Published in final edited form as:

Clin Exp Allergy. 2013 May ; 43(5): 544–551. doi:10.1111/cea.12069.

Age-dependent interaction between atopy and eosinophils in asthma cases: Results from NHANES 2005–2006

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Abstract

Background—Atopy is an established risk factor for asthma, and an elevated eosinophil level is a hallmark of atopic and non-atopic asthma. Whether atopy and eosinophils act independently or interact to influence asthma has clinical and public health implications.

Objective—To investigate the relationship between atopy and eosinophils in asthma.

Methods—Data on current asthma, atopy (IgE positive to 1 allergen), and blood eosinophil percent (dichotomized at the median) were obtained for persons aged 6 years from NHANES 2005–2006. Interaction on an additive scale was evaluated by estimating the prevalences of asthma for combinations of atopy (yes or no) and eosinophil percent (high or low) and calculating the excess prevalence due to interaction.

Results—For all ages combined, the adjusted prevalences of asthma were 4.6%, 7.6%, 6.9%, and 17.2% for persons with neither factor, atopy alone, a high eosinophil percent alone, and both factors, respectively. The excess prevalence of asthma due to interaction was 7.2%, indicating synergism. The excess prevalence was greatest in children aged 6–17 years (15.3%), and it decreased with each older age category until it was absent in adults aged 55 years (–0.2%). In children, 94% of asthma cases attributable to the 2 factors were attributable to their interaction, whereas in the oldest adults, no cases were attributable to their interaction.

Conclusions and Clinical Relevance—Interaction between atopy and an elevated eosinophil level in asthma cases was very strong in children but absent in the oldest adults, which suggests different mechanistic pathways for these factors by age and supports the notion that asthma is a heterogeneous disease. In addition, the age-dependent interaction between the factors has potential implications for the selection of asthma patients for treatments that would target either IgE or a high eosinophil level.

Keywords

Asthma; atopy; eosinophils; epidemiology; immunoglobulin E; survey

INTRODUCTION

Atopy, the genetic predisposition to develop IgE antibodies in response to allergen exposure [1], is an established risk factor for asthma incidence and severity. Although the amount of

asthma caused by atopy is debatable, estimates from the third National Health and Nutrition Examination Survey (NHANES) indicate that approximately half of current asthma cases in the U.S. are attributable to atopy [2]. The importance of IgE antibodies in the etiology of asthma led researchers to develop anti-IgE therapy, which is now being used to treat moderate to severe cases of atopic asthma. Eosinophils have also been implicated in asthma. Eosinophils, which are seen in increased numbers in the airways and peripheral blood of persons with atopic and non-atopic asthma, have been considered the principal effector cell in the pathophysiology of asthma [3–5]. In asthma, eosinophils migrate into the airways and release inflammatory proteins that directly damage the epithelium and cause the degranulation of basophils and mast cells [6]. Anti-IL-5 therapy has shown promise in the treatment of persistent eosinophilic asthma [7, 8].

Whether 2 or more risk factors act independently or interact to cause disease has implications for the understanding of causal mechanisms, assessment of disease risk, and development of efficient prevention strategies and effective treatments. In NHANES 2005–2006, allergen-specific IgE antibodies and eosinophil percent were measured in the peripheral blood of participants. The objective of this study was to investigate the relationship between atopy and elevated eosinophil levels in cases of asthma in a representative sample of the U.S. population.

METHODS

Data

This study analyzed public-use data from NHANES 2005–2006. NHANES, which is designed to assess the health and nutritional status of the civilian, noninstitutionalized, U.S. population, samples about 5000 persons each year. The National Center for Health Statistics (NCHS/CDC) releases data to the public in 2-year blocks. A detailed description of the NHANES 2005–2006 survey design and methods can be found online at <http://www.cdc.gov/nchs/nhanes.htm>. The survey was approved under Protocol #2005-06 by the NCHS Research Ethics Review Board.

