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Infant rhinitis and watery eyes predict school-age exercise-induced wheeze, emergency department visits and respiratory-related hospitalizations

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ABSTRACT

Background: Rhinitis and conjunctivitis are often linked to asthma development through an allergic pathway. However, runny nose and watery eyes can result from nonallergic mechanisms. These mechanisms can also underlie exercise-induced wheeze (EIW), which has been associated with urgent medical visits for asthma, independent of other indicators of asthma severity or control.
Objective: To test the hypothesis that rhinitis or watery eyes without cold symptoms (RWWC) in infancy predict development of EIW and urgent respiratory-related medical visits at school age, independent of seroatopy.
Methods: Within a prospective birth cohort of low-income, urban children (n = 332), RWWC was queried during the first year of life. Relative risks (RRs) for EIW, emergency department (ED) visits, and hospitalizations for asthma and other breathing difficulties at 5 to 7 years of age were estimated with multivariable models. Seroatopy was determined at 7 years of age.
Results: Infant RWWC was common (49% of children) and predicted school-age EIW (RR, 2.8; $P < .001$), ED visits (RR, 1.8; $P = .001$), and hospitalizations (RR, 9.8; $P = .002$). These associations were independent of infant wheeze. They were also independent of birth order, an indicator of increased risk of exposure to viruses in infancy, and infant ear infections, an indicator of sequelae of upper airway infections. The association between infant RWWC and ED visits at 5 to 7 years of age was attenuated (RR, 1.2; $P = .23$) when EIW at 5 to 7 years of age was included in the model, suggesting EIW mediates the association. Adjustment for seroatopy did not diminish the magnitudes of any of these associations.
Conclusion: These findings suggest a nonallergic connection between infant nonwheeze symptoms and important consequences of urban respiratory health by school age through EIW.
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Introduction

Rhinitis and conjunctivitis are risk factors for subsequent asthma development, a connection that has been considered to occur primarily through an allergic pathway.[1–3] However, nonallergic pathways, such as parasympathetic nervous system stimulation, can also cause rhinorrhea, lacrimation, and bronchial reactivity. Exercise-induced bronchoconstriction, the process that underlies exercise-induced wheeze (EIW), occurs in 5% to 15% of the general population[4,5] and 40% to 90% of the asthmatic population.[6] EIW is thought to be related to parasympathetic nerve stimulation by osmotic cellular changes or airway cooling.[7–10] Therefore, rhinitis, watery eyes, and EIW may share these physiologic responses that are independent of an allergic pathway.

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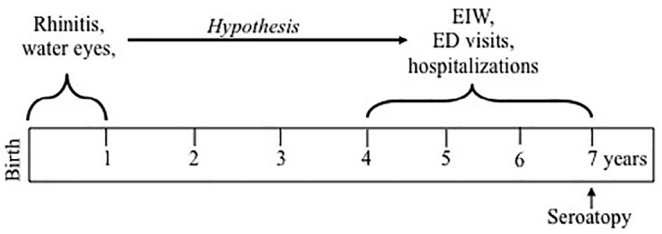

Figure 1. Overview of study measurements and hypothesis. ED, emergency department; EIW, exercise-induced wheeze.

EIW is considered both a distinct phenotype of asthma and a symptom common among individuals with poorly controlled asthma.[11–14] Previously, among middle-income children with asthma living in New York City, we observed an association between EIW and urgent medical visits for asthma.[15] Strikingly, this association was independent of established markers of asthma severity and control, including lower lung function and greater frequency of asthma symptoms, potentially linking an EIW phenotype to acute-onset exacerbations that lead to urgent medical visits.[15] Furthermore, we found that EIW was more common among children with asthma living in neighborhoods with greater asthma emergency department (ED) visits and hospitalizations, suggesting that EIW could offer some explanation for the excesses in these burdens affecting children living in lower-income neighborhoods.[15,16]

Identifying early-life predictors for school-age EIW development could help us better understand the early life causes of EIW and identify children who would benefit from interventions to prevent future ED visits and hospitalizations. Using a well-established, prospective birth cohort study of children born in low-income New York City neighborhoods with a high asthma prevalence, we tested our hypothesis (Fig 1) that rhinitis and/or watery eyes without cold symptoms (RWWC) in the first year of life would be associated with subsequent development of EIW and ED visits and hospitalizations for asthma and other breathing difficulties at 5 to 7 years of age, independent of allergic sensitization and infant wheeze.

Methods

As part of the Columbia Center for Children's Environmental Health study, 727 nonsmoking (confirmed by cotinine), pregnant African American or Dominican women aged 18 to 35 years who were free of hypertension, diabetes, and known human immunodeficiency virus and who were living in Northern Manhattan and the South Bronx were enrolled between 1999 and 2006.[17–19] The children were followed up prospectively. This study obtained ethics approval from Columbia University's Institutional Review Board. Mothers gave informed written consent, and starting at 7 years of age, children gave assent before taking part in this study.

