

Age: An Effect Modifier of the Association Between Allergic Rhinitis and Otitis Media With Effusion

Rachel E. Roditi, MD; Maria Veling, MD; Jennifer J. Shin, MD, SM

Objectives/Hypothesis: 1) To determine whether there is a significant relationship between allergic rhinitis and otitis media with effusion (OME), Eustachian tube dysfunction (ETD), or tympanic membrane retraction (TMR) in children in a nationally representative population; and 2) to determine whether age is an effect modifier of any such association because this hypothesis has yet to be tested.

Study Design: Retrospective analysis of cross-sectional national databases with limited potential for referral bias.

Setting and Subjects: National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey, 2005–2010.

Methods: Univariate, multivariate, stratified, and subgroup analyses were performed as defined a priori. The primary outcomes were OME, ETD, or TMR; the primary predictor variable was allergic rhinitis, with age evaluated as an effect modifier.

Results: Data representing 1,491,045,375 pediatric visits were examined and demonstrated that age was an effect modifier of the assessed association. More specifically, in children 6 years of age or older, the presence of allergic rhinitis significantly increased the odds of OME, ETD, or TMR (odds ratio [OR] 4.20; 95% confidence interval [CI] 2.17, 8.09; $P < 0.001$), whereas in children less than 6 years of age there was no significant association (OR 1.13; 95% CI 0.53, 2.46; $P = 0.745$).

Conclusion: Age is an effect modifier of the association between allergic rhinitis and OME; a significant relationship is observed in children 6 years of age and older, whereas there is no significant association in younger children.

Key Words: Otitis media with effusion, eustachian tube dysfunction, tympanic membrane retraction, allergic rhinitis, age, effect modifier, national database.

Level of Evidence: 2c.

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INTRODUCTION

Otitis media with effusion (OME) is a highly prevalent condition¹ that may have a significant impact on hearing, development, and quality of life. It exists along a spectrum of pathology that includes Eustachian tube dysfunction (ETD) and tympanic membrane retraction (TMR). These related conditions may result in discomfort, diminished quality of life, hearing loss, and speech manifestations—and are among the leading causes for surgical intervention.^{2–10}

Additional Supporting Information may be found in the online version of this article.

From the Harvard Medical School (R.E.R., J.J.S.), Boston, Massachusetts; and the University of Texas Southwestern Medical Center (M.V.), Dallas, Texas, U.S.A.

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Send correspondence to Jennifer J. Shin, MD, SM Department of Otolaryngology, Harvard Medical School, Boston, MA 02115.
E-mail: jennifer_shin@meei.harvard.edu

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Allergic rhinitis is the most common chronic disease in the United States today, affecting one out of 6 Americans.^{11,12} The role of allergy in the pathophysiology of OME remains a topic of debate¹³; the observed prevalence of allergic rhinitis in patients with chronic OME may be higher than that of the general population^{14,15} but varies widely, ranging from 16.3% to 89%, depending on the cohort and diagnostic criteria considered.^{13,16} Such wide variations, along with limited sample sizes and potential referral bias in many studies to date, make these results difficult to generalize.¹³ In addition, if allergic rhinitis truly causes OME, then suppressing allergy would be expected to improve OME, but meta-analyses show no benefit from antihistamines.¹⁷ Thus, the underlying impact of allergic rhinitis on middle ear health remains unclear.

In situations where the literature demonstrates such a broad range of seemingly incongruous results, it raises the question of whether there may be an additional related variable that has not been adequately studied. A variable that is an effect modifier has the capacity to alter whether there is a significant association between two conditions, as well as the strength and direction of any association that does exist. We thus considered whether age might be an effect modifier that alters the relationship between allergic rhinitis and OME such that there could be a significant association in one age group but no association in another.