Study Variables

Asthma—Current asthma, categorized as yes or no, was defined as a positive response to both of the following questions: “Has a doctor or other health professional ever told you that you have asthma?” and “Do you still have asthma?” A responsible adult provided information for participants < 16 years of age and for participants who could not self-report.

Atopy—Atopy, categorized as yes or no, was defined as at least 1 positive test for allergen-specific IgE antibodies. A positive test was defined as an IgE concentration ≥ 0.35 kU/L, the lower limit of detection. The NHANES tested participants ≥ 6 years of age for allergen-specific IgE antibodies to the following 15 aeroallergens and 4 foods: *Alternaria alternata*, *Aspergillus fumigatus*, Bermuda grass, birch, cat dander, cockroach (*Blattella germanica*), dog dander, dust mite (*Dermatophagoides farinae* and *D. pteronyssinus*, tested separately), mouse urine proteins, oak, ragweed, rat urine proteins, Russian thistle, rye grass, egg white, milk, peanut, and shrimp. The classification of atopy for this analysis was limited to participants ≥ 6 years of age who had results for the full panel of 19 allergens. Younger persons were excluded because participants under age 6 years were tested with a smaller panel of only 9 allergens and the diagnosis of asthma is difficult to establish in early childhood.

Eosinophil percent—Eosinophil percent—the percentage of white blood cells that are eosinophils—was dichotomized as low (at or below the median) and high (above the

median) to facilitate the analysis, interpretation, and presentation of 2- and 3-way interactions. In addition to eosinophil percent, NHANES reported eosinophil number (1000 cells per μL), which NHANES derived from white blood cell number (1000 cells per μL) and eosinophil percent. The eosinophil number variable had only 26 distinct values from 0.0 to 3.8, compared to 176 distinct values for eosinophil percent, and 72% of the population ≥ 6 years of age had eosinophil number values ≥ 0.2 . Therefore, eosinophil percent, which has a much wider range of values, was selected for the primary analysis. However, secondary analyses were conducted with eosinophil number.

Covariables—The results were adjusted by age categories (6–17, 18–40, 41–54, and ≥ 55 years), sex, race-ethnicity (Mexican American, non-Hispanic white, non-Hispanic black, and all others), and time of blood draw (morning, afternoon, and evening), which were significant predictors of current asthma in the regression models that produced the final adjusted results. Two other covariables—education level of the household reference person (a 5-level categorical variable defined by NHANES) and serum cotinine levels (categorized into quartiles)—were not significant predictors of current asthma and were dropped from the regression models. In a backward selection procedure, education left the full model containing main effects and an interaction term between atopy and eosinophil percent at $P = .54$, and cotinine left the model at $P = .20$.

Statistical Analyses

Analysis population—In the database, 8412 participants were ≥ 6 years of age, and of those, 8086 were seen in the mobile examination center (2-year Mobile Examination Center sample weight WTMEC2YR > 0), where blood samples were collected. Of the 8086, 27 had missing values for asthma, 818 had missing values for atopy, and 675 had missing values for eosinophil percent (637 of the 675 were missing values for both atopy and eosinophil percent, presumably because of uncollected blood or insufficient blood volumes for those assays). Analyses were conducted on the 7207 participants ≥ 6 years of age who had complete information on current asthma, atopy, and eosinophil percent, which was 86% of the 8412 participants ≥ 6 years of age.

Evaluation of interaction—Interaction was evaluated on an additive scale by the following equation, which, according to Rothman, is the most fundamental epidemiologic measure of interaction:

$$I(AB) = R(AB) - R(A\bar{B}) - R(\bar{A}B) + R(\bar{A}\bar{B}) \quad (1)$$

where $I(AB)$ is the excess risk of disease due to the interaction between risk factors A and B and R is the risk of disease for the given combination of A and B (the overscore represents absence of the factor) [9]. The statistic $I(AB)$ is equal to 0 when there is no interaction, greater than 0 when there is synergism, and less than 0 when there is antagonism.