Questionnaires

Questionnaires administered prenatally, during the third trimester, and postnatally at 3, 6, 9, and 12 months included queries about the mother and child's environmental exposures and child symptoms, including the following: rhinitis without cold ("Does your child ever get attacks of sneezing or runny nose other than from colds?"), watery eyes without cold ("Does your child ever get attacks of runny or itchy eyes other than from colds?"), and wheeze ("In the past 3 months, has your child had wheezing or whistling in the chest?"). A child was considered to have had RWWC or wheeze in the first year of life if the mother reported at least one episode on one of the questionnaires pertaining to that year. At ages 5, 6, and 7 years, EIW and other respiratory outcomes in the previous 12 months were ascertained using the International Study of Asthma and Allergies in Childhood questionnaire.[20,21]

A previously described Brief Respiratory Questionnaire was used to ascertain ED visits and hospitalizations for asthma or other breathing problems in the previous year using the following questions[22]: ED visits ("In the last 12 months, how many times did your child have an emergency visit to a doctor, clinic, or an emergency room for asthma, wheezing, cough, bronchitis, or other breathing problems?") and hospitalization for asthma or other breathing problems ("In the last 12 months, how many times did your child have to stay overnight in the hospital for asthma, wheezing, cough, bronchitis, or other breathing problems?").

Seroatopy Measurement

Allergen specific IgE was measured by ImmunoCap (Phadia, Uppsala, Sweden) in serum collected in patients aged 7 years. Seroatopy was defined as specific IgE to dust mite, cockroach, mouse, cat, dog, trees, grass pollen, ragweed pollen, or mixed mold allergens (≥0.35 IU/mL).

Statistical Analysis

Analyses were restricted to children who had at least one questionnaire completed for the first year of life and for 1 year between the ages of 5 and 7 years and who had serum IgE measured at the age of 7 years. For testing our hypothesis, symptoms in the first year of life were tested as predictors of asthma outcomes at 5 to 7 years of age. For prospective and cross-sectional analyses, respectively, relative risks (RRs) and prevalence ratios (PRs) with 95% confidence intervals (CIs) were calculated using binomial regressions in generalized estimating equations. Models included a priori determined potential confounders: age, sex, race/ethnicity, income, maternal asthma, material hardship, and presence of a smoker in the home. To assess the independence of these associations from an allergic sensitization pathway, seroatopy was tested in models to determine whether its inclusion diminished the magnitude of the association between symptoms in infancy and respiratory outcomes at school age by 10% or more. We conducted similar analyses testing for the independence from having older siblings as an indicator of increased risk of exposure to viruses in infancy and infant ear infections as an indicator of sequelae of upper-airway infections in infancy. Mediation of the association between infant RWWC and ED visits at ages 5 to 7 years by EIW at 5 to 7 years of age was assessed by including EIW at 5 to 7 years of age in the model.

We conducted analyses to confirm the association we had observed between EIW and urgent medical visits in a middle-income cohort in this lower-income cohort.[15] Given the study design, we also used the ability to examine the association prospectively and extended our outcomes to 9 years of age (to examine risk associated with EIW at 7 years of age). Analyses were restricted to the children from the main hypothesis with asthma symptoms or medication use in the past 12 months, as we did previously in our investigation of EIW and urgent medical visits among middle-income children in New York City.[15] Prospective analyses were conducted using repeated-measures models (individuals had repeated time points) using binomial regressions in generalized estimating equation models. EIW at 5 and/or 7 years of age (time 1) was tested as a predictor of ED visits and hospitalizations 2 years later (7 and/or 9 years of age, time 2). If children had data at 5, 7, and 9 years, they were included twice in the repeated-measures model. Similar confounders tested with the main hypothesis were included, as well as ED visits and hospitalizations at time 1. Analyses were conducted using SPSS statistical software, version 23 (SPSS Inc, Chicago, Illinois), and visualized in R version 3.03.

Results

The demographics of the families included in the study (n = 332) are given in Table 1. The children included in the analyses did not differ in demographics from those recruited for the Columbia Center for Children's Environmental Health study but not included in the analyses because of missing data (n = 395), except that mothers who reported being of African American race were more likely than those of Dominican Republic ethnicity to be in the analyses (eTable 1). Importantly, the prevalence of runny nose without colds, watery eyes without colds, and wheeze in the first year of life were similar among the children included in the analyses and those not included but on whom we had symptoms data in the first year of life (eTable 1).

The reports of wheeze and RWWC were common in the first year of life (Fig 2A). Although there was overlap between children with these symptoms, a substantial proportion of the children had a report of RWWC without a report of wheeze (23% of cohort). Similarly, although there was overlap between the children with a report of runny nose and watery eyes, there was some discordance in these symptoms (eFig 1). Almost all children (325 of 332 [98%]) had a report of runny nose symptoms *with* a cold in the first year of life compared with 109 of 332 (32%) who had a report of runny nose symptoms *without* a cold. In multivariable models that assessed risk factors for RWWC, only having an older sibling was statistically significantly associated with RWWC (PR, 1.3; 95% CI, 1.1–1.7; $P = .02$). Race/ethnicity, male sex, having a mother with asthma, having a report of material hardship, and living in a home with a smoker in the first year of life were not statistically significantly associated with RWWC (all $P > .05$). We also evaluated potential indoor combustion sources related to household heating and cooking. Most homes were heated with a radiator (91%) and had a gas stove (96%). Neither of these variables were statistically significantly associated with RWWC in infancy ($P > .80$).