TABLE IA. Baseline Characteristics in Children With and Without Otitis Media with Effusion, Eustachian Tube Dysfunction, or Tympanic Membrane Retraction.				
	OME/ETD/TMR Absent		OME/ETD/TMR Present	
	1,475,835,668		15,209,707	
Total (visit number)	Point Estimate	95% CI	Point Estimate	95% CI
Age (mean, years)	7.3	7.2, 7.4	4.8	4.3, 5.3
Sex (percent male)	51.3	50.7, 52.0	57.3	52.9, 61.6
Race (percent)				
Non-Hispanic white	61.9	59.2, 64.5	77.5	70.8, 83.1
Non-Hispanic black	14.1	12.4, 15.9	10.1	6.2, 16.3
Hispanic	18.3	15.8, 21.1	8.8	5.7, 13.2
Asian	4.5	3.8, 5.3	2.6	1.6, 4.2
Pacific Islander	0.3	0.2, 0.4	0.1	0.0, 0.3
American Indian/Alaska Native	0.5	0.4, 0.7	0.3	0.1, 0.8
Multiple races	0.5	0.4, 0.6	0.6	0.1, 2.9
Visit Location (percent)				
Emergency department	12.5	11.6, 13.5	2.4	1.7, 3.2
Additional Conditions (percent)				
Allergic rhinitis	2.6	2.3, 3.0	5.7	3.3, 9.8
Systemic and Other Allergic and Atopic Conditions	0.4	0.4, 0.5	0.3	0.1, 1.3
Asthma	3.7	3.3, 4.2	1.8	0.7, 4.2
Upper Respiratory Tract Infection	8.7	8.2, 9.3	8.5	5.9, 12.1
Nonallergic Rhinitis and Sinusitis	3.5	3.2, 3.8	6.1	3.8, 9.6

Given the ongoing debate regarding the role of allergy in middle ear disease and the broad range of concomitant prevalence reported from differing practice sites, as well as the proposed hypothesis that age could be an effect modifier, our objectives were: 1) to determine whether there is a significant relationship between allergic rhinitis and OME, ETD, or TMR in a nationally representative population; and 2) to determine whether age is an effect modifier of any such association.

MATERIALS AND METHODS

This study utilized data from the National Ambulatory Medical Care Survey (NAMCS) and the National Hospital Ambulatory Medical Care Survey (NHAMCS). Briefly, NAMCS describes outpatient visits to office-based physicians, while NHAMCS describes visits to hospital emergency and outpatient departments. National Ambulatory Medical Care Survey uses a three-stage probability sample of nonfederal, office-based physicians, whereas NHAMCS uses a four-stage probability sample to represent provision of ambulatory care services in hospital emergency and outpatient departments. These datasets are appended through previously described techniques, and the National Center for Health Statistics supports combining them as a means to improve reliability of estimates.^{18,19} Application of visit weights generates estimates representative of all ambulatory care visits in the United States; the National Center for Health Statistics assigns each visit its own individual weight, facilitating weighted analysis across years, setting types, and the two databases.^{20–22} Both surveys are conducted annually by the National Center for Health Statistics, and full descriptions of the databases are available online.^{23–25} We applied sampling weights throughout to obtain correct standard errors based on

the complex survey design. As recommended by the National Center for Health Statistics, we considered reliable the estimates based on more than 30 observations or those with a standard error of < 30% of the point estimate.

The planned protocol was reviewed by the Partners Institutional Review Board, who deemed the deidentified data exempt from oversight. The study population was restricted to the pediatric population, as defined by age less than or equal to 18 years. These visits occurred between 2005 and 2010. The primary outcomes of interest were OME, ETD, or TMR; the primary predictor variable of interest was allergic rhinitis. The proposed effect modifier of interest was age. Conditions analyzed as potential confounders were nonallergic rhinitis and sinusitis, upper respiratory tract infection, asthma, and other allergic and atopic condition. We defined the outcome and predictor variables, as well as potential confounding comorbidities, based on International Classification of Diseases, Ninth Revision (ICD-9) codes (supporting information Appendix 1). Data from the combined NAMCS and NHAMCS databases were utilized to test for associations among all variables; age and diagnoses were tracked in both databases and the measured variables are standardly available in both.