For this analysis, prevalence, which is the risk of being a disease case as opposed to the risk of becoming a disease case, was substituted for R in Equation 1, and atopy and eosinophil percent were factors A and B , respectively. A categorical variable consisting of the 4 combinations of atopy absent or present and eosinophil percent low or high was created and analyzed in unadjusted and adjusted logistic regression models of current asthma. Unadjusted and adjusted prevalences of current asthma for the 4 combinations of atopy and eosinophil percent were estimated from the PREDMARG statement in the SUDAAN logistic regression procedure. The statistic $I(AB)$ was estimated and tested as being different from 0 by the PRED_EFF contrast statement in the SUDAAN logistic procedure. Age-stratified prevalences reported in Table 2 were generated from a logistic regression model

containing an interaction term between age (categorical) and the 4-level atopy-eosinophil variable.

In addition to $I(AB)$, the synergy index (S) and the proportion of cases attributable to A and B that is attributable to their interaction [$AP(AB)$] were estimated from the following equations defined by Rothman [9]:

$$S = \frac{R(AB) - R(\overline{AB})}{[R(\overline{A}B) - R(\overline{A}\overline{B})] + [R(\overline{A}B) - R(\overline{A}\overline{B})]} \quad (2)$$

$$AP(AB) = \frac{S - 1}{S} \quad (3)$$

The synergy index is equal to 1 in the absence of interaction, greater than 1 for synergism, and less than 1 for antagonism. The attributable proportion, $AP(AB)$, which is a continuous measure bound by 0 and 1, is 0 when A and B act independently (no interaction) and 1 when A and B interact without independent effects. Equation 3 is not applicable to antagonistic effects, i.e., when S is less than 1. Although Equation 3 will return a value for an antagonistic effect, that value will be less than 0, the lowest theoretical value. Any negative value should be interpreted as 0.

Finally, the absolute effects (attributable risk) of atopy alone and a high eosinophil percent alone, shown in Figure 2, were calculated by subtracting the prevalence of current asthma for non-atopics with a low eosinophil percent (the background prevalence) from the asthma prevalence for atopics with a low eosinophil percent and from the asthma prevalence for non-atopics with a high eosinophil percent. In the absence of interaction, the expected prevalence of current asthma among persons with both factors is the sum of the absolute effect of atopy alone, the absolute effect of a high eosinophil percent alone, and the background effect. The excess prevalence of current asthma due to interaction is the observed prevalence of current asthma among persons with both factors minus the expected prevalence of current asthma among persons with both factors.

Statistical software—All statistics were generated in SUDAAN (Release 10.0.1, SAS-Callable, RTI International, Research Triangle Park, N.C.). The sample weight variable WTMEC2YR was used in all analyses to obtain nationally representative statistics. The survey design variables SDMVSTRA and SDMVPSU were used to adjust the variances for the complex survey design. Statistical significance was $P < .05$.

RESULTS

Distribution of Eosinophil Percent

For persons ≥ 6 years of age with non-missing information on atopy and current asthma ($N = 7207$), the median eosinophil percent was 2.4. The arithmetic and geometric means for eosinophil percent were 3.01 ($SE = 0.037$) and 2.45 ($SE = 0.036$), respectively. The geometric mean differed by the period of the day when the blood sample was collected: 2.61 for morning ($n = 3406$), 2.29 for afternoon ($n = 2537$), and 2.34 for evening ($n = 1264$) ($P < .01$). Figure 1 shows the continuous distribution of eosinophil percent stratified by age, atopy, and asthma. The median eosinophil percent was 2.7, 2.2, 2.3, and 2.6 for the 4 consecutive age groups, respectively. The median was higher for atopics than non-atopics (2.7 versus 2.2) and for persons with current asthma than those without current asthma (3.1 versus 2.3).