Table 1
Demographics of the 332 Study Participants at Birth

Demographic	Finding[a]
Male sex	155 (46.7)
Mother's age, mean (SD), y	25.3 (4.9)
Mother's race/ethnicity	
African American[b]	134 (40.4)
Dominican[b]	198 (59.6)
Asthma[c]	85 (25.6)
Maternal allergy[d]	138 (41.6)
Sociodemographics	
No high school degree[e]	118 (36.5)
Receiving Medicaid	304 (91.6)
Material hardship last 6 months[f]	139 (41.9)
Domestic environment	
Smoker in home[g]	122 (36.7)
Cockroach sightings in home	240[h] (72.7)
Rodent sightings in home	175[h] (53.0)

[a]Data are presented as number (percentage) of participants unless otherwise indicated.
[b]The mother self-identifying as being of either African American race or Dominican Republic ethnicity was an inclusion criteria.
[c]Mother reported either during pregnancy or on a questionnaire 3 months after the child was born that she had asthma.
[d]Mother replied yes to a question about having allergies herself asked during the first year after the child was born.
[e]Nine of the mothers did not report whether they had completed high school.
[f]Mother reported on the prenatal questionnaire that in the past 6 months she and her family could not afford needed food, rent, clothing or medical care or that gas/electricity was suspended because of bill nonpayment.[23]
[g]Nonsmoking during pregnancy was an inclusion criterion.
[h]There were 2 participants who did not answer questions about cockroaches or rodents. The percentages are of the 330 women who answered these questions.

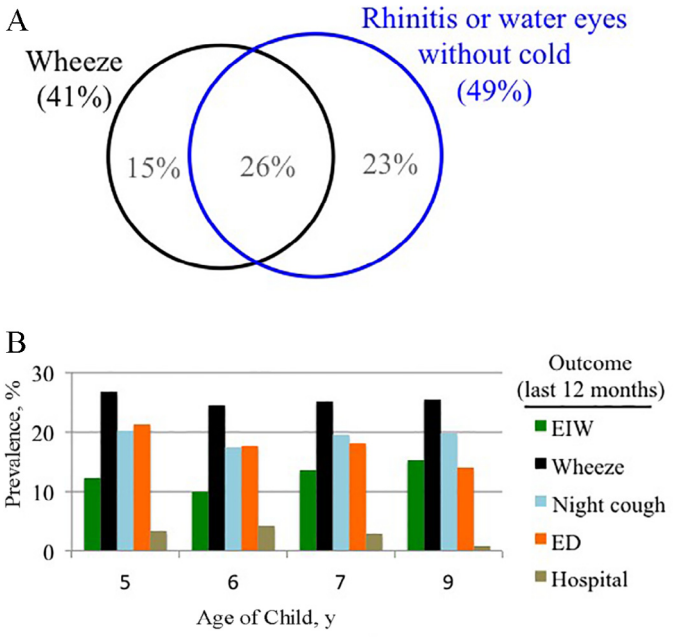

Figure 2. Reported symptoms. A, Prevalence and overlap of wheeze and runny nose and watery eyes without cold in first year of life (n = 332). B, Prevalence of exercise-induced wheeze (EIW) and other respiratory outcomes from ages 5 to 9 years reported for the previous 12 months. Data were available on 300, 283, 327, and 294 children at ages 5, 6, 7, and 9, respectively. ED, emergency department.

During school age (5–7 years), EIW, wheeze, nighttime cough without cold symptoms, and ED visits for asthma or other breathing problems were common (Fig 2B). Hospitalizations for asthma or other breathing problems were less common. Between the ages of 5 and 7 years, many of the children had at least one report of EIW (20%), wheeze (36%), nighttime cough (34%), ED visit (29%), or hospitalization (7%).

RWWC in Infancy Predicting EIW at School Age

In our cohort, both RWWC and wheeze in the first year of life predicted EIW at 5 to 7 years of age in models that adjusted for potential confounders (Fig 3A). Infant RWWC and wheeze also predicted school-age wheeze, nighttime cough without cold, and ED visits at 5 to 7 years of age (Fig 3B-D). Strikingly, hospitalizations at 5 to 7 years of age were predicted by RWWC in infancy but not by wheeze in infancy (Fig 3E). Examining the unadjusted data, we found that 21 of the 163 children (13%) with RWWC in infancy were hospitalized for breathing problems between the ages of 5 and 7 years, whereas only 2 of the 169 children (1.2%) who did not have these symptoms in infancy were hospitalized at 5 to 7 years of age.

