Early-Life Air Pollution and Asthma Risk in Minority Children

The GALA II and SAGE II Studies

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***Rationale*: Air pollution is a known asthma trigger and has been associated with short-term asthma symptoms, airway inflammation, decreased lung function, and reduced response to asthma rescue medications.**
***Objectives*: To assess a causal relationship between air pollution and childhood asthma using data that address temporality by estimating air pollution exposures before the development of asthma and to establish the generalizability of the association by studying diverse racial/ethnic populations in different geographic regions.**
***Methods*: This study included Latino (n = 3,343) and African American (n = 977) participants with and without asthma from five urban regions in the mainland United States and Puerto Rico. Residential history and data from local ambient air monitoring stations were used to estimate average annual exposure to five air pollutants: ozone, nitrogen dioxide (NO_2), sulfur dioxide, particulate matter not greater than 10 μm in diameter, and particulate matter not greater than 2.5 μm in diameter. Within each region, we performed logistic regression to determine the relationship between early-life exposure to air pollutants and subsequent asthma diagnosis. A random-effects model was used to combine the region-specific effects and generate summary odds ratios for each pollutant.**
***Measurements and Main Results*: After adjustment for confounders, a 5-ppb increase in average NO_2 during the first year of life was associated with an odds ratio of 1.17 for physician-diagnosed asthma (95% confidence interval, 1.04–1.31).**
***Conclusions*: Early-life NO_2 exposure is associated with childhood asthma in Latinos and African Americans. These results add to a growing body of evidence that traffic-related pollutants may be causally related to childhood asthma.**

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Air pollution has been associated with asthma prevalence. However, few studies look at early-life exposures before the development of childhood asthma and many are limited to populations of mostly European descent.

What This Study Adds to the Field

Using the largest pediatric gene–environment study of asthma in Latinos and African Americans in the United States, we found that exposure during infancy to NO_2, a traffic-related air pollutant, was associated with increased risk for subsequent development of childhood asthma. Our results suggest that air pollution may contribute to the higher prevalence of asthma, especially in some minority children exposed to higher levels of air pollution.

Keywords: air pollution; minority; children; asthma

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

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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). Whereas 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 meta-analysis of 17 population-based cohort studies found a statistically significant odds ratio (OR) of 1.07 (95% confidence interval [CI], 1.02–1.13) for every 10-$\mu g/m^3$ increase in nitrogen dioxide (NO_2) (24). However, both child and adult cohorts were used in this meta-analysis and many (11 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-$\mu g/m^3$ 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 United States (27). Puerto Ricans (16.6%) and African Americans (11.1%) have among the highest prevalence, significantly higher than that of white individuals (7.8%). Interestingly, Mexicans have one of the lowest prevalence rates (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, 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 and Admixture in Latino Americans (GALA II) and the Study of African Americans, Asthma, Genes and 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 United States. 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 United States (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 to 21 years old and had no history of other lung or chronic illnesses (other than atopy and allergy-related diseases in the case subjects). 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. Case subjects were defined as those with physician-diagnosed asthma plus two or more symptoms of coughing, wheezing, or shortness of breath in the 2 years before recruitment. Eligible control subjects had no reported history of asthma, lung disease, or chronic illness, and no reported symptoms of coughing, wheezing, or shortness of breath in the 2 years before enrollment. Control subjects were 1:1 frequency matched within each recruitment center by age (within 1 yr). Case subjects and control subjects were recruited from similar geographic regions (*see* Figure E2 in the online supplement). Those in the third trimester of pregnancy, current smokers, and those with an at least a 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 TomTom/Tele Atlas EZ-Locate software (TomTom, Amsterdam, The Netherlands). Regional ambient air pollution data were acquired from the U.S. Environmental Protection Agency Air Quality System. To average out yearly temporal changes, annual average exposures to ozone (O_3), NO_2, sulfur dioxide (SO_2), particulate matter not greater than 10 μm in diameter (PM_{10}), and particulate matter not greater than 2.5 μm in diameter ($PM_{2.5}$) 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 on the basis of the number of months spent at each residence. Exposures over the first 3 years of life were calculated by averaging all available pollutant values from birth to age 3.

Statistical Analysis

To account for regional characteristics, we used a two-stage analysis, allowing us to measure the between-region heterogeneity and to 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 3 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 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 three 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 case subjects). 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 to 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 case subjects; 1,655 control subjects) and 977 African Americans from SAGE II (603 case subjects; 374 control subjects) (Table 1). Case subjects who reported an age of diagnosis during the exposure history window (i.e., the first year or first 3 yr 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 2 and Table E1; and Figure 1 and Figure E1). For example, whereas Puerto Rican subjects were exposed to much lower levels of NO_2 and PM_{10}, they had some of the

TABLE 1. DEMOGRAPHIC INFORMATION FOR CHILDREN INCLUDED IN THIS STUDY*

	Case Subjects (*n = 2,291*)	Control Subjects (*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%)	1,336 (31%)
San Francisco Bay Area	903 (39%)	691 (34%)	1,594 (37%)
Sex			
Female	1,033 (45%)	1,141 (56%)	2,174 (50%)
Male	1,258 (55%)	888 (44%)	2,146 (50%)
Age at recruitment, yr			
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‡			
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%)	768 (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			
United States	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%)	71 (2%)
Age at onset, yr	2.0 (0.75–5.0)	—	—

Definition of abbreviation: SES = socioeconomic status.

* Reported as n (%), or median (IQR), for subjects with complete data on age, sex, ethnicity, and SES.

† "Other Latino" reports either one Latino ethnicity other than Mexican or Puerto Rican, or reports more than one Latino ethnicity.

‡ 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 was ever diagnosed with asthma.

TABLE 2. AVERAGE POLLUTION IN 1996 (MEDIAN YEAR OF BIRTH),* COMPARED WITH 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-h 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-h 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-h 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-h 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-h 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-h 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: ave = average; Cal EPA = California Environmental Protection Agency; EPA = U.S. Environmental Protection Agency; max = maximum; NAS = no annual standard; NO_2 = nitrogen dioxide; O_3 = ozone; $PM_{2.5}$ = particulate matter < 2.5 μm in diameter; PM_{10} = particulate matter < 10 μm in diameter; ppb = parts per billion; SF = San Francisco; SO_2 = sulfur dioxide; WHO = World Health Organization.

Data from references 51–53.

*With the exception of $PM_{2.5}$, where 2000 was used because of insufficient observations in 1996; reported as average (SD).

† Annual mean.

‡ Annual mean, over 3 years.

§ The WHO does not have an annual SO_2 guideline because they regard their 7-ppb (20-$\mu g/m^3$) 24-hour standard sufficiently protective for the annual average. In the GALA II regions, an annual average of about 3 ppb SO_2 is comparable to a daily maximal concentration of 7 ppb.

highest levels of O_3, surpassed only by Houston. Participants from the San Francisco Bay Area had the lowest exposures to 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 U.S. Environmental Protection Agency (EPA) National Ambient Air Quality Standards 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 (Figure E3).

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 3 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 2 and 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 with any other region. Analyses stratified by sex, high/low IgE, and family history (Tables E2–E4) did not reveal any statistically significant associations.

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 United States and Puerto Rico. Our results are consistent with previous findings from two meta-analyses that support a relationship between NO_2 and asthma incidence (16, 24). Some studies included in these meta-analyses lacked accurate measurements of the exposure before 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 predated their asthma diagnosis.