Univariate logistic regression was performed for the primary outcome and predictor variables, followed by multivariate logistic regression. Variables beyond those considered primary predictors, and the proposed effect modifier were selected for inclusion in the multivariate logistic regression model if the univariate assessment demonstrated a *P* value < 0.1. Subsequent sensitivity and subgroup analyses were planned a priori and performed to evaluate the impact of allergic rhinitis specifically on OME alone, as well as the impact of age 6 years or older. This age was selected as the point at which the diagnosis of allergic rhinitis has often solidified through confirmation

TABLE IB.
Baseline Characteristics in Children Stratified by Age.

Total (visit number)	Age < 6 Years		Age ≥ 6 Years	
	706,652,626		784,392,749	
	Point Estimate	95% CI	Point Estimate	95% CI
OME/ETD/TMR (percent of visits)	1.4	1.2, 1.7	0.6	0.5, 0.8
Sex (percent male)	53.7	52.8, 54.6	49.3	48.4, 50.3
Race (percent)				
Non-Hispanic white	57.7	54.6, 60.8	66.0	63.5, 68.4
Non-Hispanic black	14.1	12.3, 16.1	13.9	12.2, 15.8
Hispanic	21.8	18.8, 25.1	15.0	12.9, 17.5
Asian	5.1	4.4, 6.0	3.9	3.2, 4.7
Pacific Islander	0.3	0.2, 0.4	0.2	0.2, 0.3
American Indian/Alaska Native	0.5	0.3, 0.6	0.5	0.4, 0.7
Multiple races	0.5	0.4, 0.7	0.4	0.3, 0.5
Visit Location (percent)				
Emergency department	12.2	11.1, 13.4	12.6	11.8, 13.6
Additional Conditions (percent)				
Allergic rhinitis	1.9	1.5, 2.3	3.3	2.9, 3.8
Systemic and other allergic and atopic conditions	0.3	0.3, 0.5	0.5	0.4, 0.6
Asthma	3.2	2.8, 3.7	4.1	3.6, 4.6
Upper Respiratory Tract Infection	12.2	11.4, 13.0	5.6	5.1, 6.1
Nonallergic Rhinitis and Sinusitis	3.2	2.9, 3.6	3.8	3.4, 4.2

CI = confidence interval; ETD = Eustachian tube dysfunction; OME = otitis media with effusion; TMR = tympanic membrane retraction.

with available allergy testing²⁶; prior to this age, rhinitis is not only common but has a heterogeneous etiology, which may be difficult to specifically characterize.²⁷ Age was evaluated as a potential effect modifier through a stratified analysis, stratifying on age greater than or equal to 6 years of age versus age less than 6 years of age. A multivariate analysis was also performed, which incorporated an interaction term between allergic rhinitis and age greater than 6 years. Potential confounding diagnoses and protocols for subgroup and stratified analyses were defined a priori, as described above. Basic demographic information was also tabulated, including patient age, sex, and race/ethnicity. All analyses were performed at the 5% significance level using STATA 13.0 (College Station, TX).

TABLE II.

Univariate Analysis of the Impact on Otitis Media With Effusion, Eustachian Tube Dysfunction, or Tympanic Membrane Retraction

	OR	SE	95% CI	P Value
Age*	0.92	0.01	0.91, 0.94	<0.001
Age ≥ 6†	0.45	0.06	0.35, 0.56	<0.001
Male sex	1.27	0.12	1.06, 1.52	0.009
Nonwhite race/ethnicity	0.70	0.06	0.60, 0.83	<0.001
Allergic rhinitis	2.27	0.67	1.27, 4.03	0.005
Other allergic conditions	0.72	0.52	0.18, 2.97	0.654
Asthma	0.47	0.21	0.19, 1.14	0.131
Upper respiratory tract infection	0.97	0.20	0.65, 1.44	0.888
Nonallergic rhinitis and sinusitis	1.78	0.45	1.08, 2.91	0.021

*Describes age as a continuous variable.

†Describes age as a dichotomous variable, with age <6 as the underlying referent.

CI = confidence interval; OR = odds ratio; SE = standard error.

RESULTS

During the study timeframe there were 133,968 observations meeting our inclusion criteria. After application of visit weights, this represents 1,491,045,375 pediatric visits. Baseline demographic characteristics are shown according to OME/ETD/TMR status in Table IA and according to age in Table IB.

