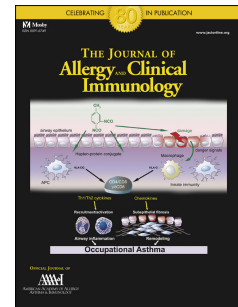


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Title

Early-Life Ozone Exposure Associated with Asthma Without Sensitization in Latino Children

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Capsule Summary

This study describes the prevalence of atopy among Latino children with asthma recruited from five US urban centers and finds an association between ozone exposure during the first year of life and asthma without allergic sensitization.

Key Words

Atopy; allergic sensitization; air pollution; ozone, childhood asthma; minority; Hispanic; Latino; Puerto Ricans; Mexican Americans

Abbreviations

CI: confidence interval
 GALA II: Genes-environments and Admixture in Latino Americans
 NO₂: nitrogen dioxide
 O₃: ozone (8 hour maximum)
 OR: odds ratio
 PM_{2.5}: particulate matter with aerodynamic diameter $\leq 2.5 \mu\text{m}$
 PM₁₀: particulate matter with aerodynamic diameter $\leq 10 \mu\text{m}$
 ppb: parts per billion
 SD: standard deviation
 SES: socioeconomic status
 SO₂: sulfur dioxide
 $\mu\text{g}/\text{m}^3$: microgram per cubic meter

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To the Editor:

The prevalence and risk factors of atopy varies across Latino subgroups.¹ However, few studies have been conducted on an entirely Latino population to corroborate these trends and identify reasons for potential differences. The hypothesis that traffic-related air pollution exposures increase the risk for atopy has been previously examined, with some studies supporting² and others refuting³ the association. Given the mixed findings, it may be beneficial to assess this topic in minorities, as they often live in or near urban areas where pollution exposures are higher.^{4,5} We sought to test the hypothesis that early-life air pollution exposures were associated with atopic status among children with asthma by performing a secondary analyses on data collected from Gene-environments in Latino Americans (GALA II), the largest domestic gene-environment case-control study of asthma in minority children.

Briefly, individuals 8-21 years old who self-identified as Latino and had four Latino grandparents were recruited from five urban regions (Chicago, IL; Bronx, NY; Houston, TX; San Francisco Bay Area, CA; Puerto Rico). Participants were classified into one of three Latino subgroups: Mexican American, Puerto Rican, or Other (South American, Central American, non-Puerto Rican Caribbean, or mixed ancestry). Asthma cases had a history of physician-diagnosed asthma but no reported history of other lung disease or chronic illness. Controls had no reported history of asthma, other lung disease, chronic illness, or atopic disease (eczema, allergic rhinitis) and were 1:1 frequency matched with cases within each recruitment center. Local Institutional Review Boards approved the study and written informed consent was obtained from all parents/participants. A detailed description of the methods has previously been published.⁶

Atopic sensitization was defined as demonstrating at least one positive allergy skin test reaction to a panel of 14 environmental allergens using the Multi-Test II device (Lincoln Diagnostics, Decatur, IL). The allergy skin test was considered valid if the histamine positive control had surrounding erythema and its wheal diameter was at least 3 mm greater than the wheal diameter of the saline negative control. A reaction to a specific allergen was considered positive if the allergen caused erythema surrounding the wheal with a diameter that was at least 3 mm

greater than the diameter of the negative control wheal. Those with allergy skin tests that failed to pass quality control measures were excluded from the analysis.

Measurements for ozone (O₃), nitrogen dioxide (NO₂), sulfur dioxide (SO₂), and particulate matter with aerodynamic diameter $\leq 10 \mu\text{m}$ (PM₁₀) and $\leq 2.5 \mu\text{m}$ (PM_{2.5}) were obtained from the US Environmental Protection Agency Air Quality System.⁷ Individual exposures were estimated by calculating the inverse distance-squared weighted average of all available values from the four closest monitoring stations (within 50 km) of where the subject resided during their first year of life. If the child moved during their first year of life, a weighted average of the pollution estimates were based on the number of months spent at each residence. The distribution of pollution exposures is available in Supplemental Table 1 in the Online Repository.

