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The Effects of Air Pollution on Asthma in Latino and African American Children

by

Katherine Keiko Nishimura

DISSERTATION

Submitted in partial satisfaction of the requirements for the degree of

DOCTOR OF PHILOSOPHY

in

Epidemiology and Translational Sciences

in the

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by

Katherine Keiko Nishimura

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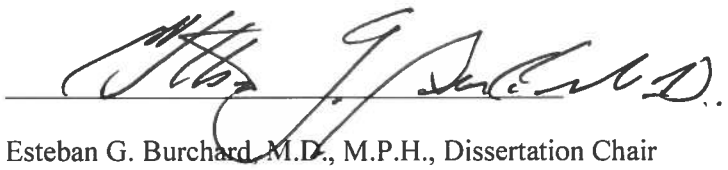
Approved: 

Esteban G. Burchard, M.D., M.P.H., Dissertation Chair

[1] Nishimura KK, Galanter JM, Roth LA, Oh SS, Farber HJ, Serebrisky D, Kumar R, Borrell LN, Brigino-Buenaventura E, Davis A, LeNoir MA, Meade K, Rodriguez-Cintron W, Avila PC, Rodriguez-Santana JR, Lurmann F, Sen S, Balmes JR, Burchard EG. Early Life Air Pollution and Asthma Risk in Minority Children: The GALA II & SAGE II Studies. Am J Respir Crit Care Med. 2013 Aug 1;188(3):309-18.

The Effects of Air Pollution on Asthma in Latino and African American Children

Katherine Keiko Nishimura

Abstract

Asthma is the most common chronic disease among children. Despite the high prevalence of asthma, there is no cure and its etiology is poorly understood. Of all racial/ethnic groups, African Americans and Puerto Ricans have the highest rates of asthma in the US. Asthma is a multifaceted disease, with genetic, social and environmental risk factors. Outdoor air pollution is a known risk factor, associated with asthma exacerbations and emergency room hospitalizations. US minorities often live in neighborhoods that are disproportionately exposed to higher levels of air pollution, yet few studies are conducted in minority groups. The objective of this dissertation was to evaluate the effects of air pollution on asthma in Latinos and African Americans.

This work utilized data from two parallel case-control studies: the Genes-environments and Admixture in Latino Americans (GALA II) and the Study of African Americans, Asthma, Genes and Environments (SAGE II). Children were recruited from five urban regions in the US, and were assigned estimates of air pollution exposure to five common pollutants for each year of their lives.

The first chapter describes the associations between early-life air pollution exposures and the subsequent risk for developing childhood asthma. Early-life exposure to NO_2, a traffic-related pollutant, was associated with an increased risk for subsequent asthma. The second chapter describes the association between recent air pollution exposures and lung function in children with asthma. Exposure to SO_2 and coarse particulate matter, both industrial-related pollutants, were associated with poorer lung function. Significant effect modification by race/ethnicity was also detected. The third chapter describes the variation in total IgE and atopy prevalence and outlines the associations between early-life air pollution exposures and the risk for developing non-atopic asthma. Ozone exposure in the first year of life was found to be associated with an increased risk for developing non-atopic asthma.

In summary, our findings suggest that air pollution impacts numerous aspects of asthma risk and morbidity. Gaining a better understanding of these associations could potentially prevent a substantial proportion of current and future asthma disparities. Replication of these findings is needed in addition populations and regions.

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CHAPTER 1. Early Life Air Pollution and Asthma Risk in Minority Children: The GALA II & SAGE II Studies

INTRODUCTION

Asthma is the most common chronic disease in American children (1). In 2011, there were approximately 25.9 million Americans with asthma, 7.1 million of those being children (2). In 2008, asthma resulted in 14.4 million missed school days and 14.2 million lost work days, costing $56.0 billion in direct and indirect costs (3). A substantial proportion of asthma cases can be prevented, underscoring the unnecessary burden of this disease. According to the World Health Organization, up to 44% of the asthma burden can be attributed to modifiable environmental factors (4), such as air pollution.

Current exposure to air pollution has been associated with short-term asthma outcomes including emergency hospitalization (5-7), reduced lung function (8-11), poor asthma control (12), and reduced response to asthma rescue medications (13). While it is generally accepted that air pollution can aggravate existing asthma, it is less clear whether exposure to air pollutants plays a causal role in the development of asthma. Cross-sectional studies have found an association between current air pollution levels and asthma prevalence, implying that pollution may increase the risk for developing asthma (14-23). However, studies that measure the association of air pollution exposures that occur before asthma onset are necessary to evaluate the causality of this association.

Fewer studies have been conducted using early life air pollution exposures and asthma incidence in children, in part because it requires costly longitudinal follow-up of a cohort, or the means to measure an exposure that has already occurred. Furthermore, most studies focus on a single geographic region with participants primarily of European descent. A recent meta-analysis of 17 population-based cohort studies found a statistically significant OR of 1.07 (95%CI, 1.02-1.13) for every 10 $\mu g/m^3$ increase in NO_2 (24). However, both child and adult cohorts were used in this meta-analysis and many (11 out of 17) were based in Europe. A similar meta-analysis with 19 studies conducted exclusively in children found a statistically significant association between the incidence of childhood asthma and NO_2 (OR=1.14,

95%CI, 1.06-1.24, per 10 μg/m^3 increase) (16). A review of these and other studies concluded that traffic-related pollution may play a role in the development of asthma, especially in individuals living near high volume roadways (25).

Latino and African American populations often live in neighborhoods with high levels of air pollution (26) and some of these groups have the highest prevalence of asthma in the U.S. (27). Puerto Ricans (16.6%) and African Americans (11.1%) have among the highest prevalence, significantly higher than Caucasians (7.8%). Interestingly, Mexicans have one of the lowest prevalence (4.9%), which challenges the practice of grouping Puerto Ricans and Mexicans together as "Hispanic/Latino." Despite the fact that African Americans and some Latino subgroups have a high prevalence of asthma and a disproportionate exposure to air pollution, very little research has been conducted in these populations (28, 29). To adequately assess the relationship between traffic-related air pollution and childhood asthma, it is important to study this association in high-risk racial/ethnic minorities, and to our knowledge, no previous study has been conducted exclusively in these groups.

The Genes-environments & Admixture in Latino Americans (GALA II) and the Study of African Americans, Asthma, Genes & Environments (SAGE II) are parallel case-control studies of Latino and African American children. Together, GALA II and SAGE II represent the largest gene-environment study of asthma of minority children in the U.S. Here, we seek to leverage the geographic and ethnic diversity in these two studies to examine the relationship between early life air pollution exposure and the subsequent onset of asthma.

METHODS

Study population

The GALA II and SAGE II studies recruited Latino and African American children with and without asthma. GALA II recruited Latinos from urban regions in the mainland U.S. (Chicago, IL; Bronx, NY; Houston, TX; San Francisco Bay Area, CA) and Puerto Rico using a combination of community and clinic-based recruitment. SAGE II recruited African Americans from the San Francisco Bay Area only.

All participants were 8-21 years old and had no history of other lung or chronic illnesses (other than atopy and allergy related diseases in the cases). Participants were eligible to participate in GALA II or SAGE II if they self-identified as Latino or African American and had four Latino or African American grandparents, respectively. Cases were defined as those with physician-diagnosed asthma plus two or more symptoms of coughing, wheezing, or shortness of breath in the two years prior to recruitment. Eligible controls had no reported history of asthma, lung disease or chronic illness, and no reported symptoms of coughing, wheezing or shortness of breath in the two years prior to enrollment. Controls were 1:1 frequency matched within each recruitment center by age (within 1 year). Cases and controls were recruited from similar geographic regions (**Appendix Figure 1.1**). Those in the third trimester of pregnancy, current smokers and those with ≥10 pack-year smoking history were not eligible. All local institutional review boards approved the study and all parents/participants provided signed written consent and assent as appropriate.

Exposure assessment

Trained bilingual (English-Spanish) interviewers administered questionnaires to the parents/caretakers of the participants to collect basic demographic information, medical histories, and environmental exposure-related information. Self-reported residential histories from birth were collected and assigned geographic coordinates for each residence using the TomTom/Tele Atlas EZ-Locate software. Regional ambient air pollution data were acquired from the U.S. Environmental Protection Agency's Air Quality System. To average out yearly temporal changes, annual average exposures to O_3, NO_2, SO_2, PM_{10} and $PM_{2.5}$ were calculated for each calendar year of life. Pollution exposures were estimated by calculating the inverse distance-squared weighted average from the four closest air pollution monitoring stations within 50 km of the residence. If a participant moved during the course of the year, their pollutant exposure assignments were weighted based on the number of months spent at each residence. Exposures over the first three years of life were calculated by averaging all available pollutant values from birth to age three.

Statistical analysis

To account for regional characteristics, we used a two-stage analysis, allowing us to measure the between-region heterogeneity and obtain a representative estimate across all regions. In the first stage, associations for each pollutant were determined separately for each study and region. Unadjusted logistic regression models and models adjusted for age, sex, ethnicity and composite socioeconomic status (SES) were used to calculate the association between pollutant exposures during the first three years of life and subsequent asthma diagnosis as a dichotomous outcome. The SES variable was calculated for each participant by assigning a low, medium or high score for income, level of education, and insurance type, and then by taking the sum of these three values. These covariates were included in the adjusted model if they resulted in a 10% or greater change in the β coefficient, or were standard in similar analyses. An interaction variable was used to test for effect modification between air pollution and ethnicity, SES and sex. We also performed a sensitivity analysis examining additional potential covariates for maternal *in utero* smoking, environmental tobacco smoke in the household between 0 and 2 years old, and maternal language of preference (as an indicator of acculturation). These variables were included in the final site-specific adjusted models if the sample size was large enough and their inclusion improved the fit of the model as indicated by the Akaike Information Criterion (AIC). The analyses were repeated limiting the exposures to the first year of life in order to ensure assessment of the air pollution-asthma relationship during critical periods of early infant lung and immunological development (30). The average pollution values were scaled to represent a 5 ppb (or $\mu g/m^3$) increase in O_3, NO_2 and PM_{10}, and a 1 ppb (or $\mu g/m^3$) increase in $PM_{2.5}$ and SO_2, based on the range of pollution exposures reported.

In the second stage, the regression coefficients for each region were combined using a random-effects meta-analysis with a restricted maximum-likelihood estimator to generate a summary OR for each pollutant. Heterogeneity between the study regions for each pollutant was evaluated using the I^2 statistic, which estimates the percentage of between-study variation due to heterogeneity. Analyses with I^2 less than 50% were considered to have acceptable heterogeneity.

We performed 3 stratified analyses: with or without family history of asthma, male or female sex, and high or low total IgE (above/below 200 IU/mL, the approximate median among cases). The analyses stratified by family history of asthma (defined as at least one parent ever diagnosed with asthma) was conducted to examine the association among children who were more or less likely to be genetically predisposed to asthma. The analyses stratified by sex addressed the mixed findings of previous studies (31-34). The analyses stratified by high/low total IgE were intended as a proxy for the risk of atopic and nonatopic asthma (35). All analyses were performed in STATA 11 (StataCorp, College Station, TX) and R version 2.15 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The GALA II and SAGE II studies have enrolled 4,157 and 1,281 participants, respectively, from 2006-2011. Participants were excluded if there was no self-reported residential history (N=674) or were missing essential covariate data (N= 1,118). The final analytical sample size was 4,320, including 3,343 Latinos from GALA II (1,688 cases; 1,655 controls) and 977 African Americans from SAGE II (603 cases; 374 controls) (**Table 1.1**). Cases who reported an age of diagnosis during the exposure history window (i.e., the first year or first three years of life) were omitted from the respective analyses to guarantee that exposures preceded the development of asthma. Additional participants were excluded from pollutant-specific analyses if the exposure data were unavailable.

The various study regions had different levels and mixtures of pollutants, reflecting the differing geography, weather and pollution sources (**Table 1.2, Appendix Table 1.1, Figure 1.1, Appendix Figure 1.2**). For example, while Puerto Rican subjects were exposed to much lower levels of NO_2 and PM_{10}, they had some of the highest levels of O_3, surpassed only by Houston. Participants from the San Francisco Bay Area had the lowest exposures of O_3, PM_{10}, and SO_2. Participants from Chicago and New York City generally had the highest level of traffic-related pollutants (NO_2, $PM_{2.5}$, and PM_{10}). In the median birth year for subjects in this study (1996), all regions were in compliance with the NAAQS for NO_2 and SO_2. However, Houston, Chicago and New York were designated by the EPA as nonattainment

areas for O_3. Chicago, New York, and a portion of Puerto Rico were designated as nonattainment areas for PM_{10}. Within each region, pollution levels remained relatively constant during the study period (**Appendix Figure 1.3**).

In the combined second stage analysis, the model adjusting for age, sex, ethnicity and SES did not differ significantly from the model using AIC model selection. In the AIC models, NO_2 exposure during the first year and first three years of life were both associated with a statistically significant increase in the odds for developing childhood asthma with summary ORs of 1.17 (95%CI, 1.04-1.31) and 1.26 (95%CI, 1.07-1.48), respectively (**Figures 1.2 – 1.3**; for NO_2, 5 ppb is equivalent to 9.4 $\mu g/m^3$). Many first-stage region-specific results were not statistically significant, presumably due to the relatively small sample size. However, some region-specific effects were detected. For example, asthma was associated with first year of life exposure to PM_{10} in Chicago (OR=1.39, 95%CI 1.04-1.86) and Puerto Rico (OR=1.25, 95%CI 1.09-1.44). An association with SO_2 was also found in Puerto Rico (OR=1.10, 95%CI 1.01-1.19). Among African Americans from the San Francisco Bay Area, first year of life exposures to NO_2 (OR=1.43, 95%CI, 1.08-1.88) and PM_{10} (OR=1.21, 95%CI, 1.01-1.45) were found to have the strongest effect compared to any other region. Analyses stratified by sex, high/low IgE, and family history (**Appendix Tables 1.2 – 1.4**) did not reveal any statistically significant associations. The results from the unadjusted models are included in **Appendix Figures 1.4 – 1.5**.

DISCUSSION

In this study, early life exposure to NO_2, a motor vehicle pollutant, was associated with an increased risk for subsequent asthma in Latino and African American children across five geographic regions in the U.S. and Puerto Rico. Our results are consistent with previous findings from two meta-analyses which support a relationship between NO_2 and asthma incidence (16, 24). Some studies included in these meta-analyses lacked accurate measurements of the exposure prior to the onset of asthma or used community level data rather than residential addresses to determine pollutant levels (36-38). Inaccuracies introduced by these methods may explain the inconsistencies seen in the literature. The current study

overcomes these limitations by using residential addresses to determine pollutant exposures and limiting the analyses to participants whose exposure pre-dated their asthma diagnosis.

Additionally, even though all participants lived in regions that met the current EPA annual air quality standard for NO_2, our results were statistically significant. This indicates that a risk still exists for levels of NO_2 pollution below the EPA annual standard, and suggests that this standard may not sufficiently protect children's health.

As expected, air pollution exposures differed greatly by region in our study. Although only the SAGE II participants in San Francisco showed a statistically significant association between NO_2 and asthma in the region-specific analysis, most regions showed a nominally positive association that was broadly consistent with one another, with very little between-study heterogeneity (I^2 for the first and first three years of life was 0% and 25%, respectively), suggesting that the association between NO_2 and asthma is generalizable across geographic regions.

For other pollutants, there was greater region-specific variability. For example, Puerto Rico showed associations between asthma and PM_{10} and SO_2, pollutants that are associated with emissions from vehicles and industrial processes using sulfur-containing fuels (coal and petroleum). The African Americans from the San Francisco Bay Area showed associations with NO_2 and PM_{10}, which are primarily traffic-related pollutants. The region-specific results suggest that susceptibility to asthma due to air pollution may not be uniform throughout the nation and could be dependent on local characteristics, such as varying proportions of different racial/ethnic groups and differing pollution sources and/or weather patterns. The I^2 statistic estimating heterogeneity was greater than 50% for PM_{10} and SO_2 (I^2, 57% and 53%, respectively), principally because of non-statistically significant inverse associations in Houston, San Francisco and New York. By using a random-effects model to combine the individual findings, our two-stage analysis allows us to take into account these inter-regional differences.

Since asthma susceptibility has a genetic contribution, we performed analyses stratified by family history of asthma. Those with a family history did not show an association between NO_2 and asthma, and those without a family history showed a similar OR compared to the combined analysis, but the finding

was not statistically significant because of the loss of power associated with the subgroup analysis. One study previously documented a stronger relationship between traffic exposures and asthma among children without a family history of asthma, while their results for children with a family history of asthma were not statistically significant (39). However, they did not measure individual pollutants or limit exposure measurements to periods before asthma diagnosis.

Our analyses stratified by sex showed some differences in pollution-associated asthma risk. However, the effect modification interaction p-values were not statistically significant. The analyses stratified by high/low IgE were also not statistically significant. There are few previous relevant studies and those that exist report contradictory findings. Additional studies are required to determine if family history, sex, or atopy increases the risk for pollution-associated asthma.

Overall, our results suggest that the timing of exposure to air pollution may play a role in the development of asthma. Most lung and immunological development is believed to occur in the first few years of life. Children have narrower airways and generally breathe more air per pound of bodyweight than adults, making them particularly susceptible to air pollution (16). One study reported that maternal exposure to NO_2 and PM_{10} was associated with altered blood lymphocyte subpopulations in fetal cord blood, suggesting that the immune system may be compromised by pollutant exposure *in utero*, which potentially increases the risk for developing asthma or allergies later in life (40).

Air pollution is hypothesized to alter biological processes through multiple pathways, such as inducing epigenetic changes resulting in gene dysregulation, oxidative stress resulting in a heightened inflammatory response, and airway wall remodeling resulting in physiological impairment (25). Exposure to $PM_{2.5}$ has been associated with a decrease in global methylation (41), hypermethylation of the *FOXP3* gene, reduced population of regulatory T-cells, and more severe asthma (42). Many chemicals found in vehicle emissions are oxidants or capable of reacting to form reactive oxygen species (ROS) (43). ROS can oxidize nearby macromolecules, resulting in cellular damage or "oxidative stress," which is thought to modify the pulmonary inflammatory response (44). There is also evidence that underlying genetic traits may alter the susceptibility to asthma in the presence of air pollution (45). Many of the previously

identified gene variants are related to immune cell responses (46) and prevention of oxidative damage from ROS (47). For example, the null mutations of *GSTM1* have been shown to increase the risk of asthma, especially among children with high levels of O_3 exposure (48).

To our knowledge, this is the largest and only study on the impact of air pollution on childhood asthma in U.S. minorities. Because geocoded childhood residences were used to extrapolate air pollutant concentrations from multiple nearby monitors prior to the development of asthma, this study benefits from high-quality estimates of pollution exposures and addresses three of the Bradford Hill Viewpoints for Causality, including demonstrating a temporal relationship between the exposure and outcome, establishing consistency by measuring the effect in multiple racial/ethnic populations from different regions, and providing evidence for biological plausibility. Uniform data collection was guaranteed by using a standardized questionnaire, diagnostic criteria, and exposure assessment in all recruitment regions, which ensures the generalizability of the results.

There are several limitations of this study which should be acknowledged. Many prior studies have used $PM_{2.5}$ as another indicator of traffic-related pollution, though a recent meta-analysis reported non-significant results for this pollutant (24). We also found no significant associations with $PM_{2.5}$. However regional monitoring for this pollutant was less complete during the window of exposure for our study population resulting in a smaller sample size compared to other pollutants. Thus, the non-significant results may be due to reduced power, rather than the absence of an association. A second limitation is that Puerto Rico has only two monitoring stations, which may reduce the accuracy of the pollutant exposure assignments and highlights the need for improved monitoring and additional research in this high-risk population.

Our study is also subject to the limitations inherent to our air pollution estimates, since we did not have the ability to measure air pollution by personal air sampling. While more accurate methods for measuring pollution are available by directly monitoring pollutants at a residence or school (17, 32), it is often infeasible to sample continuously throughout the year with these methods. Children spend extended time away from the home residence and may be exposed to different levels of air pollution at daycare or

school settings. Most children would be expected to spend most time at or near home, especially in early childhood, and air pollution estimates at their residential addresses will most accurately capture their overall exposure. There is a well-established variation in the risk of asthma by birth month (49). Although outside the scope of this study, other important seasonally-varying asthma risk factors such as respiratory viral infections and aeroallergen exposures should be included in subsequent analyses. Future work will need to more closely investigate birth timing with differing aspects of air quality and susceptibility, including their potential interactions. Our use of yearly averages overcame the potential for confounding by other temporally varying risk factors but precluded a more granular evaluation of whether infants born during seasons of high pollution are particularly vulnerable to the effect of air pollution. While we would have liked to stratify by atopic or nonatopic asthma, we did not have skin-prick testing on everyone and could only use total IgE as a proxy. Finally, we cannot exclude the possibility of unmeasured confounders. For example, we did not have the ability to adequately measure indoor or *in utero* air pollution, which are believed to be linked to asthma (36, 50).

In this study we attempt to establish the causal association between early life air pollution exposures and childhood asthma in U.S. minorities. We conclude that exposures to traffic-related air pollutants during the first and first three years of life are associated with childhood asthma. Regional differences throughout the country suggest that risk heterogeneity may exist. Finally, asthma risk appears to exist even though all regions achieved the current EPA annual air quality standards for NO_2. In future analyses, we plan to leverage the genetic data from these studies to assess gene-environment interactions and genetic ancestry to further understand this relationship.

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Table 1.1. Demographic information for childred included in this study.*

	Cases n = 2,291		Controls n = 2,029		Total n = 4,320	
Recruitment Center						
Chicago	302	(13%)	323	(16%)	625	(14%)
Houston	204	(9%)	158	(8%)	362	(8%)
New York	208	(9%)	195	(10%)	403	(9%)
Puerto Rico	674	(29%)	662	(33%)	1336	(31%)
San Francisco Bay Area	903	(39%)	691	(34%)	1594	(37%)
Sex						
Female	1,033	(45%)	1,141	(56%)	2,174	(50%)
Male	1,258	(55%)	888	(44%)	2,146	(50%)
Age at Recruitment						
8-9	580	(25%)	320	(16%)	900	(21%)
10-14	1,115	(49%)	982	(48%)	2,097	(49%)
15-19	530	(23%)	623	(31%)	1,153	(27%)
≥ 20	66	(3%)	104	(5%)	170	(4%)
Child Ethnicity						
Mexican	582	(25%)	645	(32%)	1,227	(28%)
Puerto Rican	783	(34%)	729	(36%)	1,512	(35%)
Other Latino[†]	323	(14%)	281	(14%)	604	(14%)
African American	603	(26%)	374	(18%)	977	(23%)
SES Composite Score[ǂ]						
1-3	13	(1%)	33	(2%)	46	(1%)
4-6	1,481	(65%)	1,299	(64%)	2,780	(64%)
7-9	797	(35%)	697	(34%)	1,494	(35%)
Birth Year						
1986-1990	167	(7%)	194	(10%)	361	(8%)
1991-1995	725	(32%)	786	(38%)	1,493	(35%)
1996-2000	1,149	(50%)	931	(46%)	2,080	(48%)
2001-2005	250	(11%)	136	(7%)	386	(9%)
Family History[§]						
Yes	1,073	(47%)	399	(20%)	1,472	(34%)
No	1,035	(45%)	1,469	(72%)	2,504	(58%)
Missing	183	(8%)	162	(8%)	345	(8%)
Place of Birth						
US	1,476	(64%)	1,075	(53%)	2,551	(59%)
Puerto Rico	665	(29%)	655	(32%)	1,320	(31%)
Other	106	(5%)	272	(13%)	378	(9%)
Missing	44	(2%)	27	(1%)	27	(2%)
Age of Onset	2.0 (0.8 - 5.0)		-		-	

*Reported as n (%), or median (IQR), for subjects with complete data on age, sex, ethnicity, and SES.
[†] "Other Latinos" reported either one Latino ethnicity other than Mexican or Puerto Rican, or reported more than one Latino ethnicity.
ǂ Composite based on the level of maternal education, annual household income, and type of medical insurance.
[§]Participants had a family history of asthma if either parent were ever diagnosed with asthma.