Univariate Analyses

Univariate analysis revealed a significant positive association between OME/ETD/TMR when allergic rhinitis was diagnosed (OR 2.27; 95% CI 1.27, 4.03; $P = 0.005$). There was also a significant association with nonallergic rhinitis and sinusitis (OR 1.78; 95% CI 1.08, 2.91; $P = 0.021$). There was no statistically significant association with the concurrent diagnosis of upper respiratory tract infection, other allergy conditions, or asthma (Table II).

The direct impact of age was also evaluated through univariate analysis. The risk of OME/ETD/TMR was lessened with increasing age, whether it was considered as a dichotomous (age ≥ 6 years; OR 0.45; 95% CI 0.35, 0.56; $P < 0.001$) or continuous variable (OR 0.92; 95% CI 0.91, 0.94; $P < 0.001$). Increasing age was significantly negatively associated with OME specifically, whether age was evaluated as a dichotomous (age ≥ 6 years; OR 0.35; 95% CI 0.24–0.50; $P < 0.001$) or continuous variable (OR 0.90; 95% CI 0.88, 0.93; $P < 0.001$). In contrast, older age was significantly positively associated risk of allergic rhinitis, whether age was considered as a dichotomous (age ≥ 6 years; OR 1.80; 95% CI 1.50, 2.16;

TABLE III.

Stratified Multivariate Analysis of the Association between Allergic Rhinitis and Otitis Media With Effusion, Eustachian Tube Dysfunction, or Tympanic Membrane Retraction

	OR	SE	95% CI	P Value
Children 6 Years of Age and Older				
Allergic rhinitis	4.20	1.41	2.18, 8.10	0.000
Male sex	1.39	0.23	1.00, 1.93	0.047
Nonwhite race/ethnicity	0.72	0.08	0.58, 0.90	0.003
Nonallergic rhinitis and sinusitis	1.58	0.89	0.52, 4.77	0.420
Children Less Than 6 Years of Age				
Allergic rhinitis	1.14	0.45	0.53, 2.46	0.745
Male sex	1.14	0.13	0.91, 1.43	0.253
Nonwhite race/ethnicity	0.66	0.07	0.54, 0.82	0.000
Nonallergic rhinitis and sinusitis	1.77	0.47	1.06, 2.98	0.030

CI = confidence interval; OR = odds ratio; SE = standard error.

$P < 0.001$) or a continuous variable (OR 1.04; 95% CI 1.02, 1.05; $P < 0.001$).

Age as an Effect Modifier

Based on the proposed hypothesis regarding age as a potential effect modifier (i.e., age may alter the strength and direction of an association between allergic rhinitis and the middle ear conditions studied), we next performed a stratified multivariate analysis. These data showed that in children 6 years of age or older, the presence of allergic rhinitis significantly increased the odds of OME/ETD/TMR (OR 4.20; 95% CI, 2.18, 8.10; $P < 0.001$) (Table III); however, in children less than 6 years of age, there was no longer a significant association (OR 1.14; 95% CI 0.53, 2.46; $P = 0.745$) (Table III).

We then performed a multivariate analysis incorporating an interaction term to evaluate further whether age altered the impact of allergic rhinitis on OME/ETD/TMR. These data confirmed the results of this stratified analysis; when allergic rhinitis occurred in the setting of age of at least 6 years, the odds of OME/ETD/TMR were

TABLE IV.

Multivariate Analysis of the Association Between Allergic Rhinitis and Otitis Media With Effusion, Eustachian Tube Dysfunction, or Tympanic Membrane Retraction

	OR	SE	95% CI	P Value
Allergic rhinitis	1.14	0.45	0.53, 2.47	0.740
Age $\geq$ 6 years old	0.38	0.05	0.30, 0.49	0.000
Allergic rhinitis-age $\geq$ 6 interaction	3.68	1.60	1.57, 8.62	0.003
Male sex	1.22	0.11	1.02, 1.46	0.027
Nonwhite race/ethnicity	0.68	0.06	0.57, 0.81	0.000
Nonallergic rhinitis and sinusitis	1.70	0.44	1.03, 2.81	0.039

CI = confidence interval; OR = odds ratio; SE = standard error.

TABLE V.