To test for the independence from infant wheeze of infant RWWC predicting school age outcomes and to compare the magnitude of risk associated with infant RWWC with that of infant wheeze, models were tested that included both these variables, along with the same covariates included in models in Figure 3. The magnitude of the association between infant RWWC and school-age EIW (RR, 2.6; 95% CI, 1.5–4.3; $P < .001$) was greater than the magnitude of the association between infant wheeze and RWWC (RR, 1.5; 95% CI, 0.95–2.4; $P = .08$). The 95% CIs for RWWC did not overlap with the effect estimate for wheeze, and vice versa, indicating that the magnitude of the RR for RWWC was statistically significantly greater than that for wheeze. Although the magnitude of the association between RWWC and ED visits (RR, 1.7; 95% CI, 1.2–2.4; $P = .005$) was greater than that for wheeze (RR, 1.3; 95% CI, 0.93–1.9; $P = .11$), the CIs overlapped, preventing the conclusion that RWWC was a better predictor

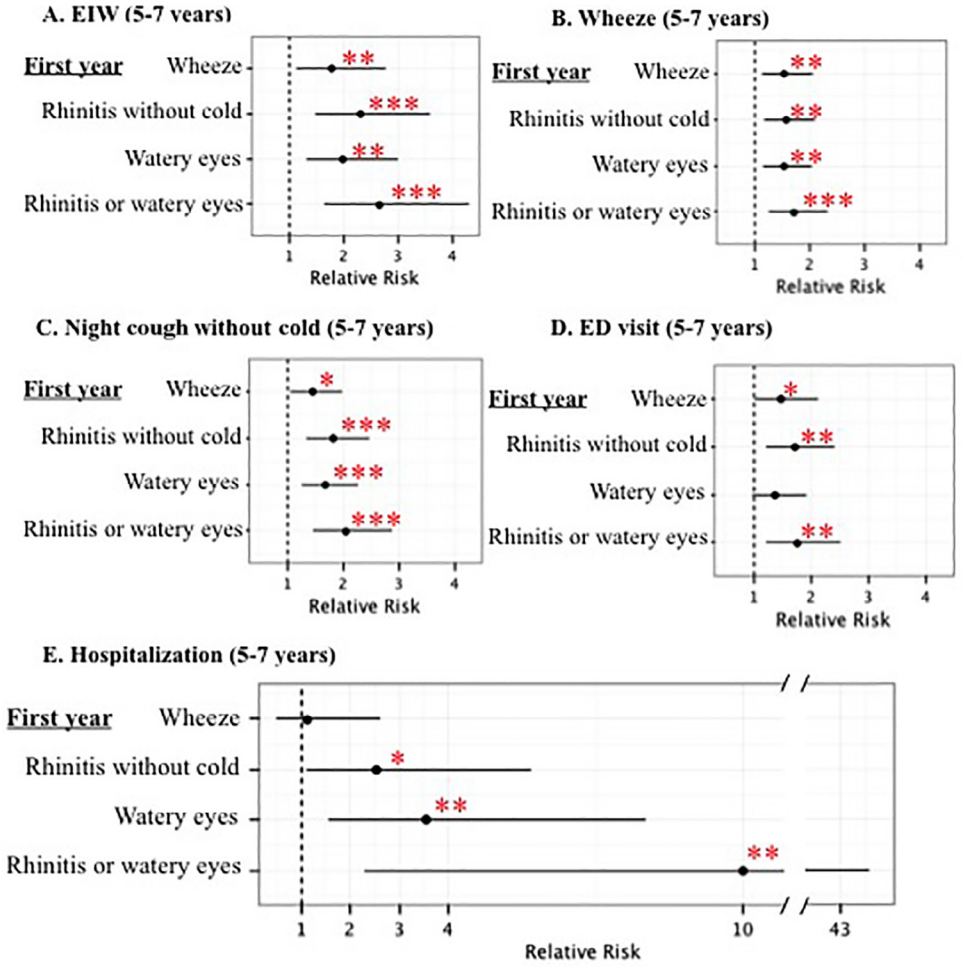

Figure 3. Relative risks for exercise-induced wheeze (EIW), wheeze (B), waking at night with cough without cold (C), emergency department (ED) visit (D), and hospitalizations in the prior year at 5 to 7 years of age with wheeze, runny nose, or watery eyes in the first year of life (E). Relative risks were adjusted for sex, race/ethnicity, maternal asthma, material hardship, and smoker in the home (prenatal and 5 years of age). The frequencies of EIW, wheeze, waking at night with cough without cold, ED visits, and hospitalization at ages 5-7 years were 20%, 36%, 34%, 29%, and 7%, respectively. $^{*}P < .05$, $^{**}P < .01$, and $^{***}P < .001$.

of future ED visits than wheeze. When evaluating the risk for school-age hospitalizations, infant RWWC predicted hospitalizations (RR, 11.1; 95% CI, 2.5–49.8; $P = .002$), but infant wheeze did not (RR, 0.66; 95% CI, 0.33–1.3; $P = .24$).

Independence of Association From Allergic Sensitization

At 7 years of age, 47% of the children had IgE antibodies (≥0.35 IU/mL) to at least 1 of the 9 allergen extracts tested. In order from most to least common, children had IgE antibodies to cockroach (29% of children), mixed tree pollen (20%), cat (19%), dog (16%), mouse (15%) dust mite (15%), mixed grass pollen (9%), ragweed (11%), or mixed mold (4.2%).