Table 1.2. Average pollution in 1996 (median year of birth),* compared to various air quality standards

	Chicago	Houston	New York	Puerto Rico	SF Bay Area	All	EPA National Air Quality Standard	Cal EPA Air Quality Standard	WHO Air Quality Guidelines
NO_2, ppb (24 hr ave)									
Mean (SD)	26.9 (3.4)	19.2 (4.6)	32.1 (5.7)	9.9 (2.9)	18.9 (3.9)	19.3 (8.0)	53†	30†	20.9†
25th percentile	25.4	15.6	30.4	8.7	16.9	12.7			
50th percentile	27.0	19.4	32.4	9.0	18.7	18.7			
75th percentile	28.4	21.9	35.1	10.1	20.9	24.0			
O_3, ppb (1 hr max ave)									
Mean (SD)	34.8 (4.8)	48.0 (5.0)	35.6 (3.6)	36.9 (9.2)	32.0 (7.2)	34.3 (7.7)	NAS	NAS	NAS
25th percentile	31.9	44.8	33.6	28.8	26.3	29.1			
50th percentile	34.2	47.7	35.2	37.0	30.5	33.8			
75th percentile	36.6	51.5	36.9	45.9	36.5	37.5			
O_3, ppb (8 hr max ave)									
Mean (SD)	28.6 (4.0)	38.1 (4.3)	28.6 (3.2)	30.2 (9.4)	25.5 (6.4)	27.6 (6.6)	NAS	NAS	NAS
25th percentile	25.8	35.1	26.8	21.7	20.1	23.0			
50th percentile	28.3	38.0	28.0	30.3	24.6	27.3			
75th percentile	30.6	41.1	29.8	39.1	30.1	30.9			
PM_{10}, $\mu g/m^3$ (24 hr ave)									
Mean (SD)	34.1 (4.5)	30.1 (6.6)	27.5 (4.1)	29.1 (4.8)	24.5 (5.5)	27.8 (6.0)	NAS	20†	20†
25th percentile	31.2	25.8	25.0	25.6	21.1	23.6			
50th percentile	33.8	29.3	27.1	28.4	23.48	27.1			
75th percentile	36.8	32.6	28.8	32.1	26.97	31.4			
$PM_{2.5}$, $\mu g/m^3$ (24 hr ave)									
Mean (SD)	17.0 (1.6)	13.2 (1.2)	14.4 (2.0)	8.1 (1.5)	12.3 (1.5)	11.8 (3.6)	12‡	12†	10†
25th percentile	16.1	12.3	14.2	7.2	11.3	8.5			
50th percentile	17.1	13.0	14.6	7.7	12.4	11.9			
75th percentile	18.0	12.9	15.4	9.1	12.8	14.5			
SO_2, ppb (24 hr ave)									
Mean (SD)	5.1 (1.2)	3.6 (1.4)	11.7 (3.3)	4.1 (2.0)	1.6 (0.9)	4.0 (3.4)	30†	NAS	3§
25th percentile	4.6	2.7	10.1	2.9	1.3	1.6			
50th percentile	5.0	3.5	11.2	3.5	1.5	3.0			
75th percentile	5.5	4.4	14.0	4.8	1.9	5.0			

Definition of abbreviations: SF = San Francisco, NO2 = nitrogen dioxide, O3 = ozone, PM10 = particulate matter < 10µm, PM2.5 = particulate matter < 2.5µm, SO2 = sulfur dioxide, ppb = parts per billion, µg/m3 = microgram per cubic meter, EPA = Environmental Protection Agency, Cal EPA = California Environmental Protection Agency, WHO = World Health Organization, NAS = no annual standard

*With the exception of PM2.5, where 2000 was used due to insufficient observations in 1996; reported as average (StdDev)

[†]Annual mean

[‡]Annual mean, over 3 years

[§]WHO does not have an annual SO2 guideline because they regard their 7 ppb (20µg/m3) 24 hr standard sufficiently protective for the annual average. In the GALA II regions, an annual average of ~3 ppb SO2 is comparable to a daily maximum concentration of 7 ppb.

Sources:
http://www.epa.gov/air/criteria.html#2
http://www.who.int/mediacentre/factsheets/fs313/en/index.html
http://www.arb.ca.gov/research/aaqs/caaqs/caaqs.htm

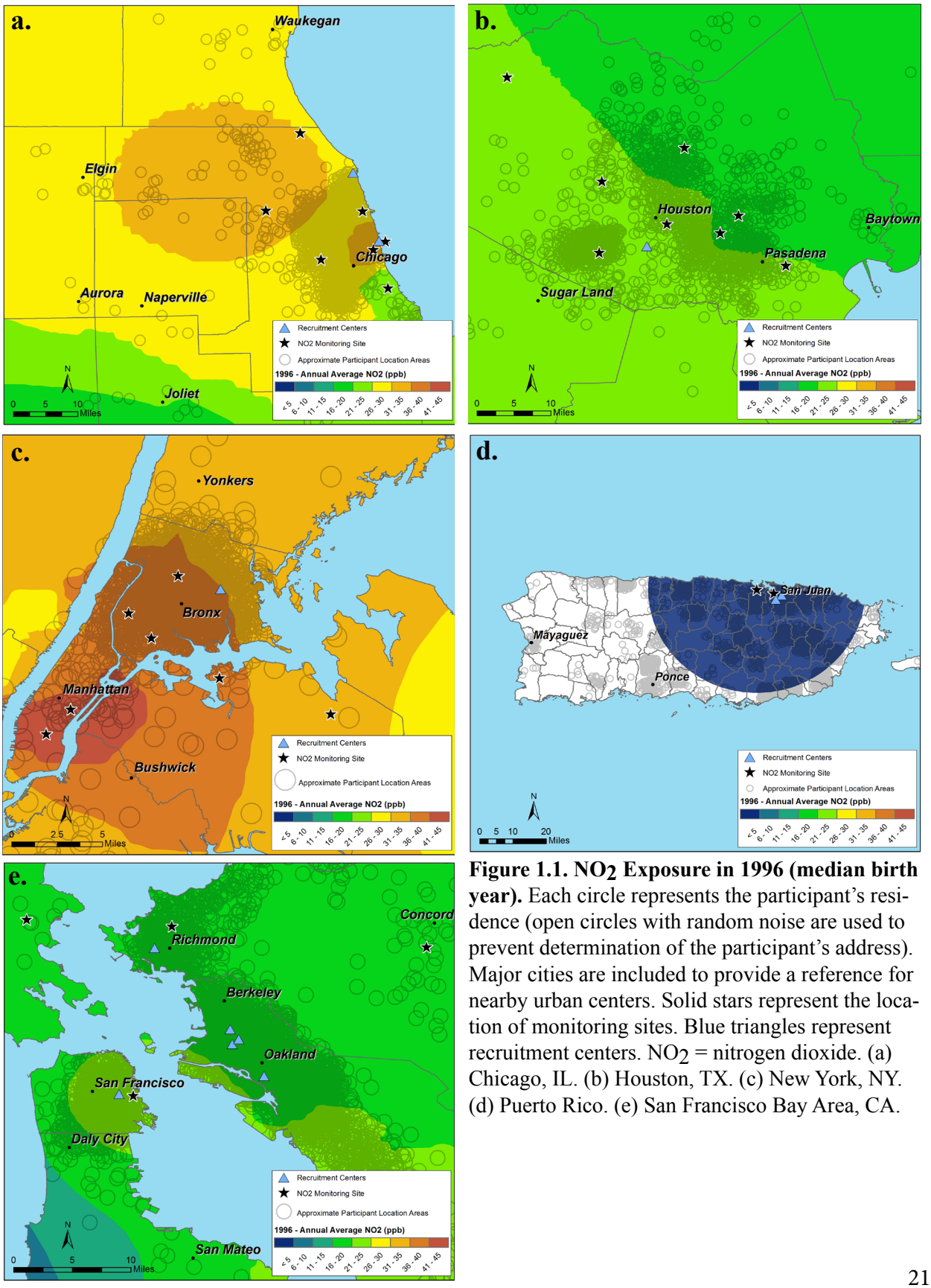
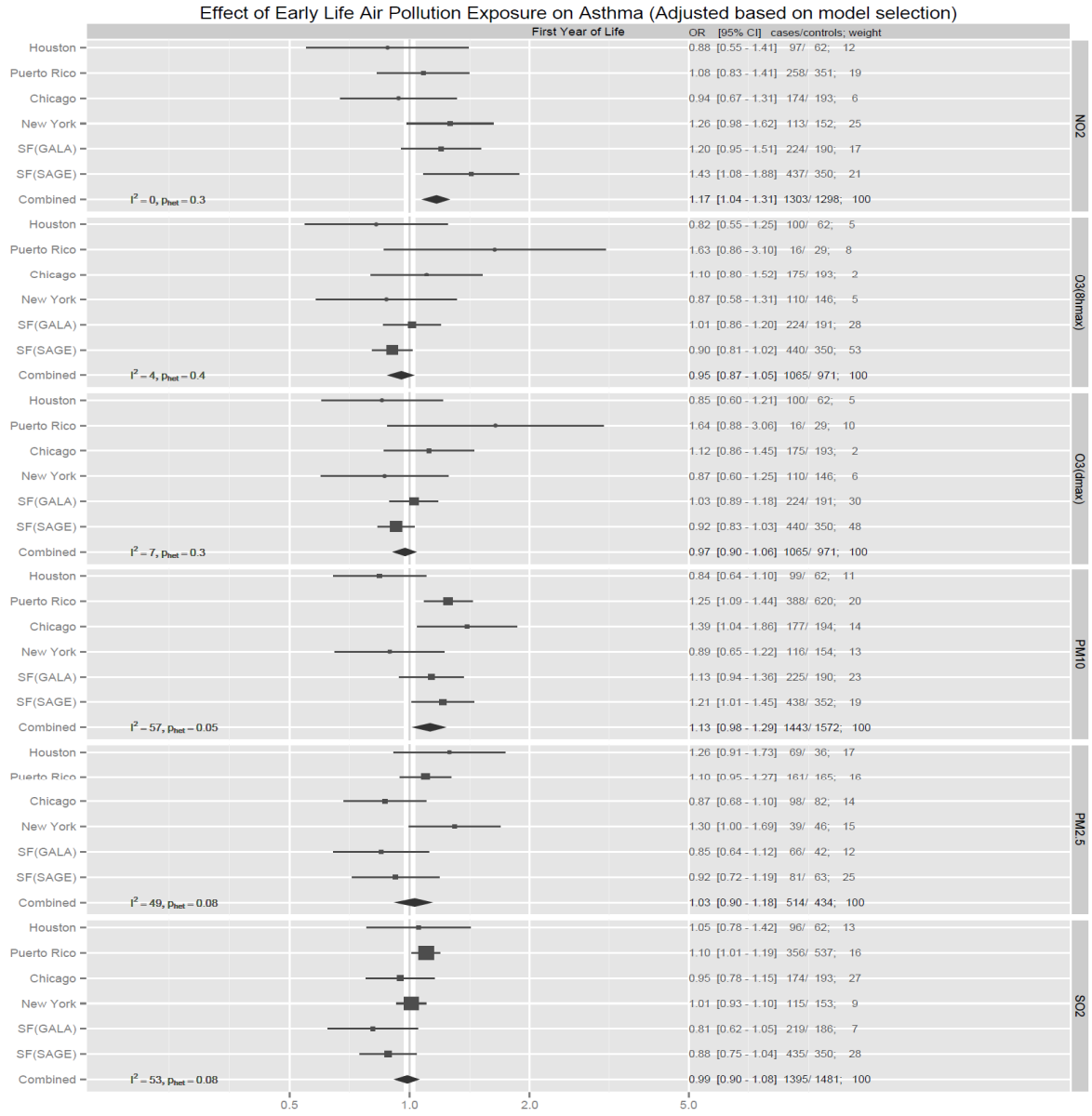


Figure 1.1. NO_2 Exposure in 1996 (median birth year). Each circle represents the participant's residence (open circles with random noise are used to prevent determination of the participant's address). Major cities are included to provide a reference for nearby urban centers. Solid stars represent the location of monitoring sites. Blue triangles represent recruitment centers. NO_2 = nitrogen dioxide. (a) Chicago, IL. (b) Houston, TX. (c) New York, NY. (d) Puerto Rico. (e) San Francisco Bay Area, CA.

Figure 1.2. Adjusted region-specific and summary OR estimates for all pollutants during the first year of life.*



Definition of abbreviations: NO_2 = Nitrogen Dioxide, OR = odds ratio, CI = confidence interval, GALA = Genes-environments & Admixture in Latino Americans, SAGE = Study of African Americans, Asthma, Genes & Environments.

*Region-specific analyses adjusted for age, SES, income, and race/ethnicity, then pooled using a random-effects model.

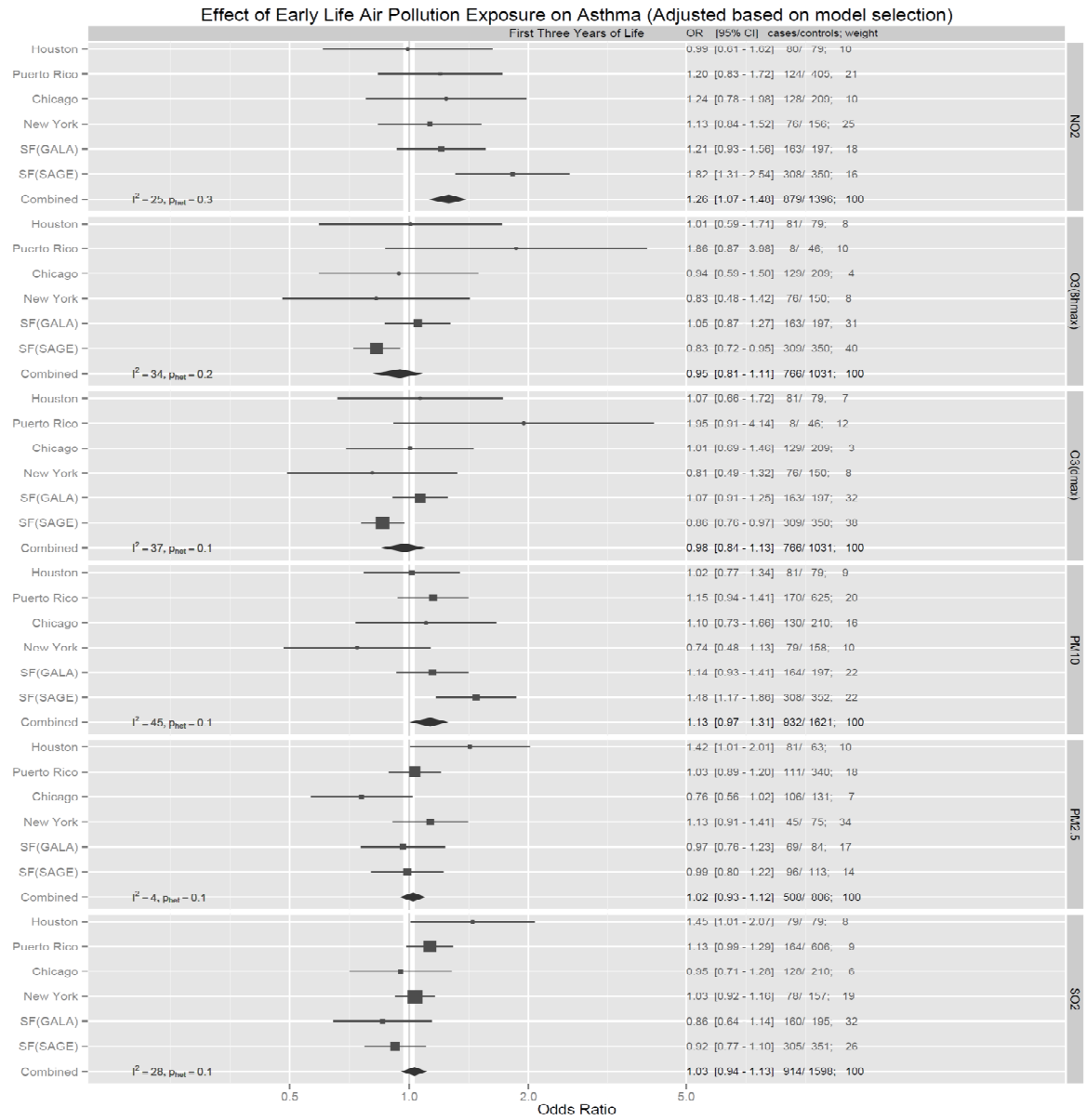
For NO_2, O_3 (1 hr max, 8 hr max), odds ratios calculated for a 5 ppb unit change.

For PM_{10}, odds ratios calculated for a 5 $\mu g/m^3$ unit change.

For $PM_{2.5}$, odds ratios calculated for a 1 $\mu g/m^3$ unit change.

For SO_2, odds ratios calculated for a 1 ppb unit change.

Figure 1.3. Adjusted region-specific and summary OR estimates for all pollutants during the first three years of life.*



Definition of abbreviations: NO_2 = Nitrogen Dioxide, OR = odds ratio, CI = confidence interval, GALA = Genes-environments & Admixture in Latino Americans, SAGE = Study of African Americans, Asthma, Genes & Environments.

*Region-specific analyses adjusted for age, SES, income, and race/ethnicity, then pooled using a random-effects model.

For NO_2, O_3 (1 hr max, 8 hr max), odds ratios calculated for a 5 ppb unit change.

For PM_{10}, odds ratios calculated for a 5 $\mu g/m^3$ unit change.

For $PM_{2.5}$, odds ratios calculated for a 1 $\mu g/m^3$ unit change.

For SO_2, odds ratios calculated for a 1 ppb unit change.

Appendix Table 1.1. Pollution definitions and sources.

Pollutants	Sources
Primary Pollutants	Pollutants that are directly emitted from chemical processes (volcanoes, motor vehicles, factories, etc.).
Nitrogen Dioxide (NO_2)	High temperature combustion from motor vehicles, electric utilities, industrial and commercial fuel burning.
Sulfur Dioxide (SO_2)	Motor vehicle combustion and industrial processes that use fuel containing sulfur (coal and petroleum).
Particulate Matter diameter <10µm (PM_{10})	"Coarse and fine particles" found in motor vehicle combustion, power plants, industrial processes, dust particles, can pass through the throat and nose and enter the lungs.
Particulate Matter diameter <2.5µm ($PM_{2.5}$)	"Fine particles" found in smoke and haze, typically directly emitted from sources such as forest fires, can enter the lung alveoli where gas exchange occurs.
Secondary Pollutants	Pollutants that are not directly emitted, but formed when primary pollutants react or interact with each other.
Ozone (O_3)	Formed by chemical reactions between NO_2 and volatile organic compounds (VOCs) in the presence of heat and sunlight.
Nitrogen Dioxide (NO_2)	Formed by chemical reactions between NO and O_3.
Particulate Matter diameter <10µm (PM_{10})	Formed by chemical reactions between SO_2, NO_2, and VOCs.
Particulate Matter diameter <2.5µm ($PM_{2.5}$)	Formed by chemical reactions between SO_2, NO_2, and VOCs.

Source: http://www.epa.gov/apti/course422/ap5.html

Appendix Table 1.2. Subgroup analysis stratified by sex.

	Pooled analysis		Boys only		Girls only	
First year of life	**n (cases, controls)**	**OR (95%CI)**	**n (cases, controls)**	**OR (95%CI)**	**n (cases, controls)**	**OR (95%CI)**
NO_2, 24 hour average*	2601 (1303, 1298)	1.16 (1.03, 1.32)	1246 (695, 551)	1.26 (1.05, 1.52)	1354 (607, 747)	1.11 (0.96, 1.29)
O_3, 1 hour max*	2036 (1065, 971)	0.98 (0.89, 1.08)	996 (576, 420)	0.98 (0.87, 1.10)	1040 (489, 551)	0.95 (0.86, 1.05)
O_3, 8 hour max*	2036 (1065, 971)	0.96 (0.87, 1.06)	996 (576, 420)	0.96 (0.85, 1.09)	1040 (489, 551)	0.93 (0.82, 1.04)
PM_{10}, 24 hour average†	3015 (1443, 1572)	1.13 (0.99, 1.28)	1472 (775, 697)	1.10 (0.89, 1.36)	1543 (668, 875)	1.15 (0.97, 1.37)
$PM_{2.5}$, 24 hour average‡	948 (514, 434)	1.03 (0.90, 1.18)	492 (280, 212)	0.92 (0.73, 1.16)	440 (218, 222)	1.13 (0.98, 1.30)
SO_2, 24 hour average§	2876 (1395, 1481)	0.99 (0.91, 1.08)	1394 (744, 650)	0.99 (0.86, 1.14)	1481 (650, 831)	1.01 (0.94, 1.08)
First three years of life						
NO_2, 24 hour average*	2275 (879, 1396)	1.26 (1.07, 1.48)	1047 (449, 598)	1.47 (1.05, 1.52)	1228 (430, 798)	1.24 (1.02, 1.50)
O_3, 1 hour max*	1797 (766, 1031)	0.98 (0.84, 1.14)	803 (381, 422)	0.96 (0.78, 1.19)	975 (384, 591)	0.96 (0.79, 1.18)
O_3, 8 hour max*	1797 (766, 1031)	0.95 (0.81, 1.12)	803 (381, 422)	0.93 (0.76, 1.13)	975 (384, 591)	0.94 (0.74, 1.19)
PM_{10}, 24 hour average†	2553 (932, 1621)	1.13 (0.97, 1.31)	1190 (474, 716)	1.08 (0.86, 1.35)	1362 (457, 905)	1.19 (1.00, 1.41)
$PM_{2.5}$, 24 hour average‡	1315 (508, 806)	1.02 (0.91, 1.16)	671 (282, 389)	0.91 (0.77, 1.06)	644 (226, 418)	1.15 (1.02, 1.30)
SO_2, 24 hour average§	2512 (914, 1598)	1.03 (0.93, 1.14)	1167 (464, 703)	1.05 (0.93, 1.19)	1345 (450, 895)	1.02 (0.92, 1.13)

Definition of abbreviations: NO_2 = Nitrogen Dioxide, O_3 = Ozone, PM_{10} = particulate matter < 10µm, $PM_{2.5}$ = particulate matter < 2.5µm, SO_2 = sulfur dioxide, ppb = parts per billion, µg/m3 = microgram per cubic meter, OR = odds ratio, CI = confidence interval

*Odds ratios calculated for a 5 ppb unit change

†Odds ratios calculated for a 5 $\mu g/m^3$ unit change

‡Odds ratios calculated for a 1 $\mu g/m^3$ unit change

§Odds ratios calculated for a 1 ppb unit change

Appendix Table 1.3. Subgroup analysis stratified by high or low total IgE.

	Pooled analysis		Total IgE > 200		Total IgE <= 200	
First year of life	**n (cases, controls)**	**OR (95%CI)**	**n (cases, controls)**	**OR (95%CI)**	**n (cases, controls)**	**OR (95%CI)**
NO_2, 24 hour average*	2601 (1303, 1298)	1.16 (1.03, 1.32)	1306 (687, 619)	1.12 (0.93, 1.36)	1295 (616, 679)	1.20 (0.91, 1.58)
O_3, 1 hour max*	2036 (1065, 971)	0.98 (0.89, 1.08)	906 (528, 378)	0.90 (0.77, 1.06)	1117 (534, 583)	1.03 (0.92, 1.15)
O_3, 8 hour max*	2036 (1065, 971)	0.96 (0.87, 1.06)	906 (528, 378)	0.90 (0.72, 1.12)	1117 (534, 583)	1.01 (0.90, 1.15)
PM_{10}, 24 hour average†	3015 (1443, 1572)	1.13 (0.99, 1.28)	1581 (783, 798)	1.12 (1.00, 1.25)	1434 (660, 774)	1.22 (0.97, 1.55)
$PM_{2.5}$, 24 hour average‡	948 (514, 434)	1.03 (0.90, 1.18)	492 (292, 200)	1.06 (0.93, 1.21)	456 (221, 235)	1.00 (0.85, 1.17)
SO_2, 24 hour average§	2876 (1395, 1481)	0.99 (0.91, 1.08)	1498 (758, 740)	1.04 (0.94, 1.15)	1378 (637, 741)	0.92 (0.80, 1.06)
First three years of life						
NO_2, 24 hour average*	2275 (879, 1396)	1.26 (1.07, 1.48)	1103 (448, 655)	1.19 (0.97, 1.46)	1172 (431, 741)	1.38 (0.90, 2.12)
O_3, 1 hour max*	1797 (766, 1031)	0.98 (0.84, 1.14)	766 (370, 396)	0.87 (0.75, 1.02)	1009 (393, 616)	1.04 (0.82, 1.32)
O_3, 8 hour max*	1797 (766, 1031)	0.95 (0.81, 1.12)	766 (370, 396)	0.85 (0.69, 1.04)	1009 (393, 616)	1.01 (0.77, 1.32)
PM_{10}, 24 hour average†	2553 (932, 1621)	1.13 (0.97, 1.31)	1296 (484, 812)	1.04 (0.83, 1.29)	1255 (448, 807)	1.35 (0.98, 1.85)
$PM_{2.5}$, 24 hour average‡	1315 (508, 806)	1.02 (0.91, 1.16)	679 (283, 396)	0.93 (0.72, 1.21)	632 (222, 410)	1.10 (0.96, 1.25)
SO_2, 24 hour average§	2512 (914, 1598)	1.03 (0.93, 1.14)	1274 (476, 798)	1.03 (0.88, 1.20)	1237 (438, 799)	1.02 (0.82, 1.27)

Definition of abbreviations: NO_2 = Nitrogen Dioxide, O_3 = Ozone, PM_{10} = particulate matter < 10µm, $PM_{2.5}$ = particulate matter < 2.5µm, SO_2 = sulfur dioxide, ppb = parts per billion, µg/m3 = microgram per cubic meter, OR = odds ratio, CI = confidence interval

*Odds ratios calculated for a 5 ppb unit change

†Odds ratios calculated for a 5 $\mu g/m^3$ unit change

‡Odds ratios calculated for a 1 $\mu g/m^3$ unit change

§Odds ratios calculated for a 1 ppb unit change

Appendix Table 1.4. Subgroup analysis stratified by family history of asthma.