Prevalence of Atopy and Asthma

The unadjusted prevalences of atopy and asthma were 44.6% and 8.8%, respectively (Table 1). The prevalence of atopy was highest in the 18–40 year-old age group, and the prevalence of asthma was highest in the 6–17 year-old age group (Table 1). Atopy and asthma were more common among persons with a high eosinophil percent than a low eosinophil percent, and asthma was more common among atopics than non-atopics (Table 1).

Interaction between Atopy and Eosinophil Percent

All age categories combined—Among the population 6 years of age and older, 31.3% (SE = 0.91) were non-atopics with a low eosinophil percent, 18.9% (SE = 0.91) were atopics with a low eosinophil percent, 24.1% (SE = 0.79) were non-atopics with a high eosinophil percent, and 25.7% (SE = 0.50) were atopics with a high eosinophil percent. The adjusted prevalence of current asthma for non-atopics with a low eosinophil percent—the background prevalence—was 4.6% (Table 2 and Figure 2, All Ages). Compared to this background prevalence, the adjusted prevalence of current asthma was moderately yet significantly elevated for atopics with a low eosinophil percent (7.6%) and for non-atopics with a high eosinophil percent (6.9%). However, among persons with both factors, the adjusted prevalence of current asthma was high (17.2%), and it was significantly higher than would be expected in the absence of interaction. On an additive scale, the expected prevalence was 9.9%, and with an observed prevalence of 17.2%, the excess prevalence due to interaction was 7.2%. This excess prevalence due to interaction was significantly greater than 0, indicating synergism on an additive scale. The synergy index was 2.3 (> 1 indicates synergism), and among persons with both exposures, 57% of the cases attributable to atopy and a high eosinophil percent were attributable to the interaction. The unadjusted results, shown in Table 2, were very similar to the adjusted results.

Differences by age—Significant differences in the interaction between atopy and eosinophil percent were found between age categories (Table 2, Figure 2). From the youngest to the oldest age group, the adjusted excess prevalence of current asthma due to interaction decreased from 15.3% to –0.2% ($P < 0.01$ for linear trend), the synergy index decreased from 16.6 to 1.0 (1 indicates no interaction), and the proportion of cases attributable to the interaction among cases attributable to the 2 factors decreased from 94% to –3% (–3% should be interpreted as 0%, see Methods). The excess prevalence of current asthma due to interaction was significantly different from 0 for the younger 2 age groups but not for the older 2 age groups, and the asthma prevalences for atopy alone and a high eosinophil percent alone were statistically different from the baseline prevalence for the oldest age group only (Table 2, Figure 2). These results indicate a transition with increasing age from a strong synergistic interaction without independent effects to only independent effects. The unadjusted age-stratified results, shown in Table 2, were very similar to the adjusted results.

In a secondary analysis, the serum cotinine variable was forced into the adjusted logistic regression model (P value for cotinine was 0.20). From that model, the excess prevalences due to interaction were 15.2%, 10.7%, 3.7%, and –0.6% for the 4 consecutive age groups, essentially the same results as the adjusted results presented in Table 2.

Eosinophil Number

In a secondary analysis, eosinophil number (1000 cells/ μ L), dichotomized as low and high (<0.2 and ≥ 0.2 ; prevalence of high = 58.5%, SE = 0.96), was substituted for eosinophil percent in the adjusted all-age and age-stratified models. The all-age prevalences of current asthma for the 4 combinations of atopy and eosinophil number (non-atopic, low number; atopic, low number; non-atopic, high number; and atopic, high number) were 4.9% (SE =

0.72), 7.4% (1.01), 6.3% (0.41), and 16.1% (1.29), respectively. The excess prevalence due to interaction between atopy and eosinophil number was 7.3% (SE = 1.89, $P < .01$), which is essentially the same value reported for the analysis with eosinophil percent (7.2%, SE = 2.06, $P < .01$). The excess prevalences due to interaction across the 4 categories of increasing age were 13.8% (SE = 3.75, $P < .01$), 11.8% (SE = 1.87, $P < .01$), 4.3% (SE = 5.77, $P = .47$), and -0.9% (SE = 2.68, $P = .73$), respectively. These results, which are similar to the results reported for eosinophil percent in Table 2, indicate synergism between atopy and eosinophil number for the younger 2 age groups and not for the older 2 age groups.