To assess the independence of these associations from allergic sensitization, models that tested the association between RWWC in infancy and EIW and respiratory outcomes at 5 to 7 years of age were built, including a variable for seroatopy at 7 years of age. Seroatopy at 7 years of age was used as an indicator of being predisposed to atopy by school age. Models also included infant wheeze to show the independence of the associations with RWWC from wheeze. The inclusion of seroatopy in these models did not change the effect estimates for RWWC and subsequent EIW and respiratory outcomes (Table 2).

Table 2
Adjusted Relative Risks (95% Confidence Intervals) for Exercise-Induced Wheeze and Other Asthma Outcomes at 5 to 7 Years of Age With Rhinitis and/or Watery Eyes Without Cold in Infancy

Asthma outcome at 5–7 years of age	Frequency of outcome, %	Relative Risk (95% Confidence Interval) [*P* Value]	
		Model adjusting for Covariates[a]	Model adjusting for Covariates[a] and Seroatopy[b] at 7 years of age
Exercise-induced wheeze	20	2.8 (1.7–4.5) [< .001]	2.8 (1.7–4.5) [< .001]
Wheeze	36	1.7 (1.3–2.3) [< .001]	1.7 (1.3–2.3) [< .001]
Nighttime cough without cold	34	2.1 (1.5–2.9) [< .001]	2.1 (1.5–2.9) [< .001]
Emergency department visit[c]	29	1.8 (1.3–2.6) [< .01]	1.8 (1.2–2.5) [< .01]
Hospitalization[c]	7	9.8 (2.2–43) [< .01]	9.8 (2.2–44.0) [< .01]

[a]All models adjusted for wheeze in the first years of life, sex, ethnicity/race, maternal asthma, material hardship, and tobacco smoke exposure in the home.
[b]Seroatopy was defined as measurable IgE (≥0.35 IU/mL) to at least one of the allergens (dust mite, cockroach, mouse, cat, dog, grass pollen, tree pollen, ragweed pollen, or mixed mold) tested at 7 years of age.
[c]Emergency department visits and hospitalizations were reported for asthma, wheezing, cough, bronchitis, or other breathing problems.

Independence of Association From Indicators of Infant Viral Exposure and Illness

To attempt to evaluate the independence of the association from viral illness, we used an indicator of increased risk of exposure of viruses, the presence of older siblings, and an indicator of sequelae after upper respiratory tract infection (ear infections reported in the first year of life). These variables were added to the models with seroatopy described in Table 2. Because of missing data on these 2 variables for 9 individuals, the sample size was smaller (n = 323). The effect estimate for EIW at 5 to 7 years of age with infant RWWC was the same (RR, 2.8; 95% CI, 1.7–4.7) in models without and with the older sibling and ear infection variables. For models that predicted ED visits at 5 to 7 years of age, the RR for RWWC was similar in models without (RR, 1.7; 95% CI, 1.2–2.5) and with (RR, 1.7; 95% CI, 1.2–2.4) the older sibling and ear infection variables. Models that predicted hospitalization at 5 to 7 years of age were also similar without (RR, 9.0; 95% CI, 2.0–41) and with (RR, 8.3; 95% CI, 2.0–35) the older sibling and ear infection variables in the model.

EIW in School Age Predicting ED Visits and Hospitalizations 2 Years Later

We conducted analyses to confirm that the association we had observed between EIW and urgent medical visits for asthma and other breathing difficulties in a middle-income cohort[15] was present in this lower-income cohort and test for a prospective association, which would better support the hypothesized directionality (ie, EIW predicting ED visits). Details on which children or measures were included in the repeated-measures analysis are described in eTable 2. In repeated-measures analysis at school age, EIW at 5 to 7 years of age predicted future (7–9 years of age, ie, measured 2 years later) ED visits (RR, 2.0; 95% CI, 1.2–3.2; $P = .005$) and hospitalizations (RR, 11.0; 95% CI, 1.2–95.0; $P = .03$). The magnitudes of these associations were not substantially diminished when ED visits or hospitalizations at baseline or allergic sensitization variables were included in the model (Table 3).

EIW as a Mediator of the Association between RWWC and ED Visits

We conducted mediation analysis to determine whether school-age EIW could be in the pathway between infant RWWC predicting school-age ED. When EIW was included in the model, the association between infant RWWC and ED visits at 5 to 7 years of age was substantially diminished and was no longer statistically significant (Fig 4). By contrast, including the variable frequent wheeze at 5 to 7 years of age (as a different indicator of poor asthma control and/or increased asthma severity), the association between RWWC and ED visits was only modestly diminished. When the model was simultaneously adjusted for both EIW and frequent wheeze at 7 years of age, the RWWC and ED visits association was similar to when only EIW (and not frequent wheeze) was included in the model.