	Pooled analysis		Family History[‖]		No Family History[‖]	
First year of life	**n (cases, controls)**	**OR (95%CI)**	**n (cases, controls)**	**OR (95%CI)**	**n (cases, controls)**	**OR (95%CI)**
NO_2, 24 hour average*	2601 (1303, 1298)	1.16 (1.03, 1.32)	842 (543, 299)	1.01 (0.73, 1.42)	1540 (632, 908)	1.19 (0.90, 1.59)
O_3, 1 hour max*	2036 (1065, 971)	0.98 (0.89, 1.08)	578 (386, 192)	0.96 (0.76, 1.21)	1263 (555, 708)	0.96 (0.82, 1.11)
O_3, 8 hour max*	2036 (1065, 971)	0.96 (0.87, 1.06)	578 (386, 192)	0.97 (0.73, 1.29)	1263 (555, 708)	0.94 (0.79, 1.11)
PM_{10}, 24 hour average[†]	3015 (1443, 1572)	1.13 (0.99, 1.28)	984 (611, 373)	1.11 (0.94, 1.30)	1803 (701, 112)	1.11 (0.93, 1.33)
$PM_{2.5}$, 24 hour average[‡]	948 (514, 434)	1.03 (0.90, 1.18)	232 (168, 64)	1.05 (0.87, 1.26)	602 (262, 340)	0.96 (0.77, 1.21)
SO_2, 24 hour average[§]	2876 (1395, 1481)	0.99 (0.91, 1.08)	930 (604, 326)	0.95 (0.76, 1.20)	1719 (677, 1042)	1.02 (0.95, 1.10)
First three years of life						
NO_2, 24 hour average*	2275 (879, 1396)	1.26 (1.07, 1.48)	642 (330, 312)	1.21 (0.72, 2.03)	1432 (447, 985)	1.27 (0.98, 1.64)
O_3, 1 hour max*	1797 (766, 1031)	0.98 (0.84, 1.14)	444 (257, 187)	0.92 (0.69, 1.21)	1164 (409, 755)	0.95 (0.76, 1.19)
O_3, 8 hour max*	1797 (766, 1031)	0.95 (0.81, 1.12)	444 (257, 187)	0.90 (0.69, 1.18)	1164 (409, 775)	0.92 (0.73, 1.17)
PM_{10}, 24 hour average[†]	2553 (932, 1621)	1.13 (0.97, 1.31)	728 (352, 376)	1.05 (0.79, 1.39)	1619 (478, 1141)	1.15 (0.95, 1.38)
$PM_{2.5}$, 24 hour average[‡]	1315 (508, 806)	1.02 (0.91, 1.16)	340 (176, 164)	1.00 (0.82, 1.23)	866 (276, 590)	0.93 (0.72, 1.19)
SO_2, 24 hour average[§]	2512 (914, 1598)	1.03 (0.93, 1.14)	710 (355, 355)	0.97 (0.79, 1.18)	1596 (468, 1128)	1.06 (0.96, 1.16)

Definition of abbreviations: NO_2 = Nitrogen Dioxide, O_3 = Ozone, PM_{10} = particulate matter < 10µm, $PM_{2.5}$ = particulate matter < 2.5µm, SO_2 = sulfur dioxide, ppb = parts per billion, µg/m3 = microgram per cubic meter, OR = odds ratio, CI = confidence interval

*Odds ratios calculated for a 5 ppb unit change

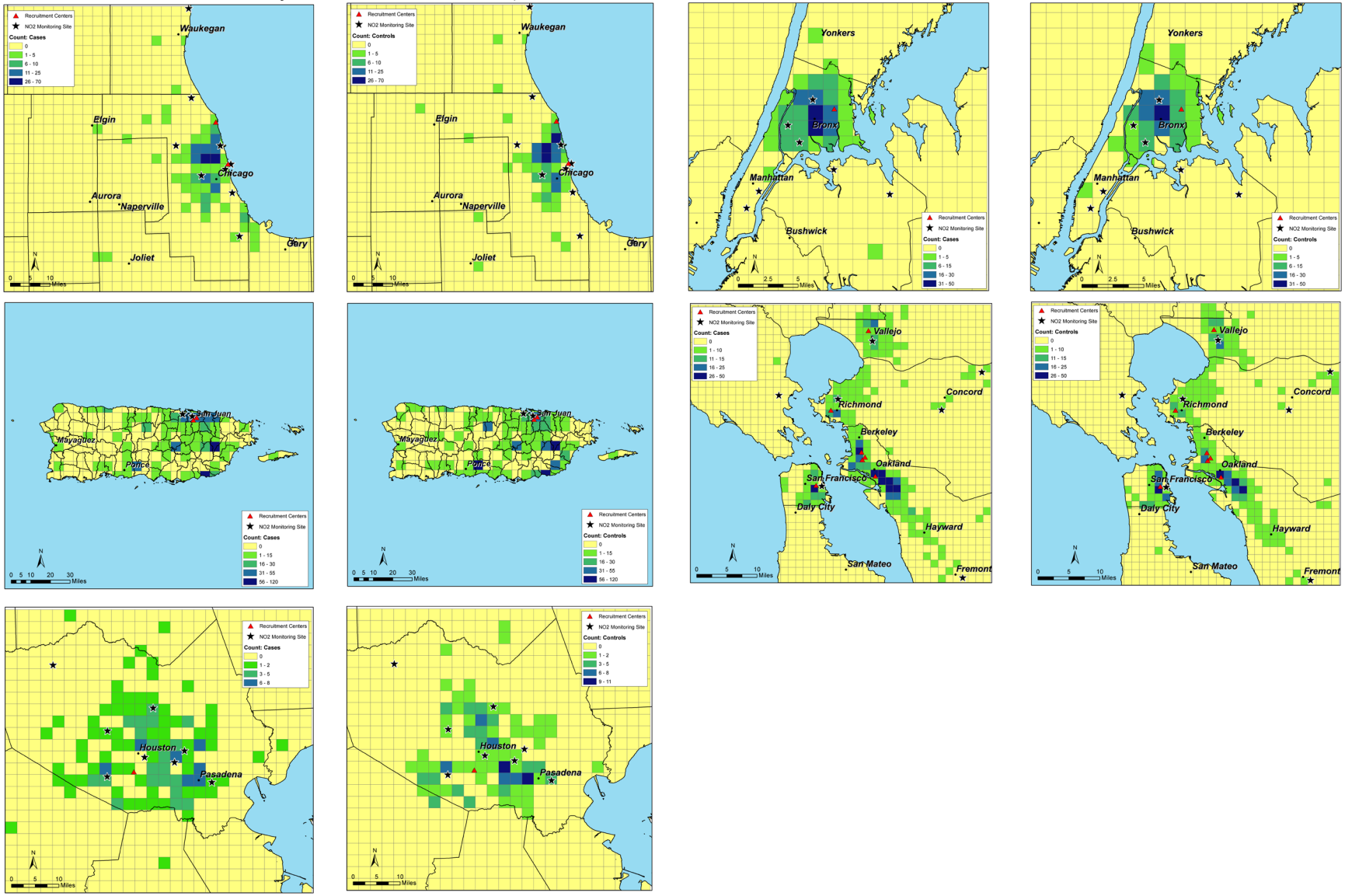
[†]Odds ratios calculated for a 5 $\mu g/m^3$ unit change

[‡]Odds ratios calculated for a 1 $\mu g/m^3$ unit change

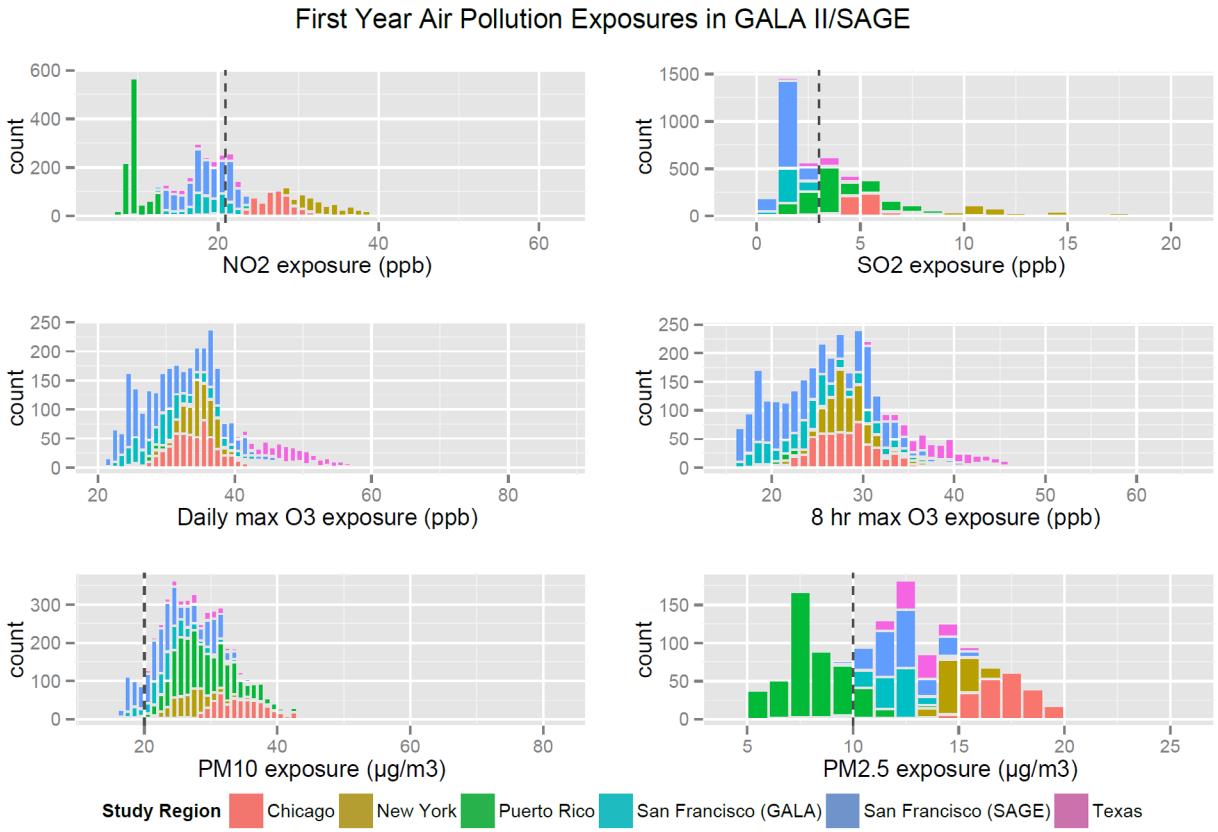
[§]Odds ratios calculated for a 1 ppb unit change

[‖]Participants had a family history of asthma if either parent were ever diagnosed with asthma.

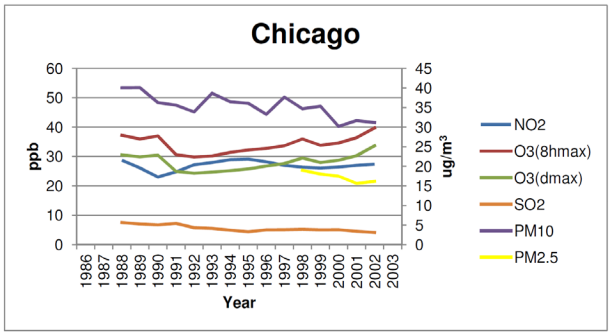
Appendix Figure 1.1. Geographic distribution of cases and controls within each recruitment region.
Density of cases (left) and controls (right) based on their address at time of recruitment in 5 recruitment regions (Chicago, IL; New York, NY; Puerto Rico; San Francisco Bay Area, CA; Houston, TX).

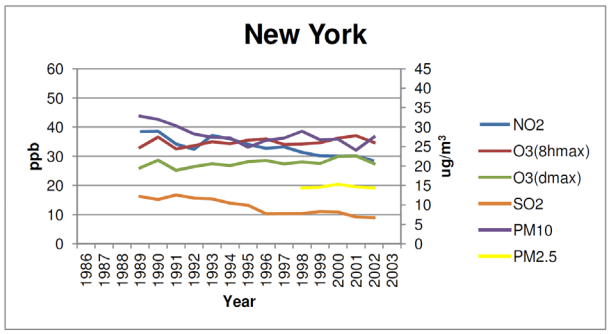


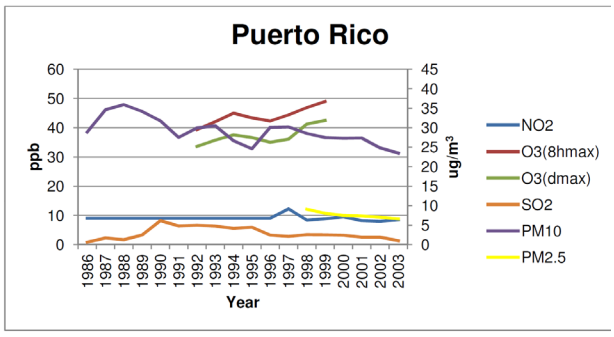
Appendix Figure 1.2. Distribution of all pollutants in the first year of life. Definition of abbreviations: NO_2 = Nitrogen Dioxide, O_3 = Ozone, PM_{10} = particulate matter < 10µm, $PM_{2.5}$ = particulate matter < 2.5µm, SO_2 = sulfur dioxide, GALA = Genes-environments & Admixture in Latino Americans, SAGE = Study of African Americans, Asthma, Genes & Environments. Dotted line = World Health Organization air quality guidelines, if available.

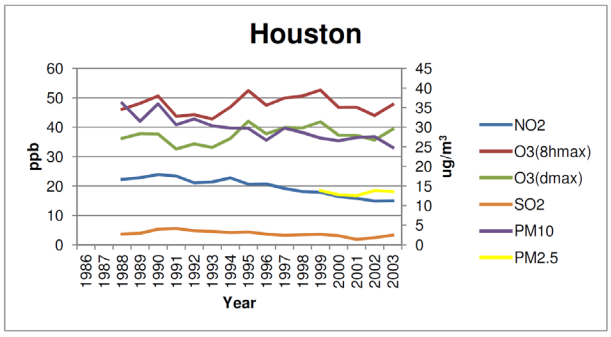


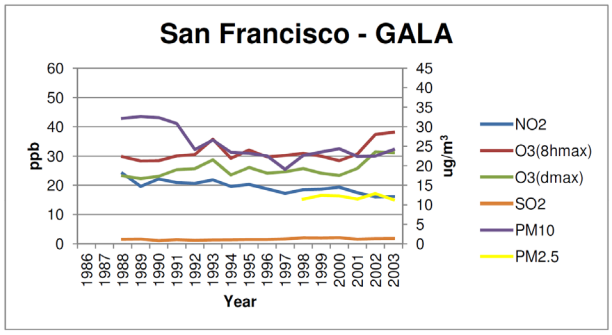
Appendix Figure 1.3. Median pollution values during the study period (1986-2003) for each region.
Definition of abbreviations: NO_2 = nitrogen dioxide, O_3 = ozone, PM_{10} = particulate matter < 10um, $PM_{2.5}$ = particulate matter < 2.5um, SO_2 = sulfur dioxide, GALA = Genes-environments & Admixture in Latino Americans, SAGE = Study of African Americans, Asthma, Genes & Environments.
NO_2, O_3 (8 hr max, 1 hr max) and SO_2 are measured in parts per billion (ppb).
PM_{10} and $PM_{2.5}$ are measured in ug/m^3.

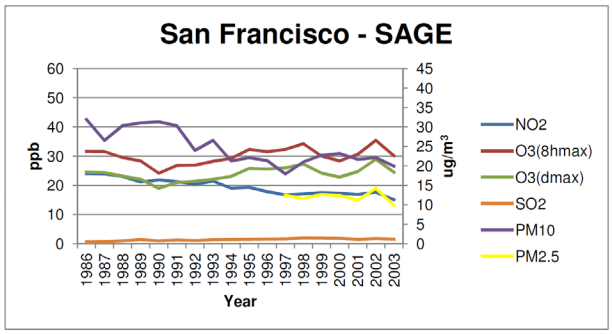




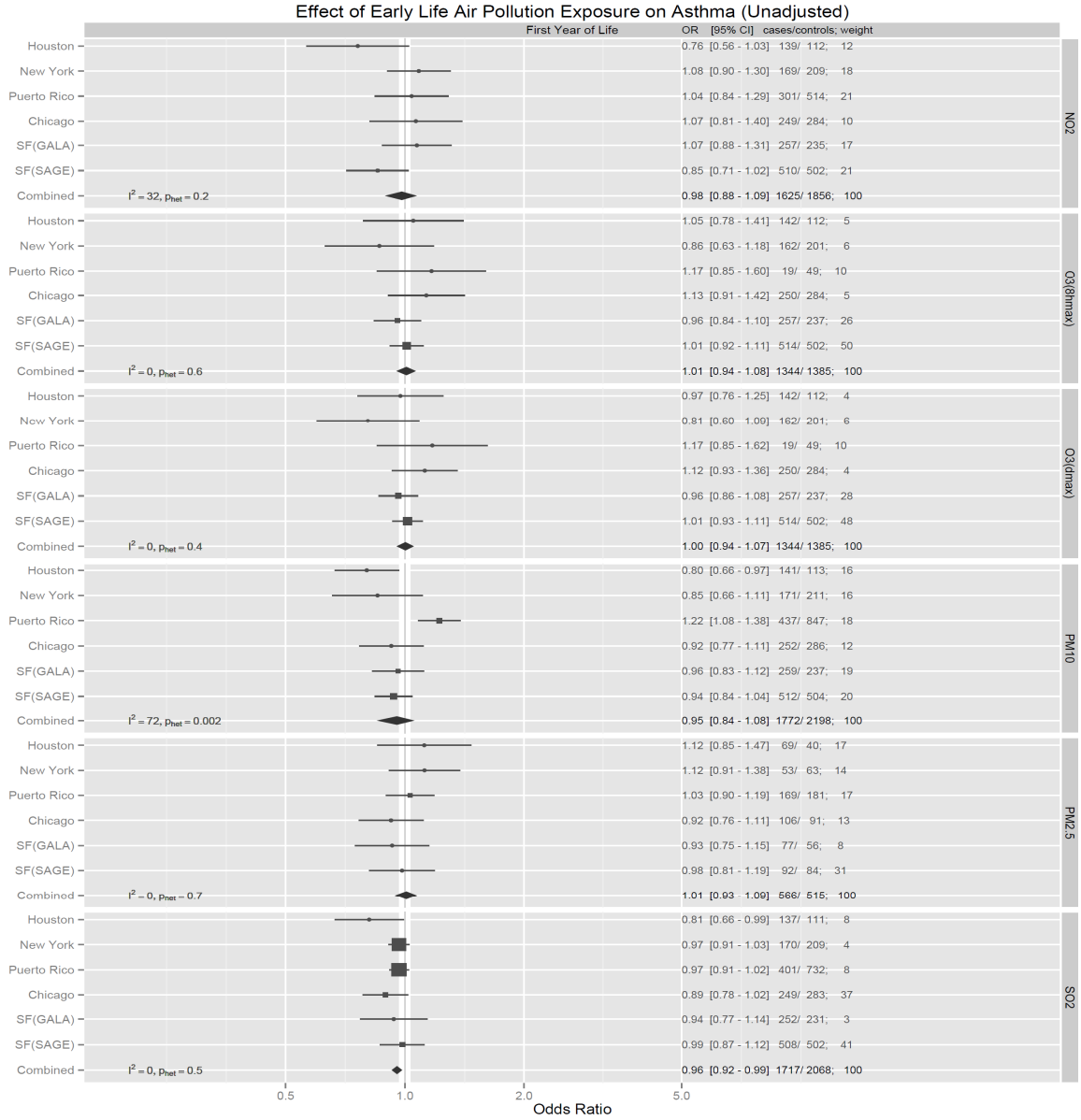








Appendix Figure 1.4. Unadjusted region-specific and summary OR estimates for all pollutants during the first year of life.*



Definition of abbreviations: NO_2 = Nitrogen Dioxide, OR = odds ratio, CI = confidence interval, GALA = Genes-environments & Admixture in Latino Americans, SAGE = Study of African Americans, Asthma, Genes & Environments.

*Region-specific analyses adjusted for age, SES, income, and race/ethnicity, then pooled using a random-effects model.

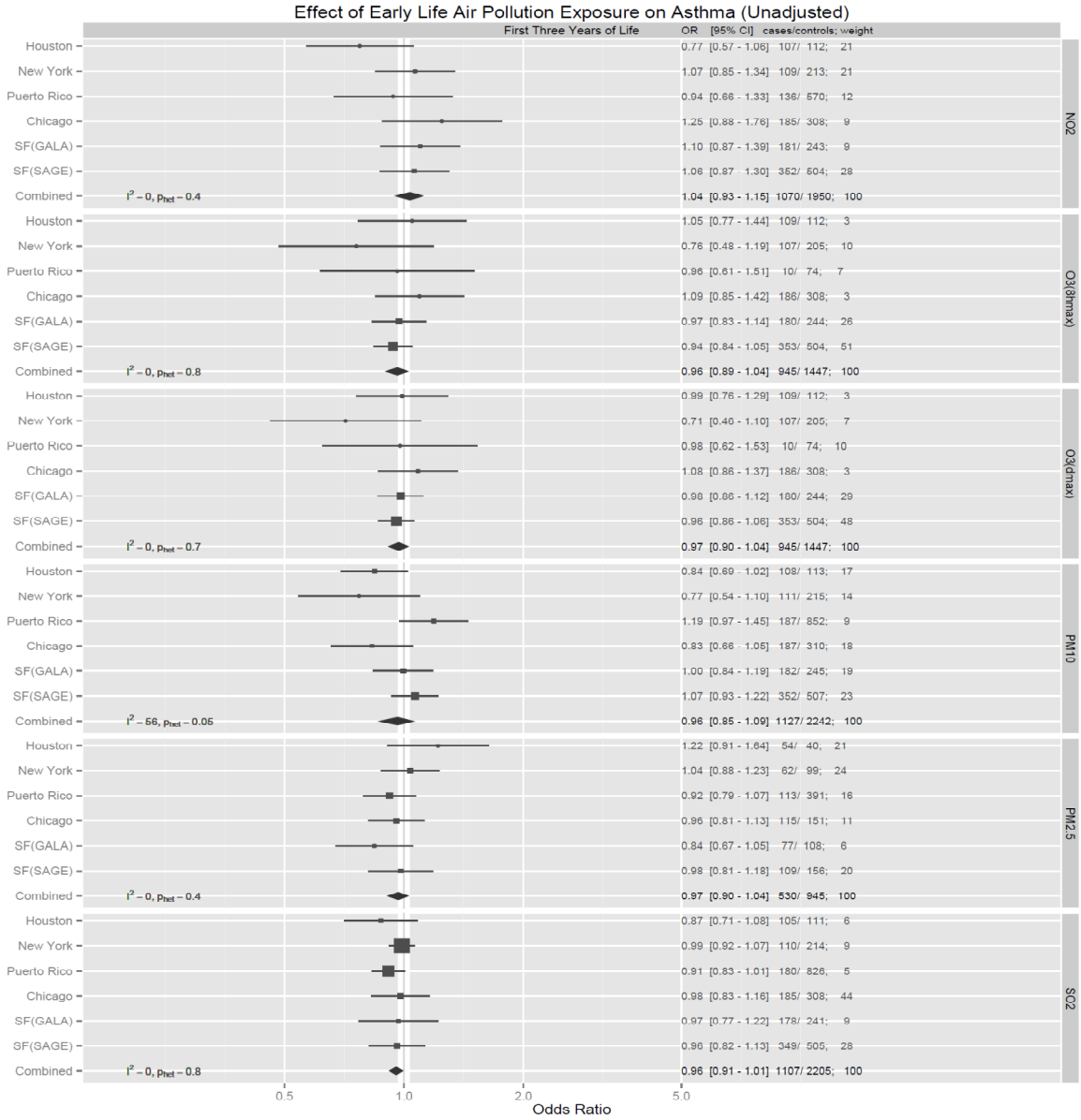
For NO_2, O_3 (1 hr max, 8 hr max), odds ratios calculated for a 5 ppb unit change.

For PM_{10}, odds ratios calculated for a 5 $\mu g/m^3$ unit change.

For $PM_{2.5}$, odds ratios calculated for a 1 $\mu g/m^3$ unit change.

For SO_2, odds ratios calculated for a 1 ppb unit change.

Appendix Figure 1.5. Unadjusted region-specific and summary OR estimates for all pollutants during the first three years of life.*



Definition of abbreviations: NO_2 = Nitrogen Dioxide, OR = odds ratio, CI = confidence interval, GALA = Genes-environments & Admixture in Latino Americans, SAGE = Study of African Americans, Asthma, Genes & Environments.

*Region-specific analyses adjusted for age, SES, income, and race/ethnicity, then pooled using a random-effects model.

For NO_2, O_3 (1 hr max, 8 hr max), odds ratios calculated for a 5 ppb unit change.

For PM_{10}, odds ratios calculated for a 5 $\mu g/m^3$ unit change.

For $PM_{2.5}$, odds ratios calculated for a 1 $\mu g/m^3$ unit change.

For SO_2, odds ratios calculated for a 1 ppb unit change.

CHAPTER 2. Race/Ethnicity Modifies the Effect of Air Pollution on Lung Function: The GALA II and SAGE II Studies

INTRODUCTION

Ambient air pollution has consistently been linked to numerous respiratory diseases (1). It is widely acknowledged to be an asthma trigger, associated with asthma symptoms (2-5), poor asthma control (6), emergency hospitalization (7-10), and reduced response to asthma rescue medications (11). Pollutants produced by traffic and industrial processes (particulate matter (PM), nitrogen dioxide (NO_2), sulfur dioxide (SO_2) and ozone (O_3)) have been linked to lung deficits. Findings from population-based epidemiologic studies have been supported in animal studies (12-14), panel studies (15), and human exposure studies (16-18), offering further verification of these results and establishing air pollution as an important target in the effort to reduce asthma morbidity and mortality.