To reduce bias due to the case-control study design, statistical analyses were restricted to asthma cases only. χ^2 tests compared the proportion of atopy between Latino subgroups. Multivariate logistic regressions were used to evaluate associations between each first year of life pollution exposure and atopic status. All regressions were controlled for age, sex, ethnicity, recruitment region, percent of African genetic ancestry, maternal *in utero* smoking, and socioeconomic status (SES). Analyses were performed using Stata13 (StataCorp, College Station, TX) and R (R Foundation for Statistical Computing, Vienna, Austria).

The GALA II study enrolled 4,157 children from 2006-2011. After excluding controls (n=2,135), those missing essential covariates (n=468), those with invalid allergy skin tests (n=392), and those missing air pollution estimates (n=130), the final sample included 1,032 children with asthma (Table 1). There were no substantial differences in the percent of atopy between the four mainland US recruitment sites (ranging from 72% in the San Francisco Bay Area, CA to 79% in Houston, TX) or between mainland Latino subgroups (ranging from 75% in Mexican Americans to 81% in Other Latinos). However, the prevalence of atopy was significantly lower among Puerto Ricans who were living in Puerto Rico (52%). While these differences were statistically significant, 55% of allergy skin tests were invalid due to poor responses to the histamine positive control and the results must be interpreted with caution.

First-year of life exposures to NO₂, PM₁₀, PM_{2.5} or SO₂ were not associated with atopic status (Table 2). However asthmatics without allergic sensitization were more likely to be exposed to higher levels of ozone during

their first year of life compared to those with atopic asthma (adjusted OR = 1.32, 95% CI, 1.11-1.57, p-value = 0.002). For every 5 ppb increase in average ozone exposure during the first year of life, the odds for having asthma without sensitization increased by 32%. The OR was not significantly changed in sensitivity analyses when the following subsets were excluded: (1) asthmatics recruited from Puerto Rico, (2) asthmatics who had moved away from their birth state, and (3) pollution outliers (asthmatics with the top and bottom 5% of exposure values).

Our findings suggest that children with asthma without allergic sensitization were more likely to be exposed to higher levels of ozone pollution during their first year of life compared to children with atopic asthma. Experimental studies in those with asthma have shown that acute exposure to ozone stimulates airway neutrophilia,^{8,9} a characteristic though not necessarily specific feature of asthma without sensitization.

Since our analysis used data from a case-control study, our samples may not be representative of the underlying population or generalizable to the population of US Latinos. It is not immediately clear whether ozone exposure in subsequent years might have contributed to risk for sensitization. Nevertheless, our study benefits from analyzing a very large and diverse Latino population recruited from multiple regions in the US. While additional studies are needed to confirm these findings, our results suggest that ozone air pollution may partially account for the prevalence of asthma without sensitization in Latino children. These controversial findings might have emerged from interactions with the assessed geographic areas or neighborhoods. Since minorities such as various Latino subgroups often live in or near urban areas where they are disproportionately impacted by air pollution, they should be studied separately and reducing exposures in Latino communities may prevent similar asthma cases.

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238 **Table 1:** Eligible participants in the GALA II study.

	Asthma Cases (n (%))
Total	1032 (100%)
Recruitment Region	
Chicago, IL	232 (22.5%)
Houston, TX	151 (14.6%)
Bronx, NY	177 (17.2%)
Puerto Rico	264 (25.6%)
San Francisco Bay Area, CA	208 (20.2%)
Age (mean (SD))	12.5 (3.2)
Sex	
Male	585 (56.7%)
Female	447 (43.3%)
Latino Subgroup	
Mexican American	427 (41.4%)
Puerto Rican	359 (34.8%)
Other Latino*	246 (23.8%)
SES Composite Score†	
3-4	184 (17.8%)
5-6	543 (52.6%)
7-9	305 (23.8%)
Family History of Atopy‡	
Yes	546 (52.9%)
No	486 (47.1%)
Atopic (based on allergy skin tests)	
Yes	726 (70.4%)
No	306 (29.7%)
Percent African Genetic Ancestry (mean (SD))	13.1 (12.7)
Maternal <i>in utero</i> smoking	
No	976 (94.6%)
Yes	56 (5.4%)
Lung Function (mean (SD))§	
FEV ₁ (L)	2.5 (0.9)
FVC (L)	2.9 (1.0)
FEV ₁ /FVC (%)	84.0 (7.4)
FEF ₂₅₋₇₅ (L/s)	2.6 (1.1)
Birth State Same as Current State	
Yes	978 (94.8%)
No	54 (5.2%)