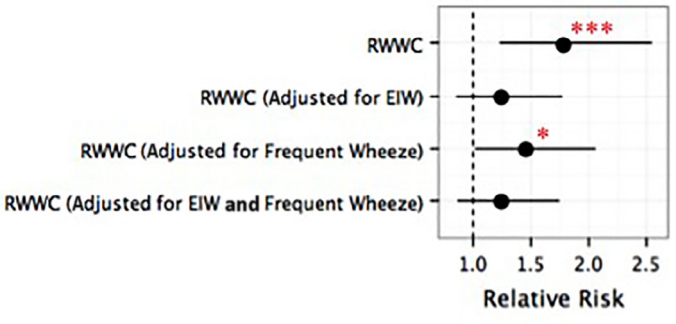

Figure 4. Test for mediation of the association between infant rhinitis or watery eyes without cold symptoms (RWWC) and emergency department (ED) visits at 5 to 7 years of age by exercise-induced wheeze (EIW) and frequent wheeze at 5 to 7 years of age. All relative risks were adjusted for the covariates described in Figure 3. The association between RWWC and ED visits was substantially diminished by inclusion of EIW in the model. $^{*}P < .05$ and $^{***}P < .001$.

Discussion

Among children living in low-income, urban neighborhoods, asthma is prevalent, and children with asthma are at a much higher risk for ED visits and hospitalizations for asthma than children with asthma in higher-income communities. Although combustion byproduct exposure, pest allergen exposure, and insufficient pharmacologic management have been implicated in these excess morbidities,[24,25] prior studies have neither satisfactorily explained these increased burdens nor developed an effective method to identify the highest-risk children early in life for interventions. Our study found an association between an asthma-related outcome defined by a rapid response to stimuli (EIW) and ED visits and hospitalizations among children with asthma living in a low-income, urban community. We have connected the manifestation of EIW in children at school age to infant reports of RWWC. Importantly, RWWC appears to be both independent of and more predictive than wheeze in infancy of these future respiratory morbidities and independent of an allergic pathway.

Table 3
RRs for EIW at 5 to 7 Years of Age Predicting ED and Hospitalizations 2 Years Later Among Children With Asthma Symptoms or Taking Asthma MedicationsVariable

	RR (95% CI) [*P* value] for ED visits[a] 2 years later (n = 151 Children, n = 211 Observations[b])			RR (95% CI) [*P* value] for hospitalization[a] 2 years later (n = 151 Children, n = 211 Observations[b])		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
EIW	2.0 (1.2–3.2) [< .01]	2.0 (1.2–3.2) [< .01]	1.8(1.1–2.8) [< .05]	10.7 (1.2–96) [< .05]	10.9 (1.2–97) [< .05]	11.9 (1.3–112.0) [< .05]
Frequent wheeze	1.6 (0.94–2.6)	1.6 (0.94–2.6)	1.5 (0.93–2.5)	2.4 (0.29–12)	2.5 (0.48–13)	2.6 (0.48–14.0)
Nighttime cough without cold	1.2 (0.74–1.8)	1.2 (0.73–1.8)	1.1 (0.72–1.7)	1.4 (0.25–7.3)	1.5 (0.24–9.7)	1.7 (0.24–12.0)
Seroatopy[c]	NA	1.1 (0.67–1.7)	1.0 (0.67–1.6)	NA	0.75 (0.13–4.4)	0.84 (0.13–5.3)
Current ED visit	NA	NA	1.5 (0.89–2.5)	NA	NA	0.64 (0.045–8.9)

Abbreviations: ED, emergency department; EIW, exercise-induced wheeze; NA, not applicable.
[a]In model 1, multivariable repeated-measures generalized estimating equation models were adjusted for sex, race, Hispanic ethnicity, material hardship, and child's age at baseline and 2 years later. Model 2 = (Model 1) + Seroatopy. Model 3 = (Model 2) + Current ED Visit.
[b]There were 151 children who had asthma symptoms or who had taken medication in the last year included in the prospective analyses. Among these children, there were 117 and 104 observations at 5 (predicting age, 7 years) and 7 (predicting age, 9 years) years of age, respectively, for a total of 211 observations (see eTable 2 for demographics).
[c]Seroatopy was defined as measurable IgE (≥0.35 IU/mL) to at least one of the allergens (dust mite, cockroach, mouse, cat, dog, grass pollen, tree pollen, ragweed pollen, or mixed mold) tested at 7 years of age.

In addition to infant RWWC predicting EIW in school-age children, it also predicted ED visits and hospitalizations for breathing problems. Mediation analyses indicated that this connection was primarily through EIW. Strikingly, school-age children with infant RWWC were much more likely to be hospitalized for asthma or other breathing problems than children without RWWC during infancy. We acknowledge the large CI for this estimate, which is the result of hospitalizations being somewhat uncommon in this general population-based study (7% were hospitalized between 5 and 7 years of age). Still, the association was statistically significant and appeared to be a robust predictor of hospitalizations. Although infant wheeze is a well-acknowledged predecessor to asthma development, the specificity of infant wheeze for future asthma is known to be low.[26–28] Indeed, with this study, we found infant wheeze to be less predictive of future EIW than RWWC and not predictive of future respiratory-related hospitalizations at all.