Compared with adults, children are more susceptible to the harmful effects of air pollution due to their small body size, higher rates of metabolism, and developing pulmonary and immune systems (19, 20). Children with asthma have been shown to have reduced lung function after recent air pollution exposures, which can contribute to the severity of their asthma (21). Minority and low socioeconomic status (SES) children are disproportionately exposed to higher levels of air pollution (22-24), are more likely to have serious asthma complications (25), and have some of the highest rates of childhood asthma in the US. (26). For these reasons, minority children with asthma are particularly vulnerable to the effects of air pollution.

While the negative effects of air pollution on lung health have been well-documented, few studies have examined the impact of air pollution on minority children in the US. A study of Californian Latinos (2) and a cohort study of mostly African American and Latino children from Detroit (27) confirmed the hypothesis that air pollution is associated with worse asthma symptoms and poorer pulmonary function in minorities with asthma. However, to the best of our knowledge, there have been no studies comparing the associations between air pollution and lung function among different minority children with asthma. In

our previous work, we found that early-life exposure to air pollution increased the risk for developing asthma later in life, and that the risk varied for different racial/ethnic groups (28). In this analysis, we aim to formally assess the effect of air pollution on lung function in our own study population. We also hypothesize that the degree of lung function impairment may differ for different racial/ethnic groups, and this may partly explain the reported heterogeneity in asthma morbidity (25).

METHODS

Study design and subjects

Together, the Genes-environments & Admixture in Latino Americans study (GALA II) and the Study of African Americans, Asthma, Genes & Environments (SAGE II) represent the largest gene-environment study of asthma in minority children in the US. GALA II and SAGE II are parallel case-control studies, recruiting participants from the same clinical centers, using identical eligibility criteria and questionnaires. GALA II recruited Latinos from five urban centers in the US (Chicago, IL; Bronx, NY; Houston, TX; San Francisco Bay Area, CA; and Puerto Rico) and SAGE II recruited African Americans from the San Francisco Bay Area only. Due to insufficient sample sizes, only asthma cases recruited from the San Francisco Bay Area and Puerto Rico were included in the current study.

A detailed description of the enrollment criteria has previously been published (28). Briefly, participants were 8-21 years old, had no history of other lung or chronic diseases (other than atopy and allergy-related diseases), were self-identified Latino or African American, and had four Latino or African American grandparents. Children with asthma had a physician diagnosis, plus two or more symptoms of coughing, wheezing, or shortness of breath in the past two years. Participants were ineligible if they were in the third trimester of pregnancy or were current smokers with more than a 10 pack per year smoking history. All local institutional review boards approved the study and all parents/participants provided signed written consent/assent.

Outcome assessment

Spirometry was performed using KoKo Spirometers (Ferraris CardioRespiratory; Pulmonary Data Services, Inc. Louiseville, CO, USA) according to the American Thoracic Society criteria (29). Participants were asked not to use their bronchodilator medication eight hours prior to spirometry testing and not to use a nasal steroid spray in the week prior to spirometry testing. Up to eight tracings were obtained to collect five reproducible flow-volume loops with less than 5% variability in forced expiratory volume during 1 second (FEV_1, in mL). The loop with the best predicted performance was extracted for analysis. Three raw lung function metrics were evaluated: FEV_1, forced vital capacity (FVC, mL), and forced expiratory flow between 25% and 75% of vital capacity (FEF_{25-75}, mL/sec).

Exposure assessment

Trained bilingual (English-Spanish) interviewers administered questionnaires to collect demographic information, medical histories, environmental exposures, and residential histories. Each residence was assigned geographic coordinates using the TomTom/Tele Atlas EZ-Locate software (TomTom, Amsterdam, the Netherlands). Regional ambient air pollution data were obtained from the US Environmental Protection Agency (EPA) Air Quality System.

Pollution values for the participant's residential geographic coordinate was estimated by calculating the inverse distance-squared weighted average from the four closest air pollution monitoring stations within 50 km of the residence. Daily average exposures were estimated for the day of spirometry testing (Lag 0) and 1-day moving averages for each of the 7 days prior to spirometry testing (Lag1, Lag 2, Lag 3, through Lag 7). Average exposures over the three days prior (Lag 1-3) and week prior (Lag 1-7) to spirometry testing were calculated by averaging all available daily exposures during those time periods. Pollution exposures were estimated for NO_2, SO_2, O_3 (8-hour daily maximum), particulate matter with aerodynamic diameter $\leq 2.5\mu m$ ($PM_{2.5}$) and particulate matter with aerodynamic diameter $\leq 10\mu m$ (PM_{10}). Particulate matter with aerodynamic diameter 2.5-10µm (PM-Coarse) was calculated by taking the difference between $PM_{2.5}$ and PM_{10}.

Analyses

Multivariable linear regressions were used to evaluate the association between five air pollution exposures (NO_2, SO_2, O_3, $PM_{2.5}$, PM-Coarse) and three lung function measures (FEV_1, FVC, FEF_{25-75}). All models were adjusted for confounders identified in previous publications, including age, sex, height, height^2, socioeconomic status (SES), self-identified ethnicity, recruitment region, current household smokers, controller medication use in the past two weeks, and genetic African ancestry. The development of the SES index has been described elsewhere (30) and was calculated by assigning a low, medium or high score for annual household income, maternal level of education, and insurance type, and then summing across these three values.

The proportion of African ancestry was included because it has previously been shown to influence lung function in African Americans (31) and Puerto Ricans (32). Methods for estimating global genetic ancestry have been described elsewhere (31, 33). Briefly, the proportion of genetic ancestry was calculated by first genotyping all subjects with the Axiom LAT1 array (World Array 4, Affymetrix, Santa Clara, CA, USA) (34). Estimates of genetic ancestry were then obtained using an unsupervised analysis in ADMIXTURE (35) to determine the proportion of African, European, and Native American ancestry for Latinos, and the proportion of African and European ancestry for African Americans. Reference haplotypes were derived from European and African individuals in HapMap phase II (http://hapmap.ncbi.nlm.nih.gov) and 71 Native American individuals genotyped on the Axiom LAT1 array. The models were not adjusted for the proportion of European ancestry because the variable would have been omitted due to collinearity in the African American subgroup analyses, given that African Americans were assigned only two ancestral proportions (African and European), which sum to one.

To determine if the effect of air pollution on lung function varied for different minority groups, we tested for effect modification by race/ethnicity using an interaction term with each pollutant, and also reported the analyses stratified by race/ethnicity. Participants were classified into one of four categories of self-identified race/ethnicity: African American, Mexican American, Puerto Rican or Other Latino (South American, Central American, non-Puerto Rican Caribbean, or mixed Latino).

Air pollution estimates were scaled based on the range of pollution exposures observed. Results are reported as the change in lung function per five unit (ppb or $\mu g/m^3$) increase in NO_2, O_3, $PM_{2.5}$ and PM-Coarse, and per one unit increase in SO_2. To correct for multiple comparisons across pollutant exposures, we applied a Bonferroni correction. Here, we report nominal p-values for air pollution, but adjust our significance level to 0.001 to account for 50 tests per outcome. We considered interaction p-values less than 0.1 to be indicative of effect modification. Analyses were performed in Stata 13 (StataCorp, College Station, TX, USA) and R version 3.0 (R Foundation for Statistical Computing, Vienna, Austria) (36).

RESULTS

The GALA II and SAGE II studies enrolled 5,501 children with and without asthma during 2006-2011. There were 1,916 participants with asthma recruited from the San Francisco Bay Area and Puerto Rico who had at least one valid air pollution estimate. Participants were excluded if missing age, sex, height, ethnicity, SES or current secondhand smoke exposure (n=376), or failed quality control measures for genotyping (n=109) or spirometry (n=54). The final analytical sample size was 1,377 and included 547 African Americans, 567 Puerto Ricans, 158 Mexican Americans, and 105 Other Latinos (**Table 1.1**). Additional participants were excluded from pollution-specific analyses if exposure data were unavailable.

Most participants had exposures that satisfied the EPA National Ambient Air Quality Standards (NAAQS) (**Table 1.2**). All participants in the final analytical sample had SO_2 and O_3 exposures that satisfied the guidelines and greater than 85% of participants had $PM_{2.5}$ and PM_{10} exposures that met the guidelines.

We did not find consistent associations between O_3, $PM_{2.5}$ or NO_2 with any of the three lung function measurements, however several associations with SO_2 and PM-Coarse were Bonferroni significant. Every 1 ppb increase in SO_2 exposure and every 5 $\mu g/m^3$ increase in PM-Coarse exposure on the day prior to spirometry was associated with lung deficits of 36 mL (95% CI, 15-57) and 32 mL (16-49), respectively (**Figure 1.1**). Associations with similar magnitudes were detected up to seven days prior

to spirometry testing. While the majority of SO_2 associations were Bonferroni significant, fewer of the PM-Coarse associations were Bonferroni significant, possibly due to the smaller number of participants with available data on particulate matter exposure. The associations for SO_2 and PM-Coarse with FVC were similar in magnitude and significance compared with FEV_1 (**Appendix Figure 1.1**). Findings with FEF_{25-75} were weaker, but trending in similar directions compared with FEV_1 and FVC (**Appendix Figure 1.2**).

Many of the race/ethnicity interaction p-values for SO_2 and PM-Coarse were also significant suggesting that race/ethnicity modifies the association between air pollution and lung function (**Figure 1.2**). For example, PM-Coarse exposure on the day prior to spirometry had a greater impact on Mexican Americans and African Americans, who on average experienced a 137 mL (53-221) and 77 mL (9-144) deficit in FEV_1, respectively, for every 5 $\mu g/m^3$ increase in PM-Coarse exposure. Puerto Ricans experienced a 26 mL (8-44) decrease in FEV_1; the association among Other Latinos was not significant. For SO_2 exposure in the week prior to spirometry, Puerto Ricans experienced the largest deficits in FEV_1, where a 1 ppb increase in SO_2 was associated with a 70 mL (39-101) decrease in FEV_1. Similar but weaker trends were seen with FVC and FEF_{25-75} (**Appendix Figure 1.3 – 1.4**).

DISCUSSION

In our study, recent air pollution exposures to SO_2 and PM-Coarse were associated with varying levels of lung impairment in Latino and African American children with asthma. The negative effects of these exposures persisted up to seven days prior to pulmonary function testing. Many associations were significant after Bonferroni correction for multiple comparisons, indicating that our findings are unlikely due to chance.

While one previous study demonstrated that Latinos with asthma have greater lung deficits than non-Latinos with asthma (37), comparisons among other US minorities have not been conducted until now. The geographical distribution of Latinos and African Americans from the San Francisco Bay Area did not appear to be related to pollution exposures (**Figure 1.3**), suggesting that residential self-selection

bias is unlikely to explain the observed racial/ethnic differences in pollution-associated lung function deficiencies.

In our analyses, we adjusted for multiple covariates that could potentially explain racial/ethnic differences in lung function. Previous studies have described racial/ethnic differences in smoking prevalence (38, 39) and socioeconomic status (30). Additionally, there is evidence that genetic ancestry may be associated with lung function (32) and may improve the fit of lung function prediction equations (31). After including genetic ancestry, presence of current household smokers, and socioeconomic status in our models, we still detected differences in pollution-associated lung deficiencies. The reasons for these differences have yet to be identified, though there are many possible explanations that should be investigated in future analyses, including specific genetic (40, 41) or epigenetic traits (42), and other environmental exposures such as parental psychosocial stress (43) and indoor air pollutants (44).

Our associations between lung function and SO_2 and PM-Coarse are consistent with previous research (45-47). However, our null findings with O_3, NO_2 and $PM_{2.5}$ are discordant with some epidemiologic studies (27, 48-50). Although our power to detect an association was weaker for some of these pollutants, the point estimates for O_3, NO_2 and $PM_{2.5}$ were mostly centered on the null, suggesting that our lack of statistically significant findings was not related to insufficient power.

Previous research has offered plausible biological mechanisms explaining the link between air pollution and pulmonary health. Recent pollution exposures may cause an inflammatory response resulting in airway obstruction (51) and airway remodeling (52). SO_2 and particulate matter has been shown to cause damage in cell culture experiments, animal models and human exposure studies (12, 45, 53). These pollutants are believed to fuel chemical reactions that produce reactive oxygen species (ROS), which can trigger inflammation and cause DNA damage, supporting the recent International Agency for Research on Cancer classification of air pollution as a carcinogen (54).

There are several limitations which must be acknowledged. While this is the largest study of lung function in minority children, the sample size for some of the stratified race/ethnicity analyses was small. This was especially problematic for particulate matter exposures in San Francisco and NO_2 exposures in

Puerto Rico, for which the majority of exposure assignments were unavailable due to insufficient monitoring. Additionally, since we utilized data from air pollution monitors to estimate exposures that occurred at the residential address, exposure misclassification may have occurred. While the children in our study were likely spending time away from the home, we were unable to measure exposures through personal monitoring or extrapolate exposures from school addresses. Finally, unmeasured confounding is often a concern with multifactorial diseases like asthma. However, our results were significant after adjustment for numerous confounders, including SES, secondhand smoke exposure, and African genetic ancestry.

Our study benefitted from the size, diversity and depth of our sample and covariate data. In addition to being one of the largest studies of pediatric lung function in minorities, our study is one of the few with the genetic data necessary to adjust for confounding by genetic ancestry. Our future work should and will include a thorough gene by environment (GxE) study to determine if specific ancestry-related genetic traits modify the air pollution – lung function relationship.

In conclusion, out study found that recent exposure to SO_2 and PM-Coarse were associated with lung deficiencies in Latino and African American children with asthma. The magnitude of the deficiencies appeared to vary for different minority racial/ethnic groups, suggesting that different minority groups may respond differently to these pollutants. These associations were found at pollution levels that satisfied the EPA air quality standards. In spite of living in neighborhoods that were in compliance with federal air quality guidelines, measurable changes in lung function were still detected. Previous studies have found that exposure to regional and traffic-related pollution could lead to reduced lung function growth during adolescence, and permanent lung function deficiencies into adulthood (55, 56), underscoring the harmfulness of these exposures. As a modifiable exposure that impacts all sectors of the community, reducing ambient air pollution is an important strategy for reducing asthma morbidity and mortality.

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Table 2.1. Demographic information for children included in this study*

Covariates	ALL n = 1377	MX n = 158	PR n = 567	OL† n = 105	AA n = 547
Age (yrs)					
8-12	770 (55.9)§	71 (44.9)	374 (66.0)	69 (65.7)	256 (46.8)
13-17	479 (34.8)	68 (43.0)	157 (27.7)	29 (27.6)	225 (41.1)
≥ 18	128 (9.3)	19 (12.0)	36 (6.4)	7 (6.7)	66 (12.1)
Sex					
Male	765 (55.6)	93 (58.9)	323 (57.0)	60 (57.1)	289 (52.8)
Female	612 (44.4)	65 (41.1)	244 (43.0)	45 (42.9)	258 (47.2)
SES‡					
3-4	196 (14.2)§	43 (27.2)	74 (13.1)	29 (27.6)	50 (9.1)
5-6	681 (49.5)	71 (44.9)	330 (44.9)	49 (46.7)	231 (42.2)
7-9	500 (36.3)	44(27.9)	163 (27.9)	27 (25.7)	266 (48.6)
Current smoker in household	1070 (77.7)§	131 (82.9)	459 (81.0)	85 (81.0)	395 (72.2)
No	307 (22.3)	27 (17.1)	108 (19.0)	20 (19.0)	152 (27.8)
Yes					
Percent genetic African ancestry	27.6 (12.9-79.6)§	4.4 (2.9-5.8)	19.7 (15.0-27.4)	6.9 (4.3-9.8)	82.2 (75.4-86.4)

Definition of abbreviations: SES = socioeconomic status. MX = Mexican American. PR = Puerto Rican. OL = Other Latino. AA = African American.

*Reported as n (%), or median (IQR), for subjects with non-missing data on demographics, outcomes, and exposures (at least one pollutant reported).

† "Other Latino" is classified as those who self-reported as South American, Central American, non-Puerto Rican Caribbean, or mixed Latino.

‡ Composite SES score based on the level of maternal education, annual household income, and the type of medical insurance.

§ Statistically significant ($p<0.05$) χ^2 tests (or ANOVA for continuous variables) for associations between baseline characteristics and race/ethnicity.

Table 2.2. Average lag 0 pollution compared with various air quality standards

Pollutant	Puerto Rico	SF Bay Area	All	EPA NAAQS (57)
NO_2, ppb (24-hr avg)				
Mean (SD)	8.1 (1.8)	13.2 (7.0)	13.0 (7.0)	NDS
25th	7.0	7.5	7.3	
50th	7.1	12.1	11.9	
75th	8.9	17.6	17.3	
SO_2, ppb (24-hr avg)				
Mean (SD)	1.6 (1.2)	1.1 (0.7)	1.3 (1.0)	NDS
25th	0.8	0.5	0.6	
50th	1.3	0.9	1.1	
75th	2.2	1.5	1.8	
O_3, ppb (8-hr max)				
Mean (SD)	10.7 (6.0)	21.0 (8.8)	17.4 (9.3)	75
25th	5.9	14.9	9.7	
50th	9.7	21.0	16.5	
75th	14.4	27.0	24.2	
$PM_{2.5}$, µg/m^3 (24-hr avg)				
Mean (SD)	12.6 (14.8)	9.3 (7.2)	10.6 (10.9)	35
25th	5.0	4.8	4.9	
50th	6.9	7.3	7.2	
75th	11.5	11.1	11.2	
PM_{10}, µg/m^3 (24-hr avg)				
Mean (SD)	32.7 (21.2)	16.7 (7.5)	28.1 (19.7)	150
25th	20.8	11.3	17.2	
50th	27.4	15.2	22.7	
75th	40.4	20.9	34.0	
PM-Coarse, µg/m^3 (24-hr avg)				
Mean (SD)	17.8 (13.1)	7.6 (5.8)	13.9 (11.9)	NDS
25th	0.1	3.8	3.7	
50th	17.7	7.2	12.3	
75th	26.4	9.8	22.1	

Definition of abbreviations: avg = average; EPA NAAQS = US Environmental Protection Agency National Ambient Air Quality Standard; Lag 0 = Pollution exposure on the day of spriometry testing; NDS = no daily standard; NO_2 = nitrogen dioxide; O_3 = ozone; $PM_{2.5}$ = particulate matter with aerodynamic diameter ≤ 2.5µm; PM_{10} = particulate matter with aerodynamic diameter ≤ 10µm; PM-Coarse = particulate matter with aerodynamic diameter between 2.5-10µm; ppb = part per billion; SF = San Francisco; SO_2 = sulfur dioxide; SD = standard deviation.

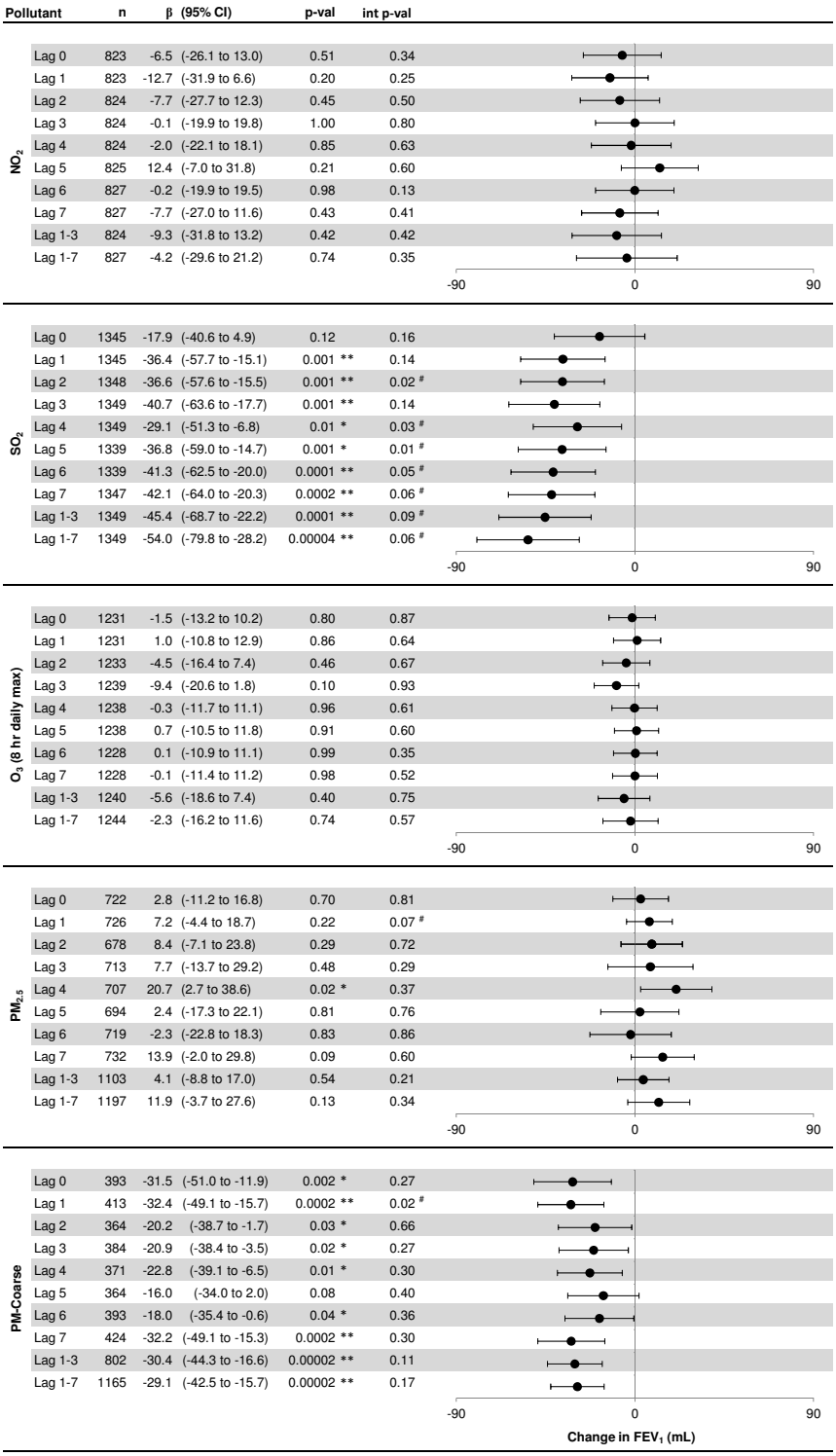


Figure 2.1. Association between exposure to ambient air pollutants and forced expiratory volume in 1 second (FEV_1).