Multivariate Analysis of the Association Between Allergic Rhinitis and Otitis Media With Effusion Only

	OR	SE	95% CI	P Value
Allergic rhinitis	0.91	0.42	0.37, 2.27	0.848
Age $\geq$ 6 years old	0.32	0.06	0.22, 0.45	0.000
Allergic rhinitis-age $\geq$ 6 interaction	2.65	1.28	1.02, 6.85	0.044
Male sex	1.20	0.14	0.95, 1.51	0.122
Nonwhite race/ethnicity	0.73	0.07	0.59, 0.89	0.002
Nonallergic rhinitis and sinusitis	1.96	0.64	1.04, 3.71	0.038

CI = confidence interval; OR = odds ratio; SE = standard error.

significantly elevated (OR 3.68; 95% CI 1.57, 8.62; $P = 0.003$, interaction term) (Table IV), whereas allergic rhinitis in younger children was not predictive.

Otitis Media With Effusion

We then did a subgroup analysis to determine whether age was an effect modifier of the impact of allergic rhinitis on OME specifically. The related multivariate model incorporating interaction terms furthered the results of this stratified analysis. In children at least 6 years of age, there was a significantly increased association between allergic rhinitis and OME specifically (OR 2.65; 95% CI 1.02, 6.85; $P = 0.044$, interaction term) (Table V), whereas allergic rhinitis in younger children was not significantly associated.

DISCUSSION

These nationally representative data demonstrate that there is a significant positive association between OME and allergic rhinitis in children 6 years of age or older, whereas no significant association is seen in younger children. Thus, age is an effect modifier of the impact of allergic rhinitis on OME.

By definition, an effect modifier changes the impact of an exposure on an outcome,^{28,29} which means that the presence or absence of an effect modifier may alter the strength and significance of an association between two variables. These data, for example, show that there is a significant association between OME and allergic rhinitis when age is at least 6 years, but the association dissipates when age is less than 6 years.

Because such associations may change based on the presence or absence of an effect modifier, if individual analyses do not consider it, there may be a resulting population of results that seems contradictory or occurs over a wider range than might be expected. Studies of subjects who have the effect modifier may show a significant positive association, whereas reports of patients without the effect modifier show no such association. To the unversed eye, it may then seem that the literature on the topic is simply a quagmire of divergent results. When the effect modifier is ultimately considered in a subsequent overarching analyses, however, it reveals a distinct pattern.

Consider, for example, prior publications regarding OME and allergic rhinitis. This literature is mixed, with some reports showing a significant positive association between OME and allergy,^{30,31} whereas others support no consistent association.³² When these prior studies are reviewed with our current findings in mind, it becomes apparent that multiple studies demonstrating a link between OME and allergy were conducted in older children (i.e., 5–9 years of age),^{30,31} whereas separate reports showing an inconsistent relationship were derived from studying younger children.³² Accounting for age as a key effect modifier in future studies may help elucidate some of the variation in the existing literature.

Otitis media with effusion is anticipated to resolve as children age, but related middle ear problems persist in a subset of children, even beyond the time frame when the anatomic challenges of the shorter, more horizontal eustachian tube should have resolved.³³ It is possible that these older children with lingering disease have a discrete pathophysiology. Prior studies have concluded that older children respond to surgical intervention differently according to age.³⁴ Similarly, children who have an ongoing need for repeat tube insertion after 6 years of age have demonstrated specific risk factors, including asthma.³⁵ This respiratory condition has a known association with allergy; among those who have allergic rhinitis, up to 38% also suffer from asthma.³⁶

Epidemiological data is clearly different than drug response data, and demonstrating this age-dependent association does not itself establish cause for systemic therapy directed at allergy, even in older children. Data from systematic review and meta-analysis of randomized controlled trials suggests that antihistamines are not beneficial and have an 11% risk of adverse effects.¹⁷ Studies included in this analysis enrolled subjects spanning the ages of 6 months to 15 years, and it is currently unclear whether stratification by age would affect these results. The impact of montelukast on middle ear effusion has been investigated with mixed results,^{37–39} although data with regard to age-specific effects are similarly lacking.