We believe the apparent independence of the association between rhinitis and later respiratory morbidity from the allergic pathway makes these findings novel. A priori, we defined our atopic population by the presence of seroatopy to common inhalant allergens at 7 years of age. Generally, inhalant allergen persists throughout childhood, once established. Thus, our seroatopy definition should capture sensitization that had been established before the end of our follow-up period. Although we acknowledge that would have led us to classify children who had transient sensitization early in childhood as nonatopic, the relevance of transient early-life sensitization to inhalant allergens in relation to rhinitis or asthma has not been demonstrated.[29,30] For related reasons, we limited the allergens we tested to inhalant allergens because these are more likely to be involved in a connection between rhinitis and asthma than food allergen sensitization.[29]

With this study, we built on our previous findings of a cross-sectional association between EIW and urgent medical visits by extending the generalizability of this finding to a lower-income urban population. We also strengthened the findings by observing that EIW predicted future ED visits and hospitalizations. We demonstrated a prospective association whereby EIW predicted future ED visits and hospitalizations, even after controlling for recent ED visits or hospitalizations. This finding suggests that asking about EIW could be an important tool for physicians to assess risk for future urgent medical visits, in addition to traditional measures of asthma severity and control. Despite EIW being the identified risk, we have not demonstrated that exercise is the trigger that leads to the ED visits or hospitalizations. Instead, EIW may identify a group of children with airway dysfunction that respond with acute bronchoconstriction to stimuli, including but not limited to exercise.

Our hypothesis suggests a complex, physiologically linked pathway from early symptoms to later consequences. This study needs replication, but the associations appear to be robust and potentially indicate a relatively high magnitude of identifiable risk. Future studies should assess the physiologic link between infant RWWC and EIW, with autonomic nervous system development as a possible target.

This study has several limitations. First, RWWC was assessed by questionnaire report by the mother. Therefore, the absence of cold was not validated by either physician examination or testing for viral or bacterial infection. The inability to identify viral infections may have led to an overreporting of symptoms without a cold. However, with only 32% of children having a positive response to this question, it clearly discriminated from runny nose symptoms reported *with* a cold, for which virtually all the children (ie, 98%) had a positive response. In addition, these symptoms were assessed prospectively (relative to the school-age outcomes), for 3-month periods, limiting the recall bias associated with this type of questionnaire-based study. Infants with older siblings are more likely to be exposed to viruses, and ear infections develop subsequent to upper respiratory tract infections, thus providing some proxy measures for risk of exposure to viruses and a measure of children more likely to have had consequential viral infections. Although we observed a modest increase in RWWC for children with older siblings, the fact that we did not observe any confounding when we included the presence of older siblings or infant ear infections offers some support that the mechanism of the association between RWWC and subsequent EIW is not through an infection mechanism. Still, future work is needed to better understand what is being indicated by reported RWWC. We also did not observe any increased risk of RWWC with environmental tobacco smoke exposure or home combustion sources related to heating or cooking. However, given that almost all the homes had boiler-based heating and gas stoves, it is likely that we were underpowered to detect any associations with these exposures.

A second limitation was that EIW was assessed by questionnaire; exercise-induced bronchoconstriction was not tested, and a physician diagnosis of EIW was not made, which could have reduced the specificity and sensitivity of our identification of EIW. A third limitation was that the questions about ED visits and hospitalizations were not specific for asthma but included other breathing difficulties. Therefore, despite asthma being a major cause for ED visits and respiratory-related hospitalizations in this community, we cannot limit these findings to asthma-related morbidity. Another related limitation was that we did not ascertain the precipitating factors for the children's ED visits and hospitalizations. Specifically, knowing whether these events were associated with an environmental trigger– or exercise-induced exacerbation would allow for a better understanding of whether we are identifying a specific asthma phenotype.

An additional limitation of this study is the lack of generalizability. These findings may apply only to children living in lower socioeconomic status, urban US neighborhoods. However, because this is a population that bears the excess burden of asthma ED visits and hospitalizations in urban communities, we believe these findings are of public health importance. It will be important to test for this association in other communities where urgent medical visits for asthma are common.

In conclusion, independent of early-life wheeze and allergic sensitization, infant RWWC predicted EIW and related respiratory morbidities in school-age children. Our observation that these associations were independent of the development of allergic sensitization suggests a novel connection through a nonallergic mechanism. Further study of mechanism(s) and confirmation is warranted, but these findings indicate that EIW may be an important component of urban respiratory health. If confirmed, our results could provide a way to identify very young children at greater risk of asthma and other respiratory morbidities who would benefit from increased surveillance to reduce their morbidities.

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Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.anai.2017.11.024.