Adjusted for age, sex, height, height^2, ethnicity, recruitment region, socioeconomic status (SES), global African ancestry, controller medication use in the past 2 weeks, and current household smokers. Regression coefficients are scaled to represent the change in FEV_1 for a 1 unit (part-per-billion [ppb] or $\mu g/m^3$) increase in SO_2, and a 5 unit increase in NO_2, O_3, $PM_{2.5}$ and PM-Coarse. NO_2 = nitrogen dioxide. SO_2 = sulfur dioxide. O_3 (8 hr daily max) = ozone, 8 hour daily maximum. $PM_{2.5}$ = particulate matter with aerodynamic diameter $\leq$ 2.5µm. PM-Coarse = particulate matter with aerodynamic diameter between 2.5-10µm. CI = confidence interval. p-val = p-value. int p-val = interaction p-value. Lag 0 = exposure on the day of spirometry testing. Lag 1 - Lag 7 = exposure on each of the 7 days prior to spirometry testing. Lag 1-3 = average exposure over the 3 days prior to spirometry testing. Lag 1-7 = average exposure over the week prior to spirometry testing. * = $p < 0.05$. ** = $p < 0.001$ (Bonferroni significant). # = interaction $p < 0.1$

Pollutant		Population	β	(95% CI)	p-val	int p-val	n
NO_2	Lag 0	All	-6.5	(-26.1 to 13.0)	0.51	0.34	823
		AA	-9.0	(-33.1 to 15.1)	0.46		547
		PR	21.2	(-847.0 to 889.3)	0.96		19
		MX	23.2	(-14.7 to 61.1)	0.23		158
		OL	-2.1	(-48.6 to 44.4)	0.93		99
	Lag 1	All	-12.7	(-31.9 to 6.6)	0.20	0.25	823
		AA	-17.6	(-42.0 to 6.8)	0.16		547
		PR	140.6	(-510.7 to 791.9)	0.64		19
		MX	16.5	(-18.7 to 51.7)	0.35		158
		OL	-12.4	(-55.8 to 31.0)	0.57		99
	Lag 1-3	All	-9.3	(-31.8 to 13.2)	0.42	0.42	824
		AA	-16.5	(-45.4 to 12.4)	0.26		547
		PR	-283.9	(-855.3 to 287.6)	0.29		20
		MX	18.7	(-20.9 to 58.3)	0.35		158
		OL	8.2	(-43.6 to 60.0)	0.75		99
	Lag 1-7	All	-4.2	(-29.6 to 21.2)	0.74	0.35	827
		AA	-9.5	(-41.2 to 22.3)	0.56		547
		PR	-282.7	(-873.7 to 308.2)	0.32		23
		MX	26.5	(-21.6 to 74.5)	0.28		158
		OL	8.1	(-51.4 to 67.5)	0.79		99

Pollutant		Population	β	(95% CI)	p-val	int p-val	n
$PM_{2.5}$	Lag 0	All	2.8	(-11.2 to 16.8)	0.70	0.81	722
		AA	-4.1	(-33.6 to 25.4)	0.79		315
		PR	6.2	(-11.8 to 24.2)	0.50		274
		MX	18.3	(-56.2 to 92.8)	0.62		74
		OL	-25.0	(-90.4 to 40.3)	0.45		59
	Lag 1	All	7.2	(-4.4 to 18.7)	0.22	0.07 #	726
		AA	-17.5	(-43.9 to 8.9)	0.19		316
		PR	9.2	(-4.6 to 23.0)	0.19		268
		MX	80.3	(21.3 to 139.3)	0.01 *		81
		OL	-2.3	(-69.4 to 64.8)	0.94		61
	Lag 1-3	All	4.1	(-8.8 to 17.0)	0.54	0.21	1103
		AA	-16.6	(-44.0 to 10.8)	0.23		507
		PR	8.7	(-8.0 to 25.3)	0.31		375
		MX	37.7	(-6.0 to 81.5)	0.09		130
		OL	-6.8	(-67.3 to 53.7)	0.82		91
	Lag 1-7	All	11.9	(-3.7 to 27.6)	0.13	0.34	1197
		AA	2.9	(-27.9 to 33.7)	0.85		547
		PR	14.5	(-7.6 to 36.7)	0.20		389
		MX	35.1	(-6.1 to 76.4)	0.09		158
		OL	5.0	(-49.1 to 59.1)	0.85		103

Pollutant		Population	β	(95% CI)	p-val	int p-val	n
SO_2	Lag 0	All	-17.9	(-40.6 to 4.9)	0.12	0.16	1345
		AA	-0.8	(-44.4 to 42.9)	0.97		546
		PR	-25.7	(-55.3 to 4.0)	0.09		537
		MX	92.3	(9.2 to 175.4)	0.03 *		157
		OL	-81.1	(-170.7 to 8.5)	0.08		105
	Lag 1	All	-36.4	(-57.7 to -15.1)	0.001 **	0.14	1345
		AA	-23.9	(-69.2 to 21.4)	0.30		546
		PR	-44.7	(-71.3 to -18.2)	0.001 *		537
		MX	81.8	(2.5 to 161.1)	0.04 *		157
		OL	-88.8	(-176.6 to -1.0)	0.05 *		105
	Lag 1-3	All	-45.4	(-68.7 to -22.2)	0.0001 **	0.09 #	1349
		AA	-16.1	(-70.9 to 38.7)	0.56		546
		PR	-60.7	(-88.9 to -32.6)	0.00003 **		541
		MX	74.2	(-16.8 to 165.3)	0.11		157
		OL	-35.0	(-124.0 to 54.0)	0.44		105
	Lag 1-7	All	-54.0	(-79.8 to -28.2)	0.00004 **	0.06 #	1349
		AA	-15.5	(-77.6 to 46.7)	0.62		546
		PR	-70.0	(-100.6 to -39.4)	0.00001 **		541
		MX	122.4	(9.2 to 235.7)	0.03 *		157
		OL	-42.8	(-154.0 to 68.4)	0.45		105

Pollutant		Population	β	(95% CI)	p-val	int p-val	n
PM-Coarse	Lag 0	All	-31.5	(-51.0 to -11.9)	0.002 *	0.27	393
		AA	-55.0	(-123.3 to 13.3)	0.11		105
		PR	-24.1	(-46.4 to -1.8)	0.03 *		237
		MX	-82.2	(-170.8 to 6.5)	0.07		23
		OL	-102.6	(-200.5 to -4.7)	0.04 *		28
	Lag 1	All	-32.4	(-49.1 to -15.7)	0.0002 **	0.02 #	413
		AA	-76.5	(-143.7 to -9.3)	0.03 *		110
		PR	-26.2	(-44.2 to -8.2)	0.005 *		246
		MX	-137.2	(-220.9 to -53.4)	0.003 *		33
		OL	-5.0	(-100.6 to 90.5)	0.91		24
	Lag 1-3	All	-30.4	(-44.3 to -16.6)	0.00002 **	0.11	802
		AA	-28.8	(-62.2 to 4.7)	0.09		324
		PR	-28.6	(-45.9 to -11.2)	0.001 *		341
		MX	-80.8	(-125.2 to -36.3)	0.001 **		82
		OL	-2.0	(-60.6 to 56.6)	0.94		55
	Lag 1-7	All	-29.1	(-42.5 to -15.7)	0.00002 **	0.17	1165
		AA	-28.3	(-58.0 to 1.3)	0.06		547
		PR	-32.2	(-50.1 to -14.4)	0.0004 **		358
		MX	-46.1	(-83.7 to -8.5)	0.02 *		158
		OL	-8.4	(-50.0 to 33.3)	0.69		102

Pollutant		Population	β	(95% CI)	p-val	int p-val	n
O_3 (8 hr daily max)	Lag 0	All	-1.5	(-13.2 to 10.2)	0.80	0.87	1231
		AA	-2.4	(-18.5 to 13.7)	0.77		547
		PR	10.7	(-13.5 to 34.8)	0.39		425
		MX	-3.0	(-31.4 to 25.3)	0.83		158
		OL	-12.5	(-48.3 to 23.3)	0.49		101
	Lag 1	All	1.0	(-10.8 to 12.9)	0.86	0.64	1231
		AA	1.1	(-15.9 to 18.1)	0.90		547
		PR	0.7	(-23.8 to 25.3)	0.95		425
		MX	1.4	(-25.2 to 28.0)	0.92		158
		OL	0.4	(-32.9 to 33.6)	0.98		101
	Lag 1-3	All	-5.6	(-18.6 to 7.4)	0.40	0.75	1240
		AA	-6.0	(-25.5 to 13.6)	0.55		547
		PR	-1.5	(-26.5 to 23.4)	0.90		434
		MX	-10.2	(-39.4 to 19.0)	0.49		158
		OL	-8.2	(-43.3 to 26.9)	0.64		101
	Lag 1-7	All	-2.3	(-16.2 to 11.6)	0.74	0.57	1244
		AA	-10.2	(-31.2 to 10.7)	0.34		547
		PR	4.6	(-21.2 to 30.4)	0.73		438
		MX	-9.7	(-41.6 to 22.2)	0.55		158
		OL	2.8	(-35.4 to 40.9)	0.89		101

Figure 2.2. Association between air pollution and forced expiratory flow in 1 second (FEV_1), stratified by race/ethnicity, and pooled with a race/ethnicity x pollution interaction term.
Linear regression models adjusted for age, sex, height, height^2, ethnicity, recruitment region, socioeconomic status (SES), global African ancestry, controller medication use in the past 2 weeks, and current household smokers. Regression coefficients are scaled to represent the change in FEV_1 for a 1 unit (part-per-billion [ppb] or $\mu g/m^3$) increase in SO_2, and a 5 unit increase in NO_2, O_3, $PM_{2.5}$ and PM-Coarse. AA = African American. PR = Puerto Rican. MX = Mexican American. OL = Other Latino (South American, Central American, non-Puerto Rican Caribbean, or mixed Latino). NO_2 = nitrogen dioxide. SO_2 = sulfur dioxide. O_3 (8 hr daily max) = ozone, 8 hour daily maximum. $PM_{2.5}$ = particulate matter with aerodynamic diameter ≤ 2.5μm. PM-Coarse = particulate matter with aerodynamic diameter between 2.5-10μm. CI = confidence interval. p-val = p-value. int p-val = interaction p-value. Lag 0 = exposure on the day of spirometry testing. Lag 1 = exposure 1 day prior to spirometry testing. Lag 1-3 = average exposure over the 3 days prior to spirometry testing. Lag 1-7 = average exposure over the week prior to spirometry testing. * = $p < 0.05$. **= $p < 0.001$ (Bonferroni significant). # = interaction $p < 0.1$

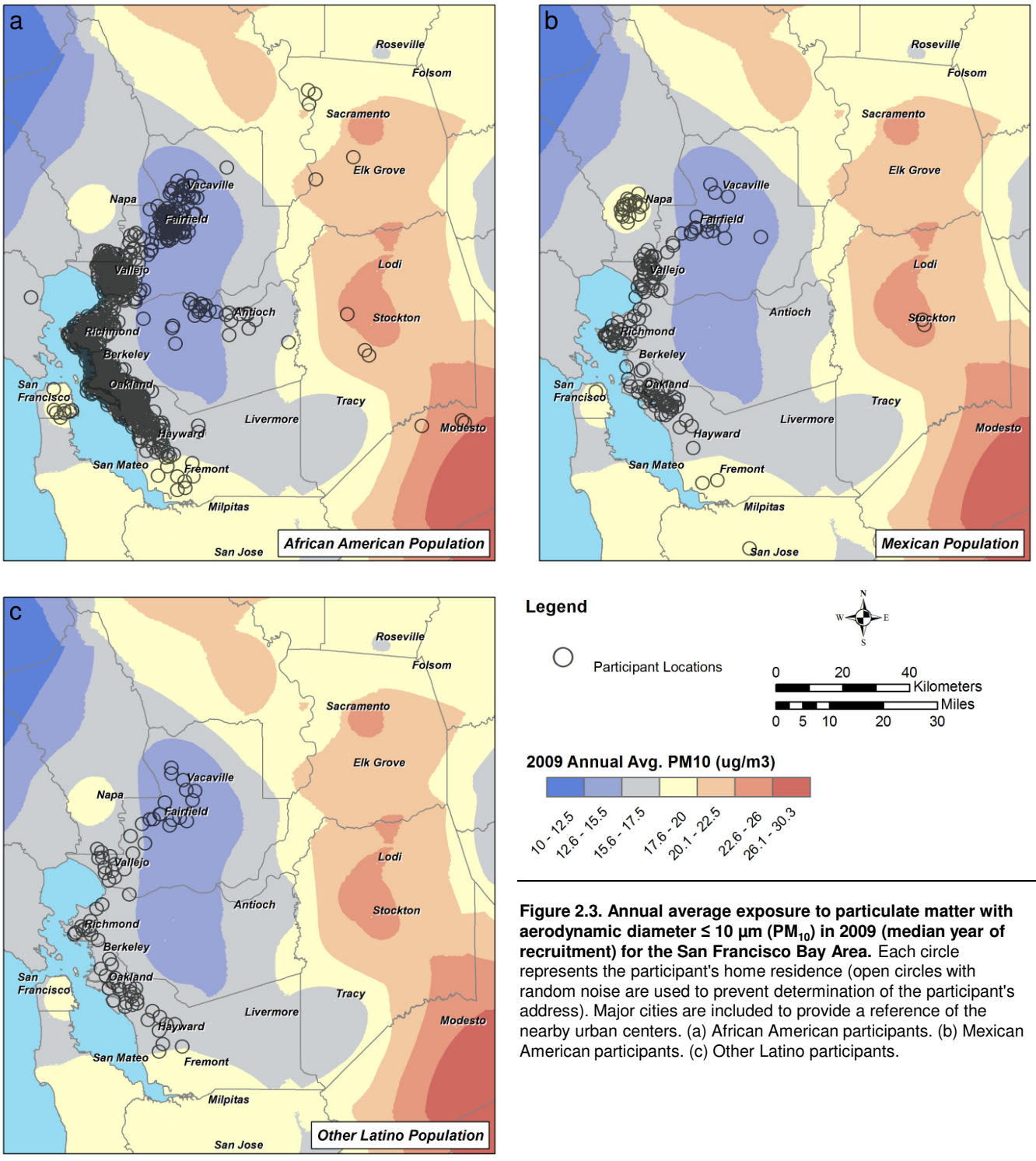
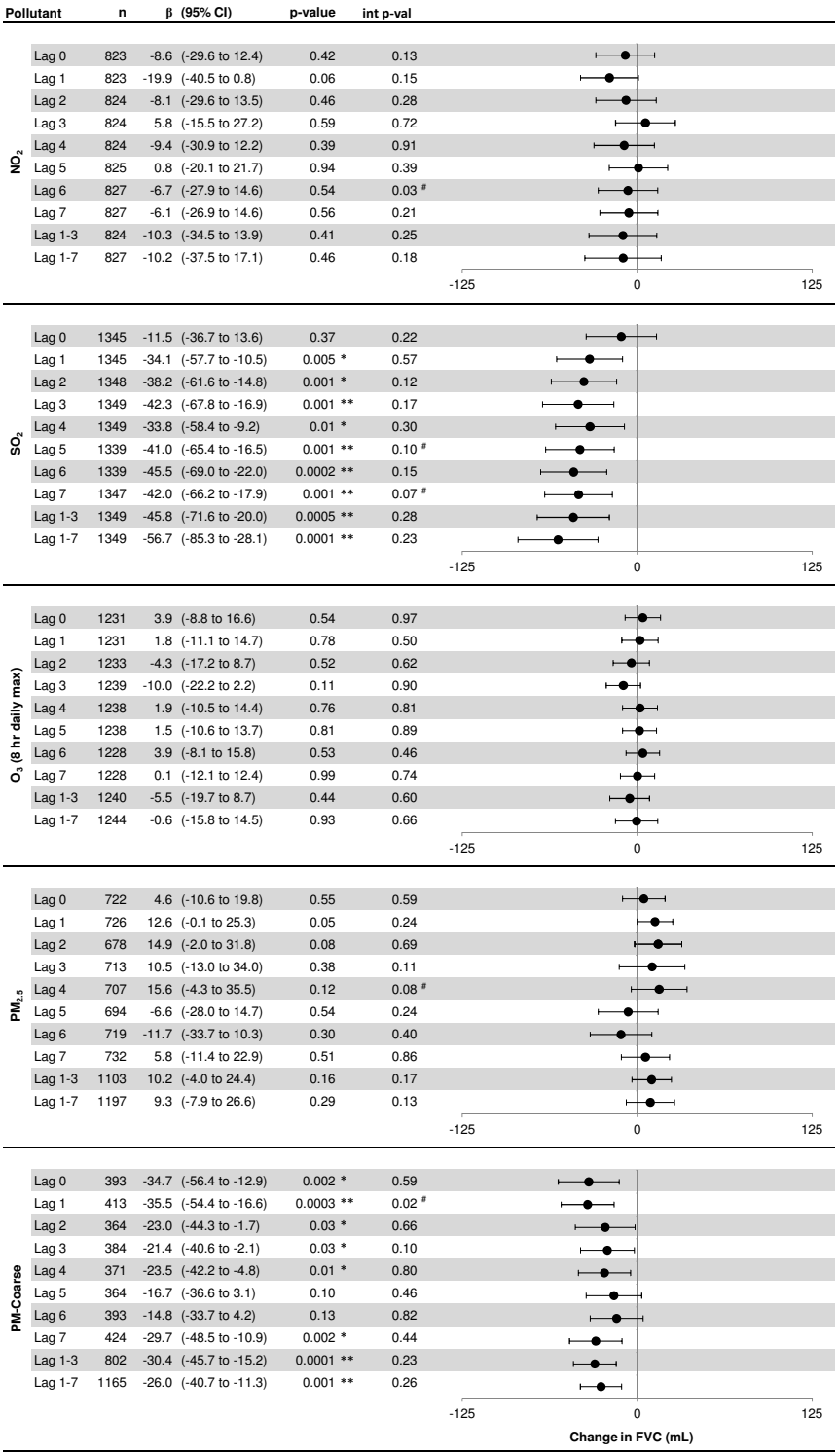
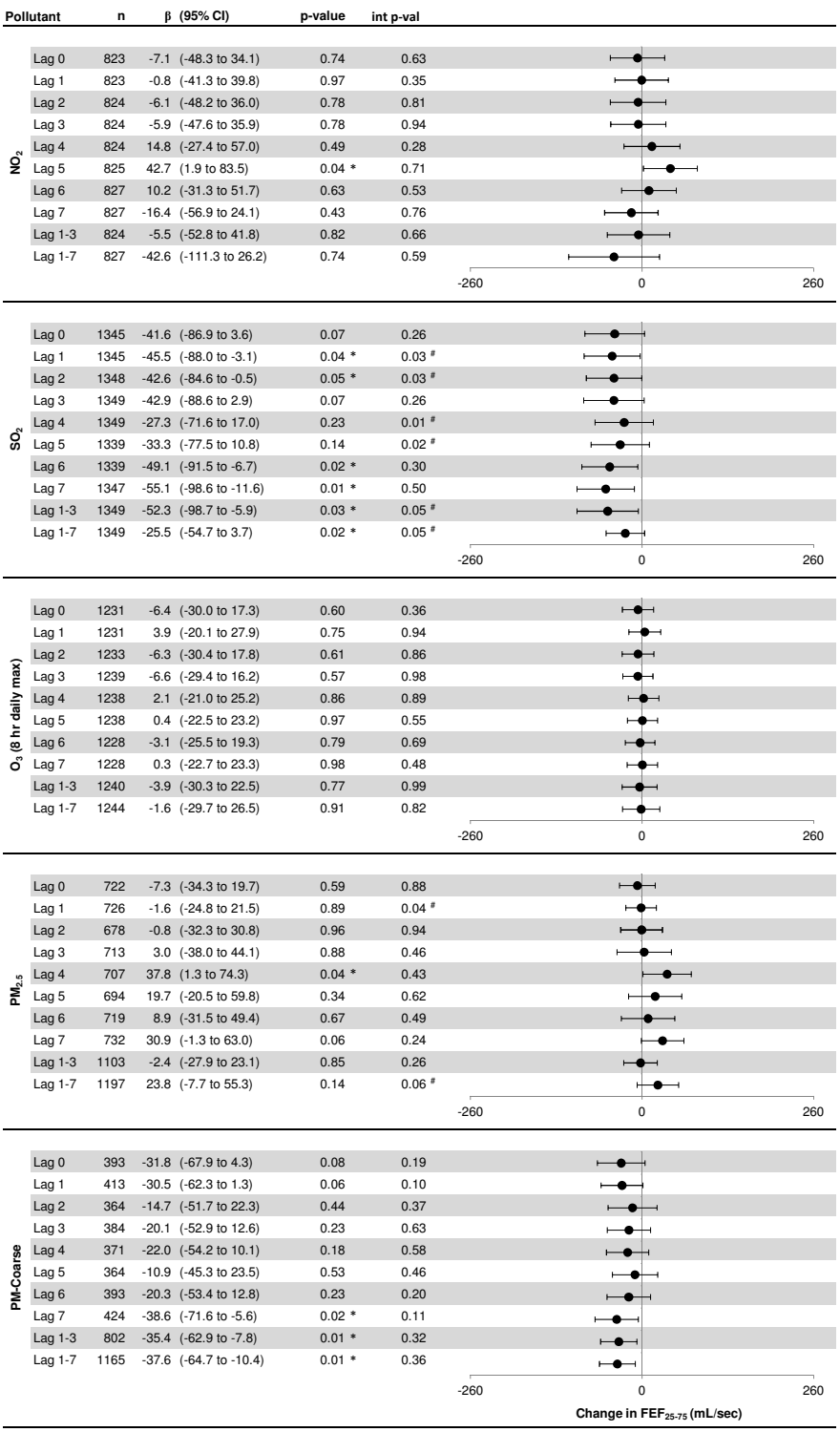


Figure 2.3. Annual average exposure to particulate matter with aerodynamic diameter ≤ 10 µm (PM_{10}) in 2009 (median year of recruitment) for the San Francisco Bay Area. Each circle represents the participant's home residence (open circles with random noise are used to prevent determination of the participant's address). Major cities are included to provide a reference of the nearby urban centers. (a) African American participants. (b) Mexican American participants. (c) Other Latino participants.



Appendix Figure 2.1. Association between exposure to ambient air pollutants and forced vital capacity (FVC). Adjusted for age, sex, height, height^2, ethnicity, recruitment region, socioeconomic status (SES), global African ancestry, controller medication use in the past 2 weeks, and current household smokers. Regression coefficients are scaled to represent the change in FVC for a 1 unit (part-per-billion [ppb] or μg/m^3) increase in SO_2, and a 5 unit increase in NO_2, O_3, $PM_{2.5}$ and PM-Coarse. NO_2 = nitrogen dioxide. SO_2 = sulfur dioxide. O_3 (8 hr daily max) = ozone, 8 hour daily maximum. $PM_{2.5}$ = particulate matter with aerodynamic diameter ≤ 2.5μm. PM-Coarse = particulate matter with aerodynamic diameter between 2.5-10μm. CI = confidence interval. p-val = p-value. int p-val = interaction p-value. Lag 0 = exposure on the day of spirometry testing. Lag 1 - Lag 7 = exposure on each of the 7 days prior to spirometry testing. Lag 1-3 = average exposure over the 3 days prior to spirometry testing. Lag 1-7 = average exposure over the week prior to spirometry testing. *= $p < 0.05$. **= $p < 0.001$ (Bonferroni significant). # = interaction $p < 0.1$



Appendix Figure 2.2. Association between exposure to ambient air pollutants and forced expiratory flow between 25% and 75% of vital capacity (FEF_{25-75}). Adjusted for age, sex, height, height^2, ethnicity, recruitment region, socioeconomic status (SES), global African ancestry, controller medication use in the past 2 weeks, and current household smokers. Regression coefficients are scaled to represent the change in FEF_{25-75} for a 1 unit (part-per-billion [ppb] or μg/m^3) increase in SO_2, and a 5 unit increase in NO_2, O_3, $PM_{2.5}$ and PM-Coarse. NO_2 = nitrogen dioxide. SO_2 = sulfur dioxide. O_3 (8 hr daily max) = ozone, 8 hour daily maximum. $PM_{2.5}$ = particulate matter with aerodynamic diameter ≤ 2.5μm. PM-Coarse = particulate matter with aerodynamic diameter between 2.5-10μm. CI = confidence interval. p-val = p-value. int p-val = interaction p-value. Lag 0 = exposure on the day of spirometry testing. Lag 1 - Lag 7 = exposure on each of the 7 days prior to spirometry testing. Lag 1-3 = average exposure over the 3 days prior to spirometry testing. Lag 1-7 = average exposure over the week prior to spirometry testing. * = $p < 0.05$. **= $p < 0.001$ (Bonferroni significant). # = interaction $p < 0.1$

Pollutant		Population	β	(95% CI)	p-val	int p-val	n
NO_2	Lag 0	All	-8.6	(-29.6 to 12.4)	0.42	0.13	823
		AA	-13.7	(-38.9 to 11.5)	0.29		547
		PR	-258.6	(-1365.4 to 848.3)	0.61		19
		MX	41.7	(-6.6 to 90.0)	0.09		158
		OL	-12.0	(-62.0 to 38.0)	0.64		99
	Lag 1	All	-19.9	(-40.5 to 0.8)	0.06	0.15	823
		AA	-28.9	(-54.4 to -3.4)	0.03 *		547
		PR	-144.0	(-991.1 to 703.1)	0.71		19
		MX	21.6	(-23.4 to 66.6)	0.34		158
		OL	-17.4	(-64.0 to 29.2)	0.46		99
	Lag 1-3	All	-10.3	(-34.5 to 13.9)	0.41	0.25	824
		AA	-21.5	(-51.7 to 8.7)	0.16		547
		PR	-503.6	(-1229.9 to 222.8)	0.15		20
		MX	33.2	(-17.3 to 83.7)	0.20		158
		OL	7.7	(-48.0 to 63.5)	0.78		99
	Lag 1-7	All	-10.2	(-37.5 to 17.1)	0.46	0.18	827
		AA	-20.2	(-53.5 to 13.0)	0.23		547
		PR	-530.4	(-1268.6 to 207.8)	0.14		23
		MX	43.5	(-17.8 to 104.8)	0.16		158
		OL	1.9	(-62.1 to 66.0)	0.95		99

Pollutant		Population	β	(95% CI)	p-val	int p-val	n
$PM_{2.5}$	Lag 0	All	4.6	(-10.6 to 19.8)	0.55	0.59	722
		AA	-11.2	(-40.1 to 17.8)	0.45		315
		PR	11.4	(-9.5 to 32.2)	0.28		274
		MX	-4.7	(-98.9 to 89.4)	0.92		74
		OL	-32.2	(-102.9 to 38.6)	0.37		59
	Lag 1	All	12.6	(-0.1 to 25.3)	0.05	0.24	726
		AA	-13.4	(-40.1 to 13.4)	0.33		316
		PR	15.9	(-0.5 to 32.3)	0.06		268
		MX	47.5	(-24.6 to 119.6)	0.19		81
		OL	16.3	(-62.8 to 95.3)	0.68		61
	Lag 1-3	All	10.2	(-4.0 to 24.4)	0.16	0.17	1103
		AA	-12.3	(-41.0 to 16.4)	0.40		507
		PR	16.7	(-2.7 to 36.0)	0.09		375
		MX	37.9	(-14.4 to 90.2)	0.15		130
		OL	-13.5	(-80.8 to 53.9)	0.69		91
	Lag 1-7	All	9.3	(-7.9 to 26.6)	0.29	0.13	1197
		AA	-17.7	(-49.9 to 14.5)	0.28		547
		PR	23.6	(-1.9 to 49.2)	0.07		389
		MX	19.6	(-33.7 to 72.8)	0.47		158
		OL	-5.7	(-64.9 to 53.4)	0.85		103