Proposed mechanisms for the association between allergic rhinitis and OME include allergic inflammation in the respiratory epithelium at the entrance and within the Eustachian tube with subsequent dysfunction.^{33,40} Additional studies analyzing the middle ear mucosa and effusion in patients with OME have demonstrated higher levels of eosinophils, T lymphocytes, eosinophil cationic protein, tryptase, mast cell peroxidase, and expression of IL-4 and IL-5 in atopic compared to nonatopic individuals.^{16,41} These studies suggest that the middle ear mucosa could be involved by an allergic reaction, as suggested by the unified airway concept.⁴²

The databases utilized in the present study cannot follow patients longitudinally because each year's data represents a cross-sectional survey. This property leads to additional considerations in the analysis, particularly for transient conditions. For example, if a patient develops an upper respiratory tract infection that subsequently blossoms into an OME that lingers for 3 months, then a cross-sectional study may have difficulty linking these two conditions. Early in that patient's

course, the patient would be positive for upper respiratory tract infection only. Midway through that course, the patient would be positive for both. In the later part of that course, the patient would remain with OME only. Given that OME may linger far longer than the typical upper respiratory tract infection, there may be more recorded instances in which OME is present, but its relationship to the inciting upper respiratory tract infection is not apparent. In addition, these databases do not permit tracking of allergy testing procedures or their results, and inclusion of this information to supplement the clinician diagnoses would have been ideal.

Data collected in cross-sectional surveys also cannot inherently prove a directional causal relationship. At the same time, although it may be proposed from these data that OME could be causative of allergic rhinitis, this effect physiologically seems less likely than the proposed reverse relationship. Also, because the diagnosed conditions cannot subsequently result in an alteration in age, there is also a clear demonstration of an age-dependent effect on the association between allergic rhinitis and OME. Another limitation of cross-sectional studies is that they may not be ideal for low-incidence diagnoses; fortunately, both allergic rhinitis and middle ear disease are conditions with high prevalence. This study is limited in that diagnoses are defined according to ICD-9 code, a process that may not perfectly reflect the patient's true disease state. Such coding also does not capture the severity or duration of disease. It also may be subject to any expectation bias inherent to the providers who select the codes; if physicians are more likely to assume that rhinitis is allergic rather than nonallergic in the setting of OME, then it could also affect the results. Diagnosis coding is, however, available across these large national level datasets that span the gamut of treatment sites and provider types, minimizing the potential for referral bias in these data. Referral bias may occur when patients who enter a study environment are distinct from the affected population at large.^{43,44} For example, patients referred to specialty practices may have a higher prevalence or severity of disease. Fortunately, studying a large population that spans multiple types of settings minimizes that potential.

CONCLUSION

Age is an effect modifier of the association between allergic rhinitis and OME. A significant relationship is observed in children 6 years of age and older, whereas there is no association in younger children. Future studies focused on OME, allergic rhinitis, and related therapies should evaluate the impact of this effect modifier through analysis of age-stratified groups.

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Appendix 1. Diagnosis Codes

Diagnosis	ICD-9 Codes
Otitis media with effusion	381.0, 381.02, 381.03, 381.04, 381.05, 381.06, 381.10, 381.19, 381.20, 381.29, 381.30, 381.40
Eustachian tube dysfunction	381.5, 381.51, 381.52, 381.60, 381.61, 381.62, 381.63, 381.7, 381.8, 381.81, 381.89, 381.9
Tympanic membrane retraction	385.10, 385.11, 385.12, 385.13, 385.19
Allergic rhinitis	477.0, 477.1, 477.2, 477.8, 477.9
Non-allergic rhinitis and rhinosinusitis	472.0, 460.0, 784.91 461.9, 461.2, 461.1, 461.0, 461.3, 461.8, 473.4, 473.5, 473.6, 473.0, 473.1, 473.2, 473.3, 473.7, 473.9, 473.8
Systemic and other allergic conditions	995.0, 995.1, 995.3, 708.0
Upper respiratory tract infection	460.0, 465.0, 465.8 465.9
Asthma	493.1, 493.2, 493.3, 493.4, 493.5, 493.6, 493.7, 493.8, 493.9