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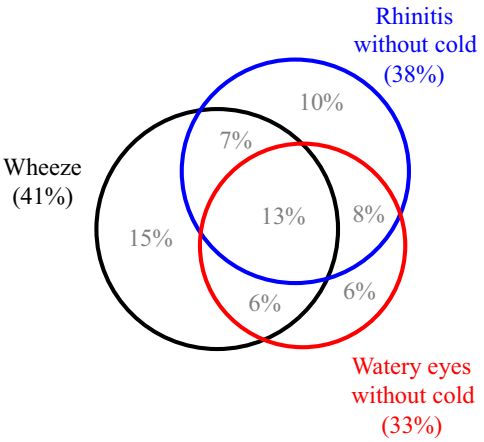
Supplementary Data



eFigure 1. Prevalence and overlap of wheeze, runny nose without cold, and water eyes without cold in first year of life (n = 332).

eTable 1
Demographics of Mothers During Pregnancy and Symptoms in the Children in the First Year of Life Among Those Included in the Analyses and Those Recruited Who Were Excluded Because of Missing Data[a]

Demographic	Included in the analyses (n = 332)	Not included in the analyses (n = 395)	Difference *P* value
Male sex	155/332 (46.7)	196/395 (49.6)	.43
Mother's age, mean (SD), y	25.2	24.9	.38
Mother's race/ethnicity			
African American[b]	134/332 (40.4)	120/395 (30.4)	.005
Dominican[b]	198/332 (59.6)	275/395 (69.6)	.005
Mother's self-reported health			
Asthma[c]	85/332 (25.3)	78/395 (19.7)	.059
Allergy[d]	138/332 (41.6)	149/354 (42.1)	.89
Sociodemographics			
No high school degree[e]	118/332 (36.5)	139/390 (35.6)	.81
Receiving Medicaid[f]	304/332 (91.6)	353/391 (90.3)	.55
Material hardship last 6 months[g]	139/332 (41.9)	182/384 (47.4)	.14
Domestic environment			
Smoker in home[g]	122/332 (36.7)	124/385 (32.2)	.20
Cockroach sightings in home[h]	240/330 (72.7)	278/389 (71.5)	.71
Rodent sightings in home[h]	175/330 (53.0)	216/390 (55.4)	.53
Child's symptoms in first year of life			
Wheeze	135/332 (40.7)	137/352 (38.9)	.64
Runny nose without colds	126/332 (38.0)	133/353 (37.7)	.94
Watery eyes without colds	109/332 (32.8)	106/353 (30.0)	.43
Runny nose or watery eyes without colds	163/332 (49.1)	173/353 (49.0)	.98

[a]Data are presented as number (percentage) of participants unless otherwise indicated.
[b]The mother self-identifying as being of either African American race or Dominican Republic ethnicity was an inclusion criteria.
[c]Mother reported either during pregnancy or on a questionnaire 3 months after the child was born that she had asthma.
[d]Mother replied yes to a question about having allergies asked during the first year after the child was born.
[e]Nine of the mothers did not report whether they had completed high school.
[f]Mother reported on the prenatal questionnaire that in the past 6 months she and her family could not afford needed food, rent, clothing or medical care or that gas/electricity was suspended because of bill nonpayment.
[g]Nonsmoking during pregnancy was an inclusion criterion.
[h]There were 2 participants who did not answer questions about cockroaches or rodents. The percentages are of the 330 women who answered these questions.

eTable 2
Demographics and Respiratory Outcomes Among the Children and Observations Included in the Repeated-Measures Analyses Testing Associations Between EIW at 5 to 7 Years of Age and ED Visits and Hospitalizations at 5 to 9 Years of Age[a]

Variable	Cross-sectional analyses (n = 175 children, n = 339 observations)	Prospective analyses (n = 151 children, n = 221 observations)
Male sex	94/175 (57.1)	82/151 (54.3)
Observations per child		
1	66	81
2	54	70
3	55	NA
Age of observations, y[b]		
5	120	117
7	116	104
9	103	NA[b]
Mother's race/ethnicity		
African American	62/175 (35.4)	56/151 (37.1)
Dominican	113/175 (64.6)	95/151 (62.9)
Child's symptoms in first year of life		
Wheeze	90/175 (51.4)	78/151 (51.7)
Runny nose or watery eyes without colds	105/175 (60.0)	94/151 (62.3)
Seroatopy at 7 years of age[c]	98/175 (56.0)	86/151 (57.0)
Symptoms and asthma outcomes in prior year (time 1)		
EIW	126/339 (37.2)	78/221 (35.3)
Night cough without cold	189/339 (55.8)	123/221 (55.7)
Frequent wheeze	61/339 (18.0)	42/221 (19.0)
ED visits	152/339 (44.8)	108/221 (48.9)
Hospitalizations	19/339 (5.6)	16/221 (7.2)
ED and hospitalizations 2 years later (time 2)		
ED visits	NA	77/221 (34.8)
Hospitalizations	NA	7/221 (3.2)

Abbreviations: ED, emergency department; EIW, exercise-induced wheeze; NA, not applicable.
[a]Data are presented as number (percentage) of children or observations unless otherwise indicated.
[b]For the prospective analyses, ages are time 1 ages. Time 1 EIW was evaluated as a predictor of time 2 ED visits and hospitalizations (2 years later).
[c]Seroatopy was defined as measurable IgE (≥0.35 IU/mL) to at least one of the allergens (dust mite, cockroach, mouse, cat, dog, grass pollen, tree pollen, ragweed pollen, or mixed mold) tested at 7 years of age.