Pollutant		Population	β	(95% CI)	p-val	int p-val	n
SO_2	Lag 0	All	-11.5	(-36.7 to 13.6)	0.37	0.22	1345
		AA	3.2	(-42.4 to 48.9)	0.89		546
		PR	-18.1	(-52.3 to 16.2)	0.30		537
		MX	109.0	(2.6 to 215.4)	0.04 *		157
		OL	-85.0	(-183.2 to 13.1)	0.09		105
	Lag 1	All	-34.1	(-57.7 to -10.5)	0.005 *	0.57	1345
		AA	-35.7	(-83.0 to 11.7)	0.14		546
		PR	-39.9	(-70.7 to -9.2)	0.01 *		537
		MX	66.0	(-36.1 to 168.2)	0.20		157
		OL	-48.0	(-145.5 to 49.6)	0.33		105
	Lag 1-3	All	-45.8	(-71.6 to -20.0)	0.0005 **	0.28	1349
		AA	-34.3	(-91.6 to 22.9)	0.24		546
		PR	-59.4	(-92.2 to -26.5)	0.0004 **		541
		MX	58.1	(-58.8 to 175.1)	0.33		157
		OL	7.5	(-90.1 to 105.2)	0.88		105
	Lag 1-7	All	-56.7	(-85.3 to -28.1)	0.0001 **	0.23	1349
		AA	-46.2	(-111.1 to 18.7)	0.16		546
		PR	-69.3	(-105.0 to -33.7)	0.0001 **		541
		MX	110.5	(-35.3 to 256.3)	0.14		157
		OL	3.2	(-118.9 to 125.2)	0.96		105

Pollutant		Population	β	(95% CI)	p-val	int p-val	n
PM-Coarse	Lag 0	All	-34.7	(-56.4 to -12.9)	0.002 *	0.59	393
		AA	-16.8	(-90.2 to 56.6)	0.65		105
		PR	-33.8	(-59.1 to -8.5)	0.01 *		237
		MX	-60.0	(-160.7 to 40.7)	0.22		23
		OL	-68.6	(-171.4 to 34.3)	0.18		28
	Lag 1	All	-35.5	(-54.4 to -16.6)	0.0003 **	0.02 #	413
		AA	-119.5	(-190.0 to -49.0)	0.001 *		110
		PR	-29.1	(-50.5 to -7.7)	0.008 *		246
		MX	-96.5	(-204.1 to 11.0)	0.076		33
		OL	12.5	(-91.2 to 116.2)	0.80		24
	Lag 1-3	All	-30.4	(-45.7 to -15.2)	0.0001 **	0.23	802
		AA	-25.7	(-62.0 to 10.6)	0.16		324
		PR	-30.2	(-50.1 to -10.3)	0.003 *		341
		MX	-75.3	(-126.2 to -24.3)	0.004 *		82
		OL	2.2	(-61.5 to 66.0)	0.94		55
	Lag 1-7	All	-26.0	(-40.7 to -11.3)	0.0005 **	0.26	1165
		AA	-17.9	(-49.0 to 13.2)	0.26		547
		PR	-33.1	(-53.5 to -12.7)	0.002 *		358
		MX	-37.5	(-86.2 to 11.2)	0.13		158
		OL	-0.9	(-46.1 to 44.3)	0.97		102

Pollutant		Population	β	(95% CI)	p-val	int p-val	n
O_3 (8 hr daily max)	Lag 0	All	3.9	(-8.8 to 16.6)	0.54	0.97	1231
		AA	3.0	(-13.9 to 19.8)	0.73		547
		PR	8.0	(-19.2 to 35.1)	0.56		425
		MX	18.0	(-18.2 to 54.2)	0.33		158
		OL	11.1	(-27.7 to 50.0)	0.57		101
	Lag 1	All	1.8	(-11.1 to 14.7)	0.78	0.50	1231
		AA	4.0	(-13.8 to 21.8)	0.66		547
		PR	4.0	(-23.6 to 31.6)	0.77		425
		MX	-6.8	(-40.8 to 27.2)	0.69		158
		OL	8.5	(-27.5 to 44.6)	0.64		101
	Lag 1-3	All	-5.5	(-19.7 to 8.7)	0.44	0.60	1240
		AA	-2.9	(-23.3 to 17.6)	0.78		547
		PR	-3.5	(-31.6 to 24.6)	0.81		434
		MX	-14.9	(-52.3 to 22.4)	0.43		158
		OL	-0.7	(-38.8 to 37.4)	0.97		101
	Lag 1-7	All	-0.6	(-15.8 to 14.5)	0.93	0.66	1244
		AA	-2.0	(-24.0 to 20.0)	0.86		547
		PR	1.9	(-27.2 to 31.0)	0.90		438
		MX	-13.3	(-54.2 to 27.5)	0.52		158
		OL	5.3	(-36.0 to 46.7)	0.80		101

Appendix Figure 2.3. Association between air pollution and forced vital capacity (FVC), stratified by race/ethnicity, and pooled with a race/ethnicity x pollution interaction term. Linear regression models adjusted for age, sex, height, height^2, ethnicity, recruitment region, socioeconomic status (SES), global African ancestry, controller medication use in the past 2 weeks, and current household smokers. Regression coefficients are scaled to represent the change in FVC for a 1 unit (part-per-billion [ppb] or μg/m^3) increase in SO_2, and a 5 unit increase in NO_2, O_3, $PM_{2.5}$ and PM-Coarse. AA = African American. PR = Puerto Rican. MX = Mexican. OL = Other Latino (South American, Central American, non-Puerto Rican Caribbean, or mixed Latino). NO_2 = nitrogen dioxide. SO_2 = sulfur dioxide. O_3 (8 hr daily max) = ozone, 8 hour daily maximum. $PM_{2.5}$ = particulate matter with aerodynamic diameter ≤ 2.5μm. PM-Coarse = particulate matter with aerodynamic diameter between 2.5-10μm. CI = confidence interval. p-val = p-value. int p-val = interaction p-value. Lag 0 = exposure on the day of spirometry testing. Lag 1 = exposure 1 day prior to spirometry testing. Lag 1-3 = average exposure over the 3 days prior to spirometry testing. Lag 1-7 = average exposure over the week prior to spirometry testing. * = $p < 0.05$. **= $p < 0.001$ (Bonferroni significant). # = interaction $p < 0.1$

Pollutant		Population	β	(95% CI)	p-val	int p-val	n
NO_2	Lag 0	All	-7.1	(-48.3 to 34.1)	0.74	0.63	823
		AA	-14.2	(-66.6 to 38.2)	0.59		547
		PR	657.3	(-1059.0 to 2373.6)	0.41		19
		MX	20.0	(-62.8 to 102.8)	0.63		158
		OL	12.1	(-86.1 to 110.3)	0.81		99
	Lag 1	All	-0.8	(-41.3 to 39.8)	0.97	0.35	823
		AA	-8.5	(-61.6 to 44.7)	0.75		547
		PR	786.8	(-434.1 to 2007.8)	0.18		19
		MX	43.0	(-33.4 to 119.4)	0.27		158
		OL	-9.6	(-101.3 to 82.2)	0.84		99
	Lag 1-3	All	-5.5	(-52.8 to 41.8)	0.82	0.66	824
		AA	-12.9	(-75.8 to 49.9)	0.69		547
		PR	166.8	(-732.7 to 1066.3)	0.69		20
		MX	20.0	(-66.2 to 106.2)	0.65		158
		OL	-1.2	(-110.7 to 108.2)	0.98		99
	Lag 1-7	All	-42.6	(-111.3 to 26.2)	0.74	0.59	827
		AA	-67.4	(-203.8 to 69.0)	0.86		547
		PR	-7.5	(-128.1 to 113.0)	0.82		23
		MX	8.7	(-113.9 to 131.3)	0.57		158
		OL	-36.1	(-216.5 to 144.2)	0.95		99

Pollutant		Population	β	(95% CI)	p-val	int p-val	n
$PM_{2.5}$	Lag 0	All	-7.3	(-34.3 to 19.7)	0.59	0.88	722
		AA	-15.5	(-79.2 to 48.3)	0.63		315
		PR	-6.0	(-37.6 to 25.7)	0.71		274
		MX	68.5	(-81.2 to 218.2)	0.36		74
		OL	-32.5	(-159.2 to 94.2)	0.61		59
	Lag 1	All	-1.6	(-24.8 to -24.8)	0.89	0.04 #	726
		AA	-38.6	(-97.3 to 20.0)	0.20		316
		PR	0.5	(-24.3 to 25.2)	0.97		268
		MX	184.2	(62.5 to 306.0)	0.004 *		81
		OL	-63.0	(-199.2 to 73.1)	0.36		61
	Lag 1-3	All	-2.4	(-27.9 to -27.9)	0.85	0.26	1103
		AA	-23.2	(-81.5 to 35.0)	0.43		507
		PR	-1.4	(-31.0 to 28.2)	0.93		375
		MX	79.3	(-16.2 to 174.8)	0.10		130
		OL	-25.1	(-148.1 to 97.8)	0.69		91
	Lag 1-7	All	23.8	(-7.7 to 55.3)	0.14	0.06 #	1197
		AA	54.0	(-12.8 to 120.8)	0.11		547
		PR	-2.0	(-42.3 to 38.3)	0.92		389
		MX	98.0	(8.9 to 187.2)	0.03 *		158
		OL	26.3	(-84.8 to 137.3)	0.64		103

Pollutant		Population	β	(95% CI)	p-val	int p-val	n
SO_2	Lag 0	All	-41.6	(-86.9 to 3.6)	0.07	0.26	1345
		AA	-36.3	(-131.1 to 58.5)	0.45		546
		PR	-49.6	(-103.1 to 3.9)	0.07		537
		MX	167.3	(-14.3 to 348.8)	0.07		157
		OL	-116.5	(-302.6 to 69.7)	0.22		105
	Lag 1	All	-45.5	(-88.0 to -3.1)	0.04 *	0.03 #	1345
		AA	-9.3	(-108.0 to 89.3)	0.85		546
		PR	-63.1	(-111.3 to -14.9)	0.01 *		537
		MX	207.8	(36.3 to 379.4)	0.02 *		157
		OL	-211.2	(-390.7 to -31.6)	0.02 *		105
	Lag 1-3	All	-52.3	(-98.7 to -5.9)	0.03 *	0.05 #	1349
		AA	19.5	(-99.6 to 138.6)	0.75		546
		PR	-76.4	(-127.8 to -24.9)	0.004 *		541
		MX	180.0	(-17.6 to 377.5)	0.07		157
		OL	-157.0	(-338.1 to 24.1)	0.09		105
	Lag 1-7	All	-25.5	(-54.7 to 3.7)	0.02 *	0.05 #	1349
		AA	-96.6	(-168.4 to -24.9)	0.57		546
		PR	-14.4	(-48.9 to 20.1)	0.002 *		541
		MX	185.9	(-106.9 to 478.7)	0.10		157
		OL	-24.1	(-158.0 to 109.7)	0.11		105

Pollutant		Population	β	(95% CI)	p-val	int p-val	n
PM-Coarse	Lag 0	All	-31.8	(-67.9 to 4.3)	0.08	0.19	393
		AA	-142.5	(-282.0 to -3.0)	0.05 *		105
		PR	-6.7	(-45.9 to 32.5)	0.74		237
		MX	-174.9	(-329.8 to -19.9)	0.03 *		23
		OL	-203.1	(-423.6 to 17.4)	0.07		28
	Lag 1	All	-30.5	(-62.3 to 1.3)	0.06	0.10	413
		AA	-36.5	(-179.0 to 106.0)	0.61		110
		PR	-20.9	(-53.2 to 11.4)	0.20		246
		MX	-250.5	(-407.7 to -93.2)	0.003 *		33
		OL	-51.7	(-201.3 to 98.0)	0.47		24
	Lag 1-3	All	-35.4	(-62.9 to -7.8)	0.01 *	0.32	802
		AA	-40.6	(-117.5 to 36.4)	0.30		324
		PR	-27.4	(-58.3 to 3.6)	0.08		341
		MX	-132.8	(-239.1 to -26.5)	0.02 *		82
		OL	-19.4	(-123.4 to 84.5)	0.71		55
	Lag 1-7	All	-37.6	(-64.7 to -10.4)	0.007 *	0.36	1165
		AA	-47.4	(-111.9 to 17.1)	0.15		547
		PR	-31.0	(-63.7 to 1.8)	0.06		358
		MX	-93.5	(-175.4 to -11.5)	0.03 *		158
		OL	-24.6	(-111.2 to 62.0)	0.57		102

Pollutant		Population	β	(95% CI)	p-val	int p-val	n
O_3 (8 hr daily max)	Lag 0	All	-6.4	(-30.0 to 17.3)	0.60	0.36	1231
		AA	-10.9	(-45.8 to 24.0)	0.54		547
		PR	34.6	(-10.3 to 79.5)	0.13		425
		MX	-33.0	(-94.4 to 28.4)	0.29		158
		OL	-12.5	(-48.3 to 23.3)	0.49		101
	Lag 1	All	3.9	(-20.1 to -20.1)	0.75	0.94	1231
		AA	2.0	(-34.9 to 38.9)	0.91		547
		PR	4.0	(-41.7 to 49.8)	0.86		425
		MX	16.0	(-41.7 to 73.7)	0.58		158
		OL	0.4	(-32.9 to 33.6)	0.98		101
	Lag 1-3	All	-3.9	(-30.3 to -30.3)	0.77	0.99	1240
		AA	-5.7	(-48.2 to 36.8)	0.79		547
		PR	6.2	(-40.6 to 52.9)	0.80		434
		MX	-1.2	(-64.9 to 62.4)	0.97		158
		OL	-8.2	(-43.3 to 26.9)	0.64		101
	Lag 1-7	All	-1.6	(-29.7 to 26.5)	0.91	0.82	1244
		AA	-19.6	(-65.2 to 26.0)	0.40		547
		PR	16.2	(-32.0 to 64.5)	0.51		438
		MX	2.7	(-66.8 to 72.2)	0.94		158
		OL	2.8	(-35.4 to 40.9)	0.89		101

Appendix Figure 2.4. Association between air pollution and forced expiratory flow between 25% and 75% of vital capacity (FEF_{25-75}), stratified by race/ethnicity, and pooled with a race/ethnicity x pollution interaction term. Linear regression models adjusted for age, sex, height, height^2, ethnicity, recruitment region, socioeconomic status (SES), global African ancestry, controller medication use in the past 2 weeks, and current household smokers. Regression coefficients are scaled to represent the change in FEF_{25-75} for a 1 unit (part-per-billion [ppb] or μg/m^3) increase in SO_2, and a 5 unit increase in NO_2, O_3, $PM_{2.5}$ and PM-Coarse. AA = African American. PR = Puerto Rican. MX = Mexican. OL = Other Latino (South American, Central American, non-Puerto Rican Caribbean, or mixed Latino). NO_2 = nitrogen dioxide. SO_2 = sulfur dioxide. O_3 (8 hr daily max) = ozone, 8 hour daily maximum. $PM_{2.5}$ = particulate matter with aerodynamic diameter ≤ 2.5μm. PM-Coarse = particulate matter with aerodynamic diameter between 2.5-10μm. CI = confidence interval. p-val = p-value. int p-val = interaction p-value. Lag 0 = exposure on the day of spirometry testing. Lag 1 = exposure 1 day prior to spirometry testing. Lag 1-3 = average exposure over the 3 days prior to spirometry testing. Lag 1-7 = average exposure over the week prior to spirometry testing. * = $p < 0.05$. ** = $p < 0.0009$ (Bonferroni significant). # = interaction $p < 0.1$

Air Pollution, Atopy and Total IgE in Latino Children with and without Asthma

INTRODUCTION

Childhood asthma is a chronic respiratory disease with genetic, environmental and social risk factors. The prevalence varies substantially between and within different racial/ethnic groups, with a low, intermediate and high prevalence in Asians (5.2%), Latinos (6.5%), and African Americans (11.2%), respectively, and wide variation within Latino subgroups, ranging from 5.4% in Mexican Americans to 16.1% in Puerto Ricans (1). Explaining asthma disparities in Latinos has proven challenging, especially given the numerous risk factors relevant to this population (2).

Atopy and air pollution have both been implicated in the development of childhood asthma. Atopy is considered a strong risk factor (3, 4), with 30-56% of asthma cases attributed to atopy (4-9). Air pollution is thought to be a weaker risk factor, but consistent evidence of association exists across numerous studies (10-13). While both are linked to the development of asthma, atopy and air pollution may impact asthma via different pathways: atopic responses result in eosinophilic inflammation and are responsive to corticosteroid treatment (14), while air pollution often elicits neutrophilic inflammation (15). While US data suggests that air pollution is associated with atopy (16), a large meta-analysis of European birth cohorts found no associations between air pollution and allergic sensitization in children (17). As such, the interplay and the relative importance of atopy and air pollution to the development of asthma remains poorly understood.

Despite being an important factor in asthma development, little research has been conducted on atopy among Latinos, the largest US minority group (18). It is well accepted that African Americans are more likely to be atopic compared with non-Hispanic Whites, but there are few descriptive studies evaluating Latinos (19). A recent study showed that the prevalence of allergic sensitization to foods, indoor, and outdoor allergens in Mexican Americans tended to be intermediate compared with non-Hispanic whites and African Americans (20), and an evaluation of children with asthma found that Puerto

Ricans were more likely to be sensitized when compared with non-Hispanic Whites and African Americans (21). However, little research has been conducted including a range of Latino populations.

While air pollution is considered an independent risk factor for asthma, it is unknown whether it may also influence the risk for developing atopy (22) especially in urban minority subjects where exposures may differ from other populations. Our previous study examined the degree of allergic sensitivity with country of origin, acculturation, region of residence, and genetic ancestry (23). In this analysis, we build on our findings to examine total IgE, atopy prevalence, and associations with air pollution. While air pollution may enhance allergen responses in already sensitized individuals (24, 25), it has not been associated with the development of sensitization in large birth cohorts (17) and is associated with the development of neutrophilic, non-atopic airway inflammation (15). As such, we hypothesize that early-life air pollution exposure will in fact be associated with non-atopic asthma and low total IgE levels in this urban Latino population.

METHODS

Study population

Data were obtained from the Genes-environments & Admixture in Latino Americans (GALA II) case-control study, the largest gene-environment asthma study of Latino children in the US. A description of the enrollment criteria has been published previously (13). Briefly, Latino children with and without asthma were recruited from five urban regions in the US (Chicago, IL; Bronx, NY; Houston, TX; San Francisco Bay Area, CA; and Puerto Rico). Participants were 8-21 years old, had no history of other lung or chronic diseases (other than atopy and allergy-related diseases in the case participants), self-identified as Latino, and had four Latino grandparents. Participants were classified into one of three Latino subgroups: Mexican American, Puerto Rican, or Other Latino (South Americans, Central Americans, non-Puerto Rican Caribbean, or mixed Latino).

Children with asthma had a physician diagnosis, plus two or more symptoms of coughing, wheezing, or shortness of breath in the past two years. Healthy controls were recruited from the same

catchment area as cases, had no reported history of asthma, lung disease, or chronic illness, and had no reported symptoms of coughing, wheezing, or shortness of breath during their lifetime, and no reported use of medication for allergies. Controls were ineligible if they reported a previous diagnosis for eczema, allergies, or allergic rhinitis. All local institutional review boards approved the study and all parents/participants provided signed written consent/assent.

Outcome assessment

Allergy skin testing was performed with the prick-puncture method, using the Multi-Test II device (Lincoln Diagnostics, Decatur, IL). The panel of 14 allergens included European dust mite (*D. pteronyssimus*), American dust mite (*D. farinae*), dog, cat, cockroach mix (*P. americana* and *B. germanica*), mouse (*M. musculus*), rat (*R. norvegicus*), oak mix (Red, Virginia Live, White Oak), olive/elm (*O. europaea*; Chicago used elm instead of olive), grass mix (rye grass (*L. perenne*) and timothy grass (*P. pretense*)), ragweed (*A. artemisiifolia*), leaf mold (*A. tenuis*), wheat mold (*H. cladosporioides*), and *Aspergillus* mix (*A. amstelodami, A. flavus, A. fumigatus, A. nidulans, A. niger*). The allergy skin test was considered valid if the histamine positive control had surrounding erythema and if its wheal diameter was at least 3 mm greater than the wheal diameter of the saline negative control. A reaction 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. Participants were excluded if their allergy skin test failed to pass quality control measures. Atopy was defined as having one or more positive skin test reaction to allergens.

Total serum IgE was measured in duplicate from a single venous sample using the ImmunoCAP^{TM} 100 system (Phadia, Kalamazoo, MI). Values below the lower limit of detection (2 IU/mL) were reassigned a value of half the limit of detection (n=37); measurements above the upper limit of detection (5000 IU/mL) were reassigned a value of 5000 IU/mL (n=19). Total IgE values were logarithmically transformed for the regression models to account for the skewed distribution.

Exposure assessment

Trained bilingual (English-Spanish) interviewers administered questionnaires to parents/caretakers of the participants to collect basic demographics, medical histories, environmental exposures, and residential histories from birth until recruitment. Each residence was geocoded using the TomTom/Tele Atlas EZ-Locate software (TomTom, Amsterdam, the Netherlands). Regional ambient air pollution data were acquired from the US Environmental Protection Agency (EPA) Air Quality System. Pollution values were estimated by calculating the inverse distance-squared weighted average from the four closest air pollution monitoring stations within 50 km of the geocoded residence. Exposures to ozone (O_3, 8-hour maximum), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and particulate matter with aerodynamic diameter ≤ 10 μm (PM_{10}) or ≤ 2.5 μm ($PM_{2.5}$) were estimated for the first year of life by averaging all available pollution values from birth until one year of age.

Statistical analysis

The chi-square (χ^2) test was used to compare the proportions of atopy, and the non-parametric Kruskal-Wallis test was used to compare the distribution of total IgE levels among Latino ethnicities in Chicago and New York (sites where all three Latino subgroups were represented). Multivariable logistic and linear regressions evaluated associations between the five pollutants and atopic status (or log-transformed total IgE). We considered atopy to be the reference group, since we hypothesize air pollution to be associated with non-atopic airway inflammation (15). All models were stratified by asthma status and adjusted for age, sex, self-identified ethnicity, recruitment region, maternal *in utero* smoking, socioeconomic status (SES), and percent African genetic ancestry. The IgE models were additionally adjusted for atopic status.

The development of the SES index has been published previously (26) and was calculated by assigning a low, medium or high score for annual household income, maternal education, and type of health insurance, and then summing across these three values. We included genetic ancestry to minimize confounding, as previous studies have examined the association between African genetic ancestry and

total IgE (27, 28) and allergic sensitization (23, 29, 30) with mixed findings. Methods for estimating genetic ancestry have been described elsewhere (31, 32). Briefly, the proportion of genetic ancestry was calculated by first genotyping all subjects with the Axiom LAT1 array (World Array 4, Affymetrix, Santa Clara, CA) (33). Estimates of genetic ancestry were then obtained using an unsupervised analysis in ADMIXTURE (34) to determine the proportion of African, European, and Native American ancestry for each participant. Reference haplotypes were derived from European and African individuals in HapMap phase II (http://hapmap.ncbi.nlm.nih.gov) and 71 Native American individuals genotyped on the Axiom LAT1 array.

Two sensitivity analyses were conducted for the IgE and atopy models: 1) excluding the upper/lower 5% of pollution values; 2) restricting the analysis to those recruited from the mainland US. One additional sensitivity analysis was conducted with the atopy models only, by stratifying the analyses for each recruitment region and using a random-effects meta-analysis to generate a pooled summary estimate. One additional sensitivity analyses was also conducted with the IgE models only, using a tobit regression model to account for the left- and right-censoring in values that exceeded the range of the limit of detection.

Air pollution estimates were scaled based on the range of pollution exposures observed, with O_3, NO_2, PM_{10}, and $PM_{2.5}$ scaled for a 5 unit change in exposure, and SO_2 scaled for a 1 unit change. To correct for multiple comparisons across pollutant exposures, we applied a Bonferroni correction. We report nominal p-values but adjust our significance threshold to 0.01 to account for 5 tests per outcome. All analyses were performed in Stata 13 (StataCorp, College Station, TX) or R version 3.0 (R Foundation for Statistical Computing, Vienna, Austria) (35).

RESULTS

The GALA II study enrolled 4,157 children with and without asthma from 2006-2011. Allergy skin tests results for appropriate controls were available for 3,106 participants (1,504 asthma cases; 1,602

controls) (**Table 1.1**), the sample analyzed in this report. Additional participants were excluded in the pollution analyses if missing data on pollution and/or essential covariates. More than 90% of allergy skin test results were available for Chicago (94%), Houston (97%), New York (99%) and San Francisco (99%), but only 45% of tests from Puerto Rico passed quality control.

As a whole, all participants had NO_2 and SO_2 exposures that satisfied the EPA National Ambient Air Quality Standards (NAAQS), but 65% of participants had $PM_{2.5}$ exposures that were above the EPA standard (**Table 1.2**). Different pollution sources, geography and weather characteristics contribute to the pollution in each region. New York and Chicago had high levels of NO_2, SO_2 and particulate matter (industrial and traffic-related pollutants), while Puerto Rico and San Francisco had lower levels of pollution.