DISCUSSION

This study of the U.S. population aged 6 years and older found a significant synergistic interaction on an additive scale between atopy and an elevated eosinophil level in current asthma. The interaction, however, was not homogeneous across age categories. Analyses of increasing age categories showed a transition from essentially complete interaction between the factors to complete independence (no interaction). Statistically significant synergism was present only for the age categories 6–17 and 18–40 years.

The examination of independence and departures from independence on an additive scale can provide insight into causal mechanisms or pathways. Independence between risk factors implies that the factors act through separate pathways and can cause disease in the presence or absence of each other [9]. Interaction between risk factors implies that the factors act jointly in one or more common pathways and that all of the factors must be present for disease to occur through their common pathways [9]. The results of this study suggest that in children, atopy and a high eosinophil level act jointly through at least one common causal pathway, whereas in the oldest adults, the 2 risk factors act independently through separate pathways. From NHANES data, it was not possible to identify those mechanistic pathways, so we can only speculate about what those pathways may be.

Both atopy and eosinophils are linked biologically to T_H2 cytokines, and T_H2 cytokines have been implicated in the etiology of asthma [6], so it would seem likely that a T_H2 -mediated pathway would be at least one common pathway through which the 2 factors interact in children and younger adults to influence asthma. In response to an inhaled allergen, T_H2 cells produce the cytokines IL-4, IL-5, and IL-13, as well as other mediators [6]. IL-4 and IL-13 signal B cells to produce IgE antibodies that bind allergen to mast cells, causing those cells to release pro-inflammatory mediators within the airways [6]. IL-5 stimulates the release of eosinophils from bone marrow into the circulation and prolongs their survival [6]. Eosinophils migrate into the airways and release inflammatory proteins, such as major basic protein, which can directly damage airway epithelium, intensify bronchial responsiveness, and cause degranulation of basophils and mast cells [6]. Therefore, T_H2 cell activation by allergen can lead to elevated levels of allergen-specific IgE and eosinophils and to IgE- and eosinophil-mediated inflammation in the airways. The results from this study imply that in children, for reasons that are not clear, the presence of both IgE and an elevated eosinophil level are required for such a pathway to cause disease. Perhaps age-related differences in the maturity of the immune system or the responsiveness of airways to the immune system determine whether only one or both factors are required.

The striking difference in synergism between atopy and eosinophils by age supports the notion that asthma is a heterogeneous disease. A study by Miranda *et al.* examined phenotypic differences between early-onset (before age 12 years) and late-onset (after age 12 years) asthma among a group of 80 severe asthmatics with and without eosinophil inflammation [10]. That study found that subjects with early-onset asthma had a higher prevalence of atopy (98% versus 76%) and more allergic symptoms, among other

characteristics. More importantly, the investigators reported that in early-onset eosinophilic disease, there were high numbers of CD3+ lymphocytes, mast cells, and chymase+ mast cells, consistent with a T_H2 pattern of inflammation, whereas in late-onset eosinophilic disease, there was no evidence for an associated T_H2 pattern of inflammation, even though 76% of the subjects with late-onset asthma were atopic. In addition, they reported that persons with late-onset asthma without eosinophilic inflammation had minimal inflammation, the lowest numbers of mast cells, and no subepithelial basement membrane thickening, which the authors stated may represent infection or gastroesophageal reflux. In NHANES, the youngest and the oldest age groups, with a median age at asthma diagnosis of 4.6 years and 45.8 years, respectively, likely represent early- and late-onset asthma (although it is not beyond the realm of possibility that the difference in age at diagnosis between the groups reflects changes in clinical practice or health-care utilization over time rather than differences in age at onset). NHANES results appear consistent with the findings by Miranda *et al.* of T_H2-mediated disease in early-onset but not late-onset asthma.