239 * Other Latino includes those with self-reported ethnicity of South American, Central American, non-Puerto
 240 Rican Caribbean, or mixed Latino.

241 † SES Composite Score is based on the level of maternal education, annual household income, and the type of
 242 medical insurance.

243 ‡ Family History of Atopy is defined as having one or more parent ever being diagnosed with allergic rhinitis,
 244 eczema or asthma.

245 § Lung function was measured in asthma cases only. FEV₁ = forced expiratory volume during 1 second (Liters);
 246 FVC = forced vital capacity (Liters); FEV₁/FVC = ratio of FEV₁ to FVC. FEF₂₅₋₇₅ = forced expiratory flow
 247 between 25% and 75% of vital capacity (Liters per second).

Table 2: Adjusted ORs for the association between atopic status and first year of life exposure to air pollution

	OR	(95% CI)	p-value	n
24-hour NO ₂ (ppb)	1.06	(0.89 – 1.26)	0.52	937
8-hour O ₃ (ppb)	1.32	(1.11 – 1.57)	0.002	768
24-hour PM ₁₀ (µg/m ³)	1.02	(0.89 – 1.78)	0.77	1,027
24-hour PM _{2.5} (µg/m ³)	0.89	(0.42 – 1.87)	0.76	392
24-hour SO ₂ (ppb)	0.99	(0.92 – 1.07)	0.85	989

Reference group = atopic (allergic sensitization as demonstrated by at least one positive allergy skin test reaction to a panel of 14 environmental allergens). Comparison group = non-atopic (no positive allergy skin test results).

Bold indicates results at a significant Bonferroni-corrected α value of 0.01.

Models are adjusted for age, sex, SES, ethnicity, recruitment region, proportion of global African ancestry and maternal *in utero* smoking. All pollutants are scaled to represent a 5-unit change in exposure, except SO₂ (1 ppb change).

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Supplemental Table 1: First year of life air pollution exposures among eligible participants compared with the EPA air quality standards.

	GALA	EPA NAAQS
NO₂, ppb (24-hr avg)		
Mean (SD)	21.8 (8.7)	53*
25th	15.5	
50th	21.5	
75th	28.6	
O₃, ppb (8-hr max)		
Mean (SD)	29.5 (6.6)	NAS
25th	25.5	
50th	28.3	
75th	33.5	
PM₁₀, µg/m³ (24-hr avg)		
Mean (SD)	29.2 (6.0)	NAS
25th	24.8	
50th	28.4	
75th	33.1	
PM_{2.5}, µg/m³ (24-hr avg)		
Mean (SD)	12.9 (3.6)	12†
25th	10.4	
50th	12.9	
75th	15.6	
SO₂, ppb (24-hr avg)		
Mean (SD)	5.0 (3.8)	30*
25th	2.2	
50th	4.0	
75th	5.7	

ppb = parts-per-billion

µg/m³ = microgram per cubic meter

avg = average

hr = hour

SD = standard deviation

max = maximum

EPA NAAQS = US Environmental Protection Agency National Ambient Air Quality Standards

NAS = no annual standard

NO₂ = nitrogen dioxide

O₃ = ozone

PM₁₀ = particulate matter with aerodynamic diameter ≤ 10 µm

PM_{2.5} = particulate matter with aerodynamic diameter ≤ 2.5 µm

SO₂ = sulfur dioxide

Data from reference (58)

*Annual mean

†Annual mean, over 3 years