Total IgE Levels

The geometric mean (GM) total IgE was 177 IU/mL (95% CI, 163-192) for asthma cases and 69 IU/mL (64-75) for controls (**Figure 1.1, Appendix Figure 1.1**). In Chicago and New York (regions where all three Latino subgroups were represented), Kruskal-Wallis tests were not significant across subgroups either when cases and controls were pooled or when tested individually, suggesting that the distribution of total IgE was similar across the three Latino subgroups. However, Kruskal-Wallis tests comparing total IgE among Puerto Ricans by recruitment site (Puerto Rico, Chicago, and New York) were significant both when cases and controls were pooled and when tested individually, suggesting that the distribution of total IgE in island Puerto Ricans was statistically different from the distribution in Puerto Ricans from the mainland.

Table 1.3 lists the regression results (β-coefficients) testing the association between air pollution exposure and total IgE levels. There were no statistically significant associations between first year of life air pollution and total IgE in asthma cases and controls. The results were unchanged in the three sensitivity analyses.

Allergen-Specific Sensitization

Allergen sensitivity varied greatly in this pediatric cohort, with participants least likely to be sensitized to rats (6%) and molds (*A. tenuis*: 8%; *H. cladosporioides*: 5%; *Aspergillus spp.*: 5%), and most likely to be sensitized to dust mites (*D. farinae*: 32%; *D. pteronyssimus*: 35%) (**Figure 1.2, Appendix Figure 1.2 – 1.3**). Of the five recruitment regions, participants from New York tended to have the highest prevalence of allergic sensitivity, with nearly half sensitized to cockroaches (48%) and dust mites (*D. farinae*: 42%; *D. pteronyssimus*: 44%). Children from Puerto Rico and San Francisco tended to have the lowest frequency of allergic sensitization. In participants from Puerto Rico, the most common allergen sensitivity was to dust mites (*D. farinae*: 27%; *D. pteronyssimus*: 29%), and fewer than 5% of participants were sensitized to any outdoor allergen. In those from San Francisco, the most common allergen sensitivities were to grass (24%), cat (21%), and dust mites (*D. farinae*: 23%; *D. pteronyssimus*: 25%). χ^2 tests across Latino subgroups in Chicago and New York were not significant when comparing the proportion sensitized to indoor allergens. However, there were significant differences comparing sensitization to outdoor allergens in Chicago participants, with 32% of Mexican Americans, 54% of Puerto Ricans, and 48% of Other Latinos sensitized to any outdoor allergen ($p < 0.0001$). When looking at the types of outdoor allergens, Mexican Americans from Chicago had the lowest rates of sensitization to any tree (16%), grass (23%), or mold (11%) compared with Puerto Ricans (32%, 43%, and 25%, respectively) and Other Latinos (28%, 33%, and 21%, respectively). This pattern of sensitization was not seen in Latinos from New York, suggesting that the level or frequency of exposures may differ between these regions.

Atopic Status

Across all regions, 52% of Latino children were atopic (asthma cases: 61%; controls: 41%) (**Figure 1.3, Appendix Figure 1.4 – 1.5**). Compared with other regions, participants from Puerto Rico had lower prevalence of atopy (asthma cases: 51%; controls: 30%). However, Puerto Rican children recruited from Chicago and New York had percentages similar to other Latino subgroups recruited from

the same region. χ^2 tests in Chicago and New York were not significant when cases and controls were pooled or tested individually, suggesting that the rates of atopy did not vary among the Latino subgroups in these regions.

In **Table 1.4,** we present the associations between air pollution exposures and atopic classification, stratified by asthma status. We found a significant association with ozone exposure among children with asthma (adjusted OR, per 5 ppb increase in ozone = 1.32, 95% CI, 1.11-1.56, p = 0.002), suggesting that children with non-atopic asthma had 32% higher exposure to ozone during the first year of life compared to those with atopic asthma. The association among children without asthma was closer to the null and not significant. The overall conclusion remained unchanged in the first two sensitivity analyses. In the meta-analysis sensitivity analysis, the result for ozone similar was (OR = 1.28, 95% CI, 1.04-1.58, p = 0.02) but no longer Bonferroni significant.

DISCUSSION

Our study provides a description of atopy and total IgE levels in a large, diverse population of Latino children. Despite differences in asthma prevalence in Mexican American and Puerto Rican children, the prevalence of atopy did not differ among Latino subgroups in our study. The proportion of Mexican American children with atopy were comparable to previously reported findings (20, 36), with 61% being atopic. The 39% prevalence in island Puerto Rican children was much lower compared with Puerto Ricans from Chicago (70%) and New York (76%), and when compared with another pediatric study conducted in Puerto Rico (37). However, this study used a wider variety of outdoor allergens suggesting that our inability to test island-specific allergens may be partly responsible for this discrepancy. Additionally, our previous study found that mainland Puerto Ricans, Caribbean Islanders, and mixed Latinos had a higher degree of atopy (defined as the number of positive allergy skin test reactions) when compared with Mexican Americans (23). Indeed, degree of atopy may be a spectrum (38), and more atopic individuals may have greater inflammation (39), and it may represent one of the more severe endotypes of asthma (40, 41).

While we did not find differences in total IgE levels among different pediatric Latino subgroups in Chicago and New York, the high total IgE levels in Puerto Rican children, despite a relative absence of atopy, appears to be unique to those recruited from Puerto Rico, implying that high total IgE among island Puerto Ricans is due to regional exposures unique to the island. Others have found an inverse correlation between parasitic infection and atopic disease (42). While the reasons for elevated total IgE levels and lower prevalence of skin test reactivity are not known, parasitic load could be one potential confounder in Puerto Rican islanders.

Even though first year of life pollution exposures were not associated with total IgE levels, children with non-atopic asthma were more likely to be exposed to higher levels of ozone in the first year of life when compared to those with atopic asthma, supporting the hypothesis that air pollution may trigger non-atopic airway inflammation, resulting in non-atopic asthma. In the random-effects meta-analysis, which took into account the variability of exposures across the different recruitment sites and assessed the generalizability of the findings, the OR was unchanged but no longer Bonferroni significant. However, the value was near significant ($p = 0.02$), suggesting that regional variability may exist and further investigation is needed assess this association across additional regions in the US.

Prior epidemiologic studies found associations between air pollution and non-atopic diseases (43, 44), and experimental studies of those with asthma have shown that acute exposure to ozone stimulates production of mediators of neutrophil recruitment and airway neutrophilia (45-49), both considered distinct features in the pathogenesis of non-atopic asthma (50). Asthma patients with neutrophilia often have more severe airway obstruction and may be resistant to corticosteroid treatment, which can lead to chronic narrowing of the airways (51). Our findings suggest that ozone may be an important risk factor for non-atopic asthma, possibly acting through chronic neutrophilia and airway remodeling. This may be specific to the pediatric population, since this has not been reported elsewhere. It remains to be determined whether the remodeling process, which occurs over a continuum, may ultimately result in a change in functional status as a child matures.

A limitation of this study, as with case-control studies, is the ability to definitively assess temporality. While first year of life air pollution exposures likely occurred before the development of atopy, we were unable to verify that atopy occurred prior to the development of asthma. However, the development of atopy are likely to precede the development of atopic asthma (52, 53). Additionally, since controls were ineligible if they had allergies, eczema, or allergic rhinitis, and children with these conditions are also very likely to be atopic, our control population was under-represented in atopic children who may have been exposed to environmental conditions that trigger both atopy and asthma. Therefore, an analysis pooling atopic and non-atopic asthma cases and controls may be biased away from the null due to the excluded atopic children in the control sample. For this reason, we examined the associations stratified by asthma status, with the acknowledgement that the control group is not representative of the actual non-asthmatic Latino population.

Misclassification could also be a potential source of bias, as some argue that allergy skin tests should be used in combination with clinical history to diagnose atopic asthma (54). Unfortunately we could not determine specific allergen triggers for most participants. Finally, since 55% of allergy skin tests from Puerto Rico were not analyzed, the low prevalence of sensitization we found in this region may be inaccurate compared to an earlier study (37).While this previous study only evaluated individuals with physician diagnoses of atopic disease and had a larger panel of outdoor allergens, the rates of sensitization to indoor allergens (dust mite, cat, and dog) in this study were still much higher than that seen in our asthma cases from Puerto Rico. Many of the tests administered in Puerto Rico resulted in reactions in the negative control and occurred across multiple recruitment centers and recruiter personnel, suggesting a widespread problem with the tests rather than an isolated issue, such as a poorly trained recruiter or contaminated/defective equipment. The reason for the high number of reactions in the negative controls is currently unknown and these results should be interpreted with caution. However, the atopy prevalence measured in mainland participants (including mainland Puerto Ricans) remain valid, as do the results from the air pollution association analyses, which were unchanged when those recruited from Puerto Rico were dropped from the analysis.

Despite these limitations, this study benefits from having a large and diverse sample across multiple regions of the US, inclusive of children from multiple Latino ethnicities. Participants across all sites were recruited with stringent inclusion criteria and identical questionnaires. The biological samples were processed in the same laboratory and total IgE levels were measured on the same equipment, ensuring a well-characterized study population with consistent data across all study sites. Additionally, all participants had estimates of African genetic ancestry. Latinos have varying levels of genetic admixture, and researchers have suspected that genetic ancestry may be related to atopy (23, 29, 30) and total IgE values (27, 28). While genetic ancestry was not the primary focus of our study, it was robustly controlled for in our analyses.

In summary, our findings suggest that air pollution may partially account for non-atopic asthma in Latino children. Gaining a better understanding of both atopic and non-atopic asthma in Latinos is an important step in reducing asthma disparities. Minority children are often disproportionately exposed to higher levels of air pollution (55-57), and given the evidence that early-life ozone exposure increases the likelihood of developing non-atopic asthma, reducing air pollution in Latino communities could potentially prevent a substantial proportion of current and future asthma morbidity. Further longitudinal studies are needed to examine this association and the effects of environmental pollution within the first years of life.

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Table 3.1. Characteristics of participants in the GALA II study with allergy skin tests that passed quality control measures.

	Total **n (%)** 3106 (100)	**Cases** **n (%)** 1504 (100)	**Controls** **n (%)** 1602 (100)
Recruitment Region			
Chicago, IL	650 (20.9)	304 (20.2)	346 (21.6)
Houston, TX	369 (11.9)	202 (13.4)	167 (10.4)
Bronx, NY	574 (18.5)	306 (20.4)	268 (16.7)
Puerto Rico	776 (25.0)	354 (23.5)	422 (26.3)
San Francisco Bay Area, CA	737 (23.7)	338 (22.5)	399 (24.9)
Age (mean (SD))	13.3 (3.5)	12.7 (3.3)	13.9 (3.6)
Sex			
Male	1503 (48.4)	821 (54.6)	682 (42.6)
Female	1603 (51.6)	683 (45.4)	920 (57.4)
Latino Subgroup			
Mexican American	1359 (43.8)	611 (40.6)	748 (46.7)
Puerto Rican	979 (31.5)	480 (31.9)	499 (31.2)
Other Latino*	768 (24.7)	413 (27.5)	355 (22.2)
SES Composite Score[†]			
3-4	518 (16.7)	226 (15.0)	292 (18.2)
5-6	1310 (42.2)	677 (45.0)	633 (39.5)
7-9	699 (22.5)	358 (23.8)	341 (21.3)
Missing	579 (18.1)	243 (16.2)	336 (21.0)
Family History of Atopy[‡]	1184 (38.1)	775 (51.5)	409 (25.5)
Percent African Genetic Ancestry (mean (SD))	12.5 (12.2)	13.2 (12.8)	11.8 (11.7)
Maternal *in utero* smoking			
No	2938 (94.6)	1412 (93.9)	1526 (95.3)
Yes	137 (4.4)	80 (5.3)	57 (3.6)
Missing	31 (1.0)	12 (0.8)	19 (1.2)
Lung Function (mean (SD))[§]			
FEV_1 (L)	-	2.5 (0.8)	-
FVC (L)	-	3.0 (1.0)	-
FEV_1/FVC (%)	-	83.9 (7.6)	-
FEF_{25-75} (L/s)	-	2.7 (1.1)	-
Controller Medication Use			
Ever Prescribed	-	898 (59.7)	-
Use in Past Two Weeks	-	645 (42.9)	-

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

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

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

[§] Lung function was measured in asthma cases only. FEV_1 = forced expiratory volume during 1 second (Liters); FVC = forced vital capacity (Liters); FEV_1/FVC = ratio of FEV_1 to FVC. FEF_{25-75} = forced expiratory flow between 25% and 75% of vital capacity (Liters per second).

Table 3.2. First year of life air pollution exposures compared with the EPA air quality standards.

	All Regions	Chicago, IL	Houston, TX	Bronx, NY	Puerto Rico	San Francisco Bay Area, CA	EPA NAAQS
NO_2, ppb (24-hr avg)							
Mean (SD)	22.1 (8.8)	27.0 (3.2)	19.1 (4.3)	32.2 (5.4)	10.0 (3.7)	19.5 (5.3)	53*
25th	15.7	25.5	15.8	30.4	9.0	17.5	
50th	21.9	27.1	19.4	32.5	9.0	19.1	
75th	28.9	28.5	21.7	35.1	9.6	20.7	
O_3, ppb (8-hr max)							
Mean (SD)	28.9 (6.2)	28.3 (4.0)	38.0 (4.3)	28.5 (3.2)	26.5 (7.3)	25.5 (6.4)	NAS
25th	25.2	25.7	35.1	26.8	21.0	20.9	
50th	27.9	28.0	38.1	27.8	22.7	24.5	
75th	31.8	30.1	40.9	29.7	32.6	28.5	
PM_{10}, µg/m^3 (24-hr avg)							
Mean (SD)	29.3 (6.0)	34.5 (4.5)	29.7 (6.8)	27.6 (3.9)	29.5 (4.9)	24.9 (5.8)	NAS
25th	25.9	31.5	25.2	25.1	25.7	21.8	
50th	28.5	34.4	28.8	27.2	28.9	23.9	
75th	33.1	37.3	32.6	29.0	32.7	26.4	
$PM_{2.5}$, µg/m^3 (24-hr avg)							
Mean (SD)	13.0 (3.6)	17.1 (1.6)	13.2 (1.4)	14.5 (1.8)	8.1 (1.5)	12.3 (1.6)	12†
25th	10.6	16.1	12.3	14.2	7.2	11.4	
50th	13.4	17.2	13.1	14.6	7.7	12.3	
75th	15.7	18.0	13.9	15.5	9.1	12.6	
SO_2, ppb (24-hr avg)							
Mean (SD)	5.4 (4.0)	5.2 (1.4)	3.5 (1.3)	11.8 (3.2)	4.3 (2.4)	1.7 (0.9)	30*
25th	2.3	4.6	2.6	10.3	2.8	1.2	
50th	4.4	5.1	3.4	11.3	3.6	1.6	
75th	6.8	5.5	4.3	14.1	5.5	2.0	

ppb = parts-per-billion
µg/m^3 = 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
NO_2 = nitrogen dioxide
O_3 = ozone
PM_{10} = particulate matter with aerodynamic diameter ≤ 10 µm
$PM_{2.5}$ = particulate matter with aerodynamic diameter ≤ 2.5 µm
SO_2 = sulfur dioxide
Data from reference (58)
*Annual mean
†Annual mean, over 3 years

Table 3.3. Adjusted coefficients for the association between first year of life air pollution exposure and log transformed total IgE.*

	Asthmatic Participants				Non-Asthmatic Participants			
	Coef.	**(95% CI)**	**p-value**	**n**	**Coef.**	**(95% CI)**	**p-value**	**n**
NO_2 (ppb)	0.005	(-0.09 – 0.10)	0.92	924	-0.029	(-0.17 – 0.11)	0.68	624
Ozone (8 hr max.) (ppb)	0.004	(-0.10 – 0.11)	0.93	756	-0.092	(-0.23 – 0.05)	0.20	554
PM_{10} ($\mu g/m^3$)	-0.071	(-0.16 – 0.01)	0.10	1014	-0.039	(-0.15 – 0.07)	0.47	705
$PM_{2.5}$ ($\mu g/m^3$)	0.274	(-0.14 – 0.69)	0.19	380	-0.173	(-0.78 – 0.43)	0.57	205
SO_2 (ppb)	-0.006	(-0.05 – 0.04)	0.80	975	0.001	(-0.05 – 0.52)	0.98	669

* Analyses restricted to those with allergy skin tests that passed quality control. Models are adjusted for age, sex, SES, ethnicity, recruitment region, proportion of global African ancestry, maternal *in utero* smoking, and atopic status. All pollutants are scaled to represent a 5 unit change in exposure, except SO_2 (1 unit change).

Table 3.4. Adjusted ORs for the association between first year of life air pollution exposure and being non-atopic (reference category was atopy).*

	Asthmatic Participants				Non-Asthmatic Participants			
	OR	**(95% CI)**	**p-value**	**n**	**OR**	**(95% CI)**	**p-value**	**n**
NO_2 (ppb)	1.06	(0.89 – 1.26)	0.49	942	1.08	(0.86 – 1.34)	0.51	706
Ozone (8 hr max.) (ppb)	**1.32**	**(1.11 – 1.56)**	**0.002**	**771**	1.10	(0.89 – 1.35)	0.37	582
PM_{10} ($\mu g/m^3$)	1.01	(0.88 – 1.17)	0.84	1035	0.94	(0.80 – 1.10)	0.43	820
$PM_{2.5}$ ($\mu g/m^3$)	0.88	(0.42 – 1.86)	0.75	394	1.46	(0.57 – 3.72)	0.42	242
SO_2 (ppb)	0.99	(0.91 – 1.07)	0.80	995	0.99	(0.90 – 1.06)	0.56	771

Boldface type indicates significant results at a significant Bonferroni-corrected α value of 0.01.
* Analyses restricted to those with allergy skin tests that passed quality control. 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 SO_2 (1 unit change).

Figure 3.1. Variation in total IgE levels in the GALA II study, stratified by region, Latino subgroup, and asthma status.
Symbols represent the geometric mean, whiskers represent the 95% CI. Data were omitted if there were fewer than 20 observations for a given category.

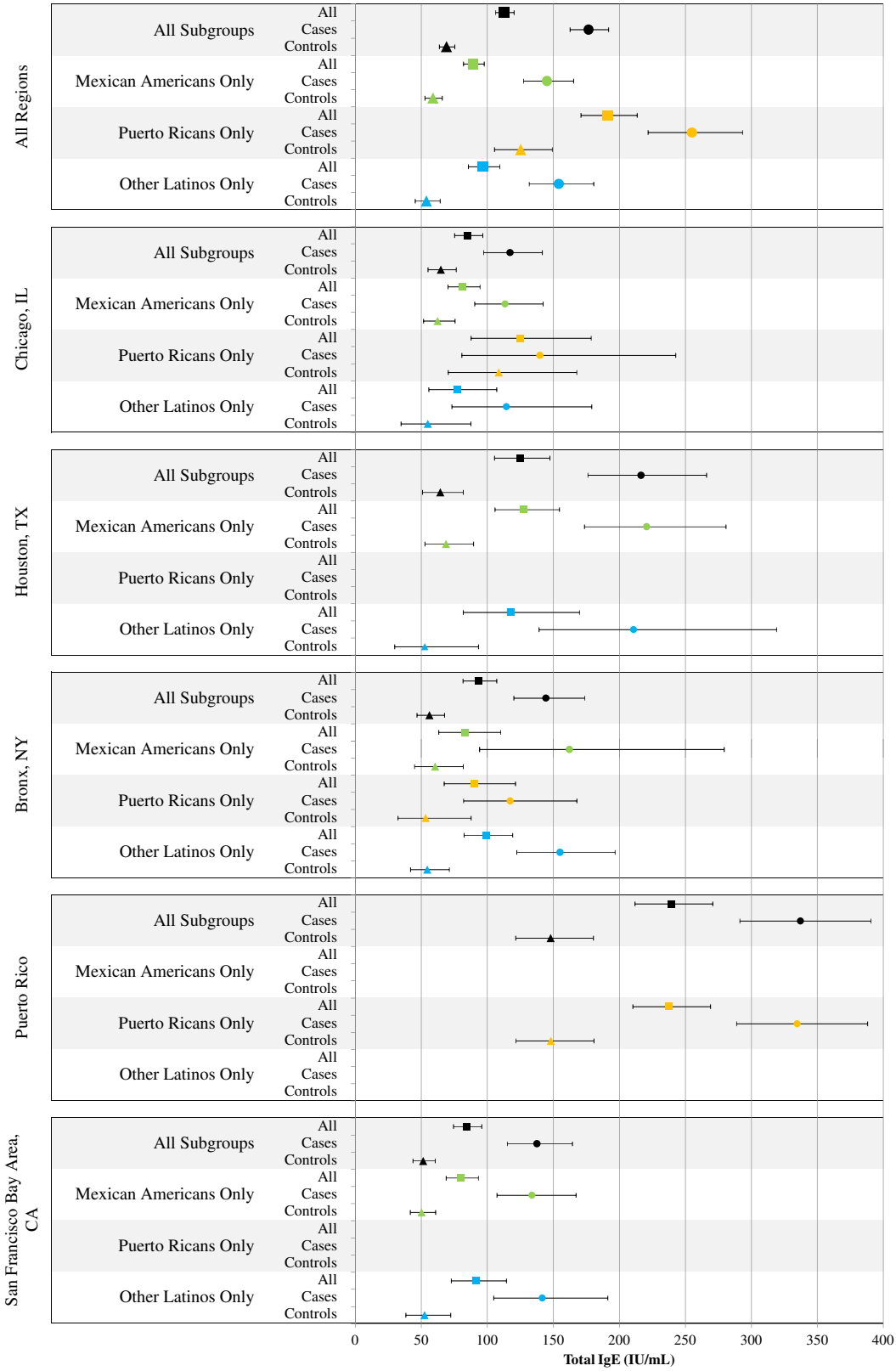


Figure 3.2. Allergen-specific sensitivity, stratified by recruitment region, and asthma status.

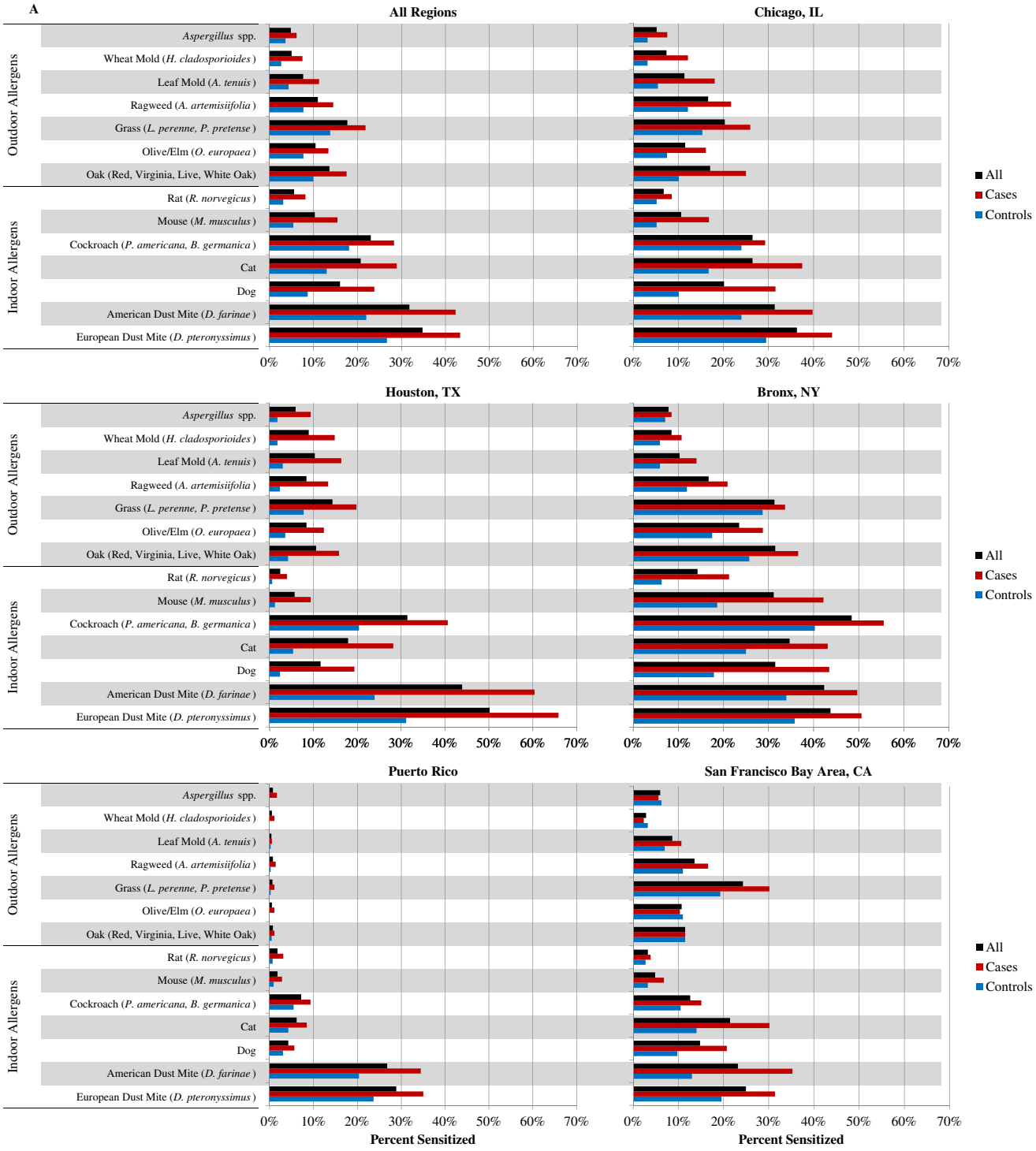


Figure 3.2. Allergen-specific sensitivity, stratified by Latino subgroup and asthma status.