The strong interaction between atopy and eosinophils in children and the absence of such an interaction in the oldest adults have potential implications for treatment. As shown in Figure 2, for the youngest age group, atopy in the absence of a high eosinophil level and a high eosinophil level in the absence of atopy contributed to very few asthma cases over and above the background level; however, when the two factors were present together, they accounted for a large number of asthma cases. This observation suggests that in an asthmatic child with atopy, a treatment that targets atopy, such as an anti-IgE therapy, would have a low probability of success unless the child also has a high eosinophil level. Likewise, in an asthmatic child with a high eosinophil level, a treatment that targets eosinophils, such as anti-IL-5 therapy, would have a low probability of success unless the child is also atopic. In contrast to children, there was no interaction in the oldest age group between atopy and eosinophils. Atopy and a high eosinophil level contributed to significant numbers of asthma cases independent of each other. Therefore, in older adults with asthma, a treatment that targets atopy could be implemented without regard to the levels of eosinophils, and a treatment that targets high levels of eosinophils could be implemented without regard to atopy. Obviously, these inferences about treatment would have to be confirmed in a clinical trial before being implemented, and effective therapies specific for atopy and high eosinophil levels would have to be developed.

The primary limitation of this study is that the results are based on associations between atopy, eosinophils, and asthma observed in a cross-sectional survey. The statistical methods used in the analyses assume a cause-effect relationship between the risk factors and asthma, and the presence of atopy and a high eosinophil level before the onset of asthma cannot be established in these data. An analysis of data from a prospective study of asthma development is needed to confirm these findings.

In conclusion, findings from this cross-sectional study provide evidence of important roles for atopy and an elevated serum eosinophil level in current asthma. Significant differences in the interaction between the factors by age suggest that the mechanistic pathways through which these factors influence asthma differ by age and support the contention that childhood and adult asthma may not be the same disease. Finally, the strong interaction between atopy and eosinophils in children and the absence of such an interaction in the oldest adults have potential implications for the selection of asthma patients for treatments that target either IgE or a high eosinophil level.

Acknowledgments

The authors are appreciative of Theresa Scocca, PhD (Rho, Inc., Chapel Hill, NC), who reviewed a draft of the article and provided useful edits and comments. This research was supported in part by the National Institute of Allergy and Infectious Diseases under contract number HHSN2722010000521. None of the authors has a financial relationship with a biotechnology or pharmaceutical manufacturer that has an interest in the subject matter or materials discussed in the submitted manuscript.

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Figure 1.

Distribution of eosinophil percent (5th, 25th, 50th, 75th, and 95th percentiles) in the U.S. population aged 6 years and older, stratified by age categories, atopy, and current asthma. Above each group of boxplots is the *P* value for a test of any difference between eosinophil percent means (log₁₀ transformed data).

Figure 2.

Adjusted prevalences of current asthma for combinations of atopy absent (A-) or present (A+) and eosinophil percent low (E-) or high (E+). The unweighted sample size for a given atopy-eosinophil combination is shown below its column. The asterisk (*) signifies a significant difference in asthma prevalence between that column and the A-E- column ($P < .05$). The dagger (†) signifies that the excess prevalence due to interaction is significantly different from 0 ($P < .05$), indicating interaction on an additive scale.

