urban area which could impact external validity.

Consistent with several prior reports, our study observed that only 42% of adolescents with reported FA had an epinephrine auto-injector. In addition, only 13% of these adolescents reported that they carried their epinephrine auto-injector daily and 18% of adolescents reported that the school nurse had their epinephrine auto-injectors for them. In addition to comorbid asthma, the low rate of possession of this life-saving medication is a risk factor for increased morbidity and mortality.⁷ Those at highest risk of anaphylactic reactions from FA are adolescents

with asthma.⁷ In a review of fatal anaphylactic reactions from foods, Pumphrey cites that among 48 food related anaphylactic deaths, the majority (26) was in an age distribution of 11 – 30 years.³¹ Explanations may include peer-pressure to consume allergic foods, low rates of carriage of epinephrine devices, risk-taking behavior in eating foods with known allergens, inability to recognize symptoms and the fact that the history of food allergic reaction may be a remote or mild one. New York State has a comprehensive anaphylaxis policy, and each RCSD school should have an adult and child dosed epinephrine auto- injector with a standing order for anyone in need to receive epinephrine. Despite these policies, it is unclear whether the adolescents in this cohort specifically disclosed their reported FA to the school nurse. This warrants further investigation.

School based asthma programs are powerful tools to improve care for high risk children with common chronic diseases. Our study harnesses the advantage of this setting, and highlights that this cohort has a high prevalence of multiple atopic conditions, including reported FA, allergic rhinitis and atopic dermatitis, in addition to poorly controlled asthma. The identification of reported significant atopy within this cohort provides the opportunity to develop comprehensive models to address these co-morbidities. Next steps include specialist evaluation, identification of specific sensitization patterns, confirmation of FA, and the development of comprehensive, community based treatment plans to address not only mechanisms of disease, but systemic factors that may place these children at risk.

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Table 1. Sample descriptive statistics

Independent variables	Analytic sample N=342	No food allergy N=241	Food allergy N=101	p-value
Adolescent characteristics				
Sex				0.28
Male	188 (55.0%)	137 (56.8%)	51 (50.5%)	
Age (years), mean (SD)	13.4 (1.3)	13.4 (1.3)	13.5 (1.3)	0.64
Race				0.21
White	15 (4.4%)	12 (5.0%)	3 (3.0%)	
Black	189 (55.3%)	126 (52.3%)	63 (62.4%)	
Other	138 (40.4%)	103 (42.7%)	35 (34.7%)	
Ethnicity				0.033
Hispanic	106 (31.0%)	83 (34.4%)	23 (22.8%)	
Medicaid coverage				0.64
Is on Medicaid	289 (84.8%)	202 (84.2%)	87 (86.1%)	
Allergic rhinitis (AR)				0.001
Yes AR	258 (75.4%)	170 (70.5%)	88 (87.1%)	
Atopic dermatitis (AD)				<0.001
No AD	152 (44.4%)	129 (53.5%)	23 (22.8%)	
Yes AD	190 (55.6%)	112 (46.5%)	78 (77.2%)	
Caregiver characteristics				
Age (years), mean (SD)	40.2 (8.1)	40.1 (8.1)	40.6 (8.3)	0.58
Marital status				0.82
Married	102 (29.8%)	71 (29.5%)	31 (30.7%)	
Educational attainment				0.23
High school graduate or less	193 (56.4%)	141 (58.5%)	52 (51.5%)	
Household poverty				0.66
At or below federal poverty line	204 (59.8%)	146 (60.6%)	58 (58.0%)	
Above federal poverty line	137 (40.2%)	95 (39.4%)	42 (42.0%)	
Cigarette smoke exposure at home				0.77
Smoker at home	187 (54.7%)	133 (55.2%)	54 (53.5%)	

Table 2. Asthma outcomes by food allergy status

Dependent variables	Analytic sample N=342	No food allergy N=241	Food allergy N=101	p-value	*Beta/ Adjusted p value
Continuous variables					
Number of symptom-free days in past 2 weeks, mean (SD)	8.7 (4.4)	8.7 (4.5)	8.7 (4.4)	0.93	-0.10* 0.85 (95 % CI -1.16-0.95)
Number of days with daytime asthma symptoms in past 2 weeks, mean (SD)	5.3 (4.4)	5.3 (4.5)	5.3 (4.4)	0.98	0.06* 0.91(95% CI -0.99 -1.12)
Number of days with nighttime asthma symptoms in past 2 weeks, mean (SD)	1.7 (3.2)	1.6 (3.1)	2.0 (3.5)	0.30	0.39* 0.31 (95% CI-0.37-1.15)
Number of days in past 2 weeks on which rescue medication was used, mean (SD)	2.3 (3.5)	2.3 (3.5)	2.2 (3.4)	0.94	0.02* 0.96 (95% CI -0.81 -0.85)
Number of days in past 2 weeks on which activity was limited, mean (SD)	2.5 (3.4)	2.3 (3.2)	3.1 (4.0)	0.032	0.97* 0.02 (95% CI 0.16-1.77)
FEV 1%, mean (SD)	86.4 (18.7)	86.5 (19.3)	86.1 (17.2)	0.85	0.22* 0.92 (95% CI -4.18-4.62)
FeNO ppb, mean (SD)	38.0 (37.4)	33.9 (34.1)	47.5 (43.0)	0.002	13.5* 0.003 (95% CI 4.73-22.3)
Dichotomous variables					
					aOR*/Adjusted p-value
Missed school due to asthma				0.055	1.64* 0.04 (95%1.01-2.66)
Did not miss any school due to asthma	173 (50.6%)	130 (53.9%)	43 (42.6%)		
Missed ≥1 school day due to asthma	169 (49.4%)	111 (46.1%)	58 (57.4%)		
ED visit due to asthma				0.92	1.10* 0.75 (95% CI 0.61-2.00)
No ED visits due to asthma	269 (79.4%)	190 (79.5%)	79 (79.0%)		
At least 1 ED visit due to asthma	70 (20.6%)	49 (20.5%)	21 (21.0%)		
Hospitalization due to asthma				0.36	1.88* 0.23 (95% CI0.67-5.27)
No hospitalization due to asthma	323 (94.7%)	230 (95.4%)	93 (93.0%)		

At least 1 hospitalization due to asthma	18 (5.3%)	11 (4.6%)	7 (7.0%)		
Urgent care visit due to asthma				0.99	1.03* 0.94 (95% 0.46-2.32)
No urgent care visit due to asthma	298 (89.8%)	210 (89.7%)	88 (89.8%)		
At least 1 urgent care visit due to asthma	34 (10.2%)	24 (10.3%)	10 (10.2%)		

Multivariate linear and logistic regression models adjusted for adolescent characteristics: race, ethnicity, sex, age, smoke exposure and insurance and caregiver characteristics: age, educational attainment, marital status, and household poverty.

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