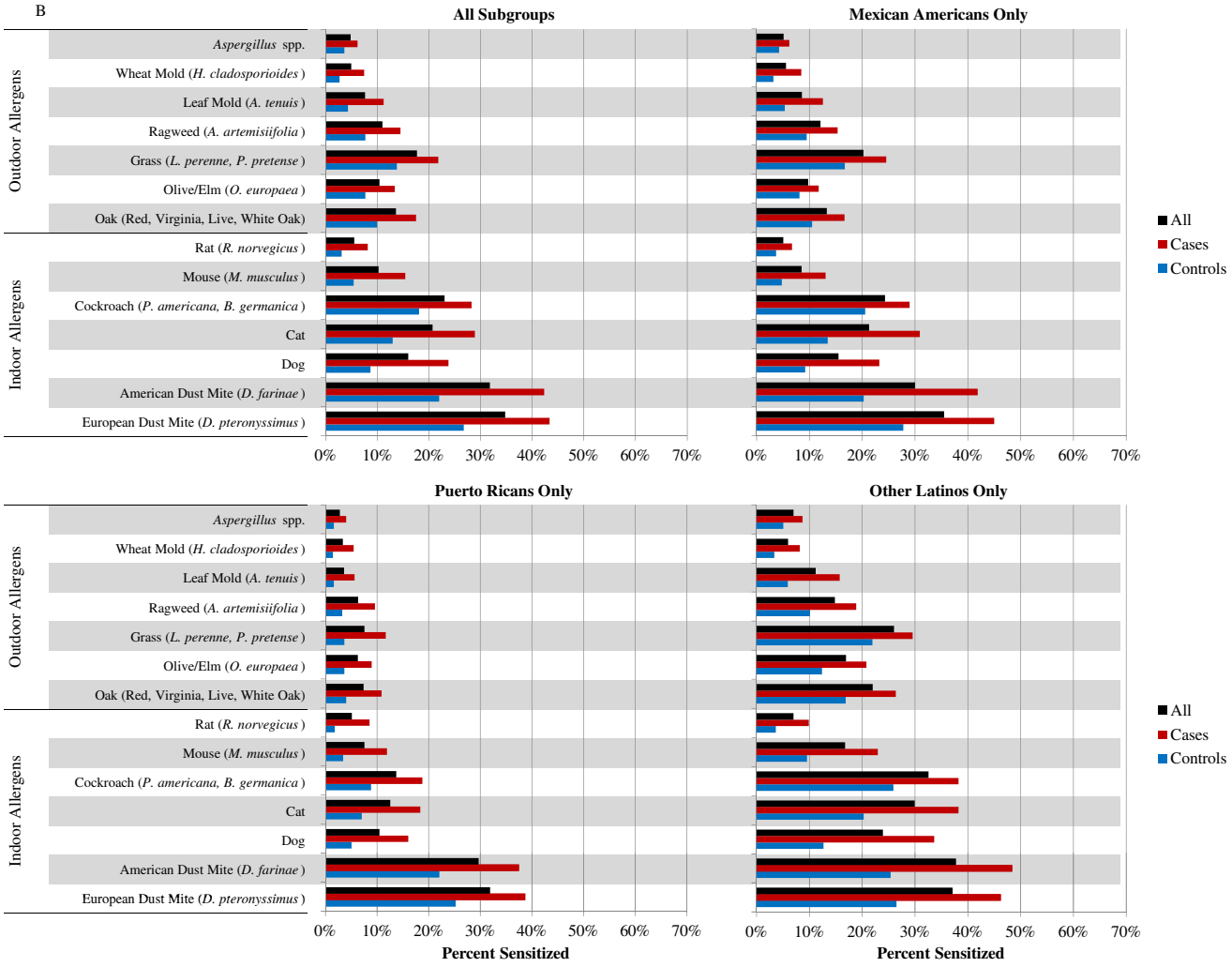


Figure 3.3. Percent of atopic participants, stratified by Latino subgroup, recruitment region, and asthma status. Data were omitted if there were fewer than 20 observations for a given category.

A

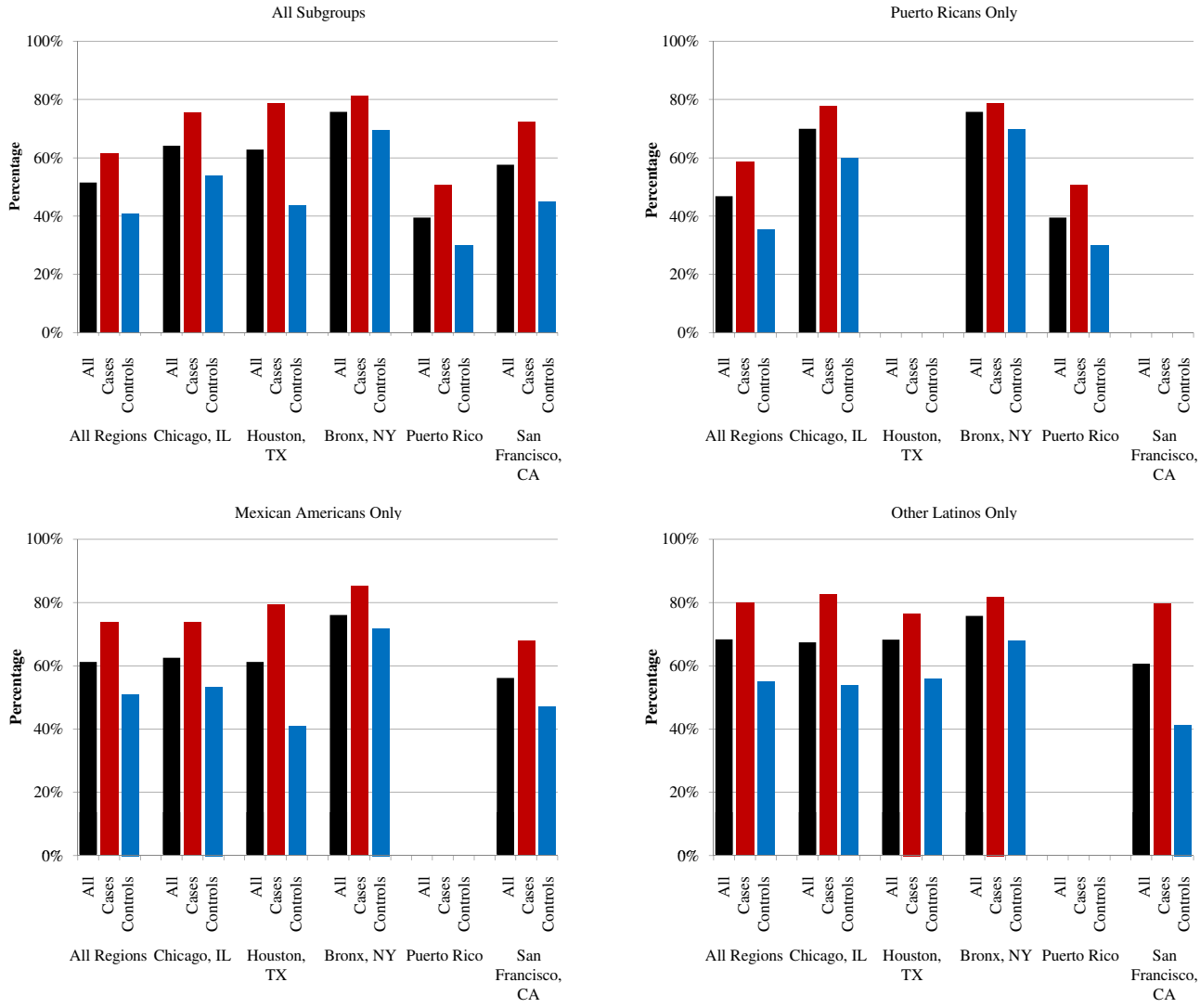
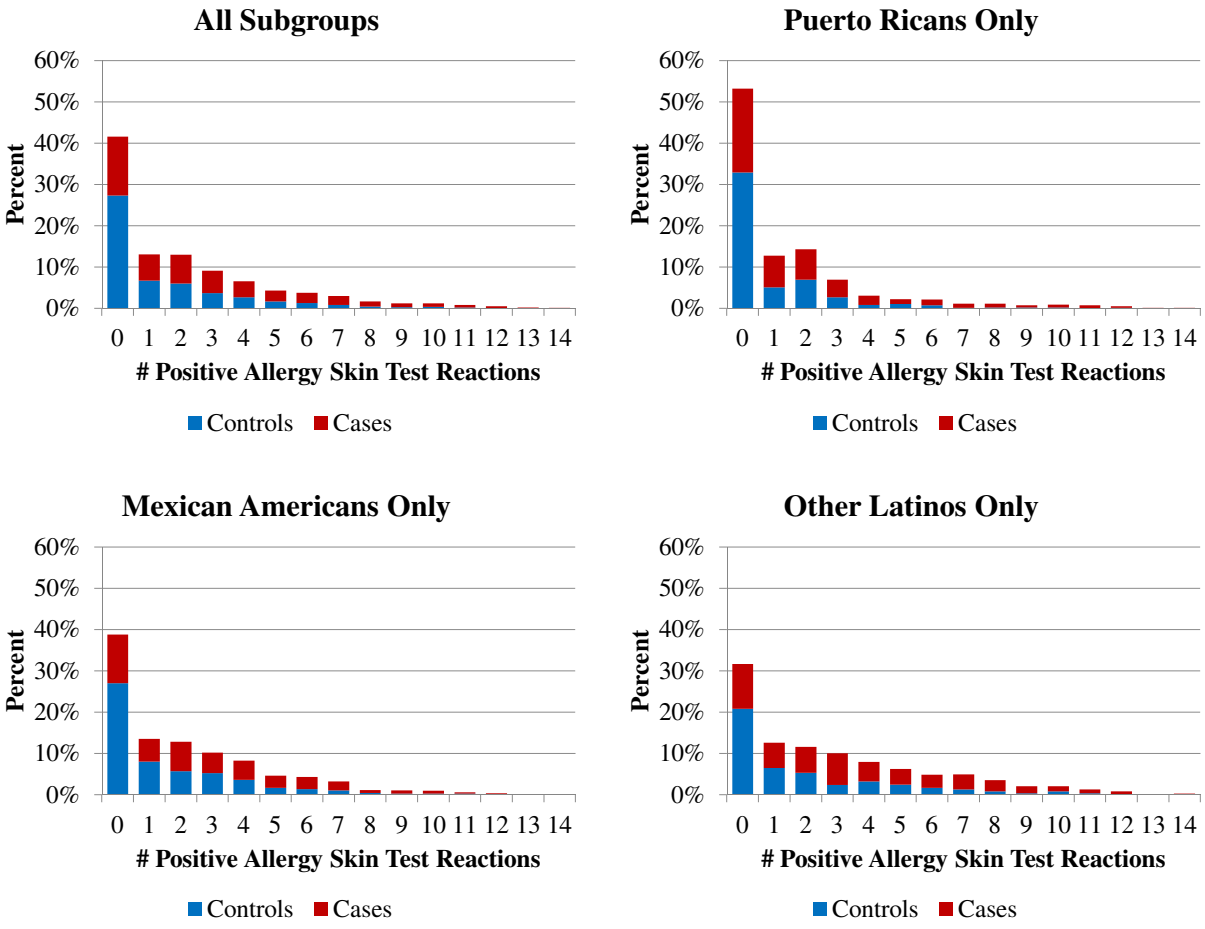


Figure 3.3. Percent of participants with positive skin test reactions, stratified by Latino subgroup and asthma status.

B



Appendix Figure 3.1. Geometic mean total IgE levels stratified by region, Latino subgroup, and asthma status. Data were omitted if there were fewer than 20 observations for a given category. GM = geometric mean. CI = confidence interval.

			GM (95% CI)	n
All Regions	All Subgroups	All	113.1 (106.3 - 120.2)	2813
		Cases	176.7 (162.7 - 191.8)	1473
		Controls	69.2 (63.6 - 75.3)	1340
	Mexican Americans Only	All	89.4 (81.9 - 97.6)	1355
		Cases	145.2 (127.5 - 165.3)	597
		Controls	58.9 (52.8 - 65.8)	694
	Puerto Ricans Only	All	191.0 (170.9 - 213.5)	1510
		Cases	255.0 (221.7 - 293.2)	470
		Controls	125.4 (105.4 - 149.2)	323
	Other Latinos Only	All	96.8 (85.6 - 109.4)	752
		Cases	154.2 (131.6 - 180.5)	406
		Controls	53.9 (45.3 - 64.2)	323
Chicago, IL	All Subgroups	All	85.2 (75.1 - 96.6)	620
		Cases	117.2 (97.1 - 141.6)	286
		Controls	64.8 (55.0 - 76.4)	334
	Mexican Americans Only	All	81.4 (70.2 - 94.4)	450
		Cases	113.4 (90.4 - 142.3)	200
		Controls	62.5 (51.7 - 75.5)	250
	Puerto Ricans Only	All	125.1 (87.7 - 178.6)	77
		Cases	139.9 (80.6 - 242.6)	43
		Controls	108.6 (70.4 - 167.6)	34
	Other Latinos Only	All	77.2 (55.7 - 107.0)	93
		Cases	114.4 (73.1 - 179.1)	43
		Controls	55.0 (34.6 - 87.5)	50
Houston, TX	All Subgroups	All	124.6 (105.4 - 147.3)	362
		Cases	216.4 (176.1 - 266.0)	197
		Controls	64.5 (50.8 - 81.8)	165
	Mexican Americans Only	All	127.9 (105.7 - 154.6)	278
		Cases	220.7 (173.5 - 280.7)	148
		Controls	68.7 (52.7 - 89.5)	130
	Puerto Ricans Only	All	- -	-
		Cases	- -	-
		Controls	- -	-
	Other Latinos Only	All	117.8 (81.8 - 169.7)	81
		Cases	210.7 (139.2 - 319.1)	47
		Controls	52.8 (29.8 - 93.3)	34
Bronx, NY	All Subgroups	All	93.5 (81.6 - 107.1)	567
		Cases	144.4 (120.1 - 173.6)	306
		Controls	56.2 (46.7 - 67.5)	261
	Mexican Americans Only	All	83.4 (63.2 - 110.0)	123
		Cases	162.2 (94.1 - 279.4)	40
		Controls	60.5 (44.8 - 81.7)	83
	Puerto Ricans Only	All	90.3 (67.3 - 121.3)	127
		Cases	117.3 (82.0 - 167.8)	85
		Controls	53.2 (32.3 - 87.7)	42
	Other Latinos Only	All	99.1 (82.4 - 119.2)	317
		Cases	155.1 (122.3 - 196.7)	181
		Controls	54.6 (41.9 - 71.1)	136
Puerto Rico	All Subgroups	All	239.4 (211.8 - 270.7)	592
		Cases	337.1 (291.1 - 390.3)	346
		Controls	148.0 (121.5 - 180.2)	246
	Mexican Americans Only	All	- -	-
		Cases	- -	-
		Controls	- -	-
	Puerto Ricans Only	All	237.8 (210.2 - 269.1)	584
		Cases	334.7 (288.7 - 388.0)	339
		Controls	148.2 (121.6 - 180.7)	245
	Other Latinos Only	All	- -	-
		Cases	- -	-
		Controls	- -	-
San Francisco Bay Area, CA	All Subgroups	All	84.4 (74.4 - 95.7)	672
		Cases	137.6 (115.2 - 164.4)	338
		Controls	51.5 (43.7 - 60.5)	334
	Mexican Americans Only	All	80.1 (68.8 - 93.2)	440
		Cases	133.9 (107.2 - 167.2)	209
		Controls	50.3 (41.7 - 60.8)	231
	Puerto Ricans Only	All	- -	-
		Cases	- -	-
		Controls	- -	-
	Other Latinos Only	All	91.2 (72.7 - 114.4)	230
		Cases	141.5 (104.8 - 191.2)	128
		Controls	52.6 (38.2 - 72.3)	102

Appendix Figure 3.2. Allergen-specific sensitivity, stratified by recruitment region, and asthma status.

		All Regions			Chicago, IL			Houston, TX			Bronx, NY			Puerto Rico			SF Bay Area		
		All	Cases	Controls	All	Cases	Controls	All	Cases	Controls	All	Cases	Controls	All	Cases	Controls	All	Cases	Controls
Outdoor Allergens	*Aspergillus* spp.	5%	6%	4%	5%	8%	3%	6%	9%	2%	8%	9%	7%	1%	2%	0%	6%	6%	6%
	Wheat Mold (*H. cladosporioides*)	5%	7%	3%	7%	12%	3%	9%	15%	2%	9%	11%	6%	1%	1%	0%	3%	2%	3%
	Leaf Mold (*A. tenuis*)	8%	11%	4%	11%	18%	5%	10%	16%	3%	10%	14%	6%	0%	1%	0%	9%	11%	7%
	Ragweed (*A. artemisiifolia*)	11%	14%	8%	17%	22%	12%	8%	13%	2%	17%	21%	12%	1%	1%	0%	14%	17%	11%
	Grass (*L. perenne, P. pretense*)	18%	22%	14%	20%	26%	15%	14%	20%	8%	31%	34%	29%	1%	1%	0%	24%	30%	19%
	Olive/Elm (*O. europaea*)	10%	13%	8%	12%	16%	8%	8%	12%	4%	24%	29%	18%	1%	1%	0%	11%	10%	11%
	Oak (Red, Virginia, Live, White Oak)	14%	17%	10%	17%	25%	10%	11%	16%	4%	32%	37%	26%	1%	1%	0%	12%	12%	12%
Indoor Allergens	Rat (*R. norvegicus*)	6%	8%	3%	7%	9%	5%	2%	4%	1%	14%	21%	6%	2%	3%	1%	3%	4%	3%
	Mouse (*M. musculus*)	10%	15%	5%	11%	17%	5%	6%	9%	1%	31%	42%	19%	2%	3%	1%	5%	7%	3%
	Cockroach (*P. americana, B. germanica*)	23%	28%	18%	26%	29%	24%	31%	41%	20%	48%	56%	40%	7%	9%	5%	13%	15%	11%
	Cat	21%	29%	13%	26%	38%	17%	18%	28%	5%	35%	43%	25%	6%	8%	4%	21%	30%	14%
	Dog	16%	24%	9%	20%	32%	10%	12%	19%	2%	32%	43%	18%	4%	6%	3%	15%	21%	10%
	American Dust Mite (*D. farinae*)	32%	42%	22%	31%	40%	24%	44%	60%	24%	42%	50%	34%	27%	34%	20%	23%	35%	13%
	European Dust Mite (*D. pteronyssimus*)	35%	43%	27%	36%	44%	29%	50%	66%	31%	44%	51%	36%	29%	35%	24%	25%	31%	20%

Appendix Figure 3.3. Allergen-specific sensitivity, stratified by Latino subgroup and asthma status.

		All Subgroups			Mexican Americans Only			Puerto Ricans Only			Other Latinos Only		
		All	Cases	Controls	All	Cases	Controls	All	Cases	Controls	All	Cases	Controls
Outdoor Allergens	*Aspergillus* spp.	5%	6%	4%	5%	6%	4%	3%	4%	2%	7%	9%	5%
	Wheat Mold (*H. cladosporioides*)	5%	7%	3%	6%	9%	3%	3%	5%	1%	6%	8%	3%
	Leaf Mold (*A. tenuis*)	8%	11%	4%	9%	13%	5%	4%	6%	2%	11%	16%	6%
	Ragweed (*A. artemisiifolia*)	11%	14%	8%	12%	15%	9%	6%	10%	3%	15%	19%	10%
	Grass (*L. perenne, P. pretense*)	18%	22%	14%	20%	25%	17%	8%	12%	4%	26%	30%	22%
	Olive/Elm (*O. europaea*)	10%	13%	8%	10%	12%	8%	6%	9%	4%	17%	21%	12%
	Oak (Red, Virginia, Live, White Oak)	14%	17%	10%	13%	17%	11%	7%	11%	4%	22%	26%	17%
Indoor Allergens	Rat (*R. norvegicus*)	6%	8%	3%	5%	7%	4%	5%	9%	2%	7%	10%	4%
	Mouse (*M. musculus*)	10%	15%	5%	9%	13%	5%	8%	12%	3%	17%	23%	10%
	Cockroach (*P. americana, B. germanica*)	23%	28%	18%	24%	29%	21%	14%	19%	9%	33%	38%	26%
	Cat	21%	29%	13%	21%	31%	14%	13%	18%	7%	30%	38%	20%
	Dog	16%	24%	9%	16%	23%	9%	10%	16%	5%	24%	34%	13%
	American Dust Mite (*D. farinae*)	32%	42%	22%	30%	42%	20%	30%	38%	22%	38%	48%	25%
	European Dust Mite (*D. pteronyssimus*)	35%	43%	27%	36%	45%	28%	32%	39%	25%	37%	46%	26%

Appendix Figure 3.4. Percent of atopic participants, stratified by Latino subgroup, recruitment region, and asthma status. Data were omitted if there were fewer than 20 observations for a given category.

Latino Subgroup	Region	Asthma Status	% Atopic
All Ethnicities	ALL	All	52%
		Cases	61%
		Controls	41%
	CH	All	64%
		Cases	76%
		Controls	54%
	TX	All	63%
		Cases	79%
		Controls	44%
	NY	All	76%
		Cases	81%
		Controls	69%
	PR	All	39%
		Cases	51%
		Controls	30%
	SF	All	58%
		Cases	72%
		Controls	45%

Latino Subgroup	Region	Asthma Status	% Atopic
Mexican Americans Only	ALL	All	61%
		Cases	74%
		Controls	51%
	CH	All	63%
		Cases	74%
		Controls	53%
	TX	All	61%
		Cases	79%
		Controls	41%
	NY	All	76%
		Cases	85%
		Controls	72%
	PR	All	-
		Cases	-
		Controls	-
	SF	All	56%
		Cases	68%
		Controls	47%

Latino Subgroup	Region	Asthma Status	% Atopic
Puerto Ricans Only	ALL	All	47%
		Cases	59%
		Controls	35%
	CH	All	70%
		Cases	78%
		Controls	60%
	TX	All	-
		Cases	-
		Controls	-
	NY	All	76%
		Cases	79%
		Controls	70%
	PR	All	39%
		Cases	51%
		Controls	30%
	SF	All	-
		Cases	-
		Controls	-

Latino Subgroup	Region	Asthma Status	% Atopic
Other Latinos Only	ALL	All	68%
		Cases	80%
		Controls	55%
	CH	All	67%
		Cases	83%
		Controls	54%
	TX	All	68%
		Cases	76%
		Controls	56%
	NY	All	76%
		Cases	82%
		Controls	68%
	PR	All	-
		Cases	-
		Controls	-
	SF	All	61%
		Cases	80%
		Controls	41%

Appendix Figure 3.5. Percent of participants with positive skin test reactions, stratified by Latino subgroup and asthma status.

All Ethnicities				
# Positive Rxns	n (cases)	% (cases)	n (controls)	% (controls)
0	441	14%	849	27%
1	197	6%	209	7%
2	217	7%	186	6%
3	169	5%	115	4%
4	121	4%	82	3%
5	81	3%	52	2%
6	78	3%	39	1%
7	68	2%	25	1%
8	39	1%	14	0%
9	28	1%	9	0%
10	26	1%	12	0%
11	18	1%	7	0%
12	13	0%	2	0%
13	4	0%	1	0%
14	3	0%	0	0%

Mexican Americans Only				
# Positive Rxns	n (cases)	% (cases)	n (controls)	% (controls)
0	160	12%	367	27%
1	75	6%	109	8%
2	97	7%	77	6%
3	68	5%	71	5%
4	63	5%	49	4%
5	40	3%	23	2%
6	40	3%	19	1%
7	30	2%	14	1%
8	9	1%	6	0%
9	10	1%	4	0%
10	9	1%	4	0%
11	4	0%	4	0%
12	4	0%	1	0%
13	2	0%	0	0%
14	0	0%	0	0%

Puerto Ricans Only				
# Positive Rxns	n (cases)	% (cases)	n (controls)	% (controls)
0	198	20%	322	33%
1	75	8%	50	5%
2	72	7%	68	7%
3	42	4%	26	3%
4	22	2%	8	1%
5	12	1%	10	1%
6	14	1%	7	1%
7	10	1%	1	0%
8	9	1%	2	0%
9	5	1%	2	0%
10	7	1%	2	0%
11	7	1%	0	0%
12	4	0%	1	0%
13	1	0%	0	0%
14	1	0%	0	0%

Other Latinos Only				
# Positive Rxns	n (cases)	% (cases)	n (controls)	% (controls)
0	83	11%	160	21%
1	47	6%	50	7%
2	48	6%	41	5%
3	59	8%	18	2%
4	36	5%	25	3%
5	29	4%	19	2%
6	24	3%	13	2%
7	28	4%	10	1%
8	21	3%	6	1%
9	13	2%	3	0%
10	10	1%	6	1%
11	7	1%	3	0%
12	5	1%	1	0%
13	1	0%	0	0%
14	2	0%	0	0%

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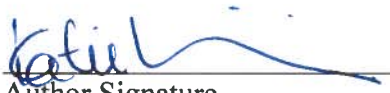

Author Signature

June 3. 2014

Date