Table 1

U.S. prevalences of a high eosinophil percent, atopy, and current asthma among persons aged 6 years and older

Variable	Unweighted N	Unadjusted Percent (SE)		
		High Eosinophil Percent (> 2.4)	Atopy	Current Asthma
Total	7207	49.8 (0.79)	44.6 (1.14)	8.8 (0.54)
Age in years				
06–17	2333	56.1 (2.30)	47.0 (1.38)	12.0 (0.85)
18–40	2248	45.7 (0.95)	51.8 (1.82)	8.0 (0.84)
41–54	1010	46.7 (1.49)	42.4 (1.24)	8.6 (1.27)
55	1616	53.9 (1.36)	34.9 (1.69)	7.9 (0.84)
Eosinophil percent				
Low (≤ 2.4)	3689	--	37.6 (1.65)	5.7 (0.58)
High (> 2.4)	3518	--	51.6 (1.08)	11.9 (0.80)
Atopy				
Yes	3480	57.6 (1.16)	--	12.6 (0.96)
No	3727	43.4 (1.14)	--	5.7 (0.43)
Current Asthma				
Yes	645	67.2 (2.35)	63.9 (1.82)	--
No	6562	48.1 (0.87)	42.7 (1.28)	--

Note: All bivariate comparisons shown in the table were statistically significant at $P \leq 0.05$

Table 2

Prevalence of current asthma for combinations of atopy (absent or present) and eosinophil percent (low or high) and measures of interaction between atopy and a high eosinophil percent

Age in Years		Percent (SE) with Current Asthma				Measures of Interaction		
		Non-atopic, Low Eosinophil	Atopic, Low Eosinophil	Non-atopic, High Eosinophil	Atopic, High Eosinophil	Prevalence (% SE) due to interaction	Synergy Index	Attributable Proportion [§]
All	Unadjusted	4.8 (0.74)	7.4 (0.97) [‡]	7.0 (0.43) [‡]	16.5 (1.45) [‡]	6.8 (2.09) [‡]	2.4	.58
	Adjusted [*]	4.6 (0.71)	7.6 (0.98) [‡]	6.9 (0.45) [‡]	17.2 (1.53) [‡]	7.2 (2.06) [‡]	2.3	.57
6–17	Unadjusted	7.3 (1.61)	7.5 (1.74)	7.5 (1.36)	21.6 (1.92) [‡]	13.9 (2.97) [‡]	34.6	.97
	Adjusted [*]	7.4 (1.70)	7.8 (1.74)	8.0 (1.48)	23.7 (2.24) [‡]	15.3 (3.25) [‡]	16.6	.94
18–40	Unadjusted	3.7 (0.73)	5.6 (1.13)	5.6 (1.30)	16.7 (2.30) [‡]	9.3 (2.52) [‡]	3.5	.71
	Adjusted [*]	3.7 (0.69)	5.8 (1.15)	5.7 (1.34)	18.6 (2.44) [‡]	10.8 (2.44) [‡]	3.6	.72
41–54	Unadjusted	4.8 (1.62)	9.4 (1.99)	7.1 (1.89)	15.0 (2.78) [‡]	3.2 (3.76)	1.5	.31
	Adjusted [*]	4.6 (1.55)	9.3 (2.01)	7.0 (1.80)	15.5 (2.88) [‡]	3.7 (3.84)	1.5	.34
55	Unadjusted	4.4 (0.86)	9.3 (2.00) [‡]	7.9 (1.07) [‡]	12.5 (2.70) [‡]	−0.3 (3.36)	1.0	−.03
	Adjusted [*]	3.9 (0.78)	8.9 (2.02) [‡]	7.2 (0.98) [‡]	11.9 (2.60) [‡]	−0.2 (3.18)	1.0	−.03

^{*} Adjusted for age (in All Ages model only), sex, race-ethnicity, and time of blood draw

[‡] Significantly different from corresponding value in the non-atopic, low eosinophil percent column at *P* .05

[‡] Prevalence due to interaction is significantly different from 0 at *P* .05, indicating interaction on an additive scale

[§] Proportion of cases attributable to atopy and a high eosinophil percent, among the jointly exposed, that is attributable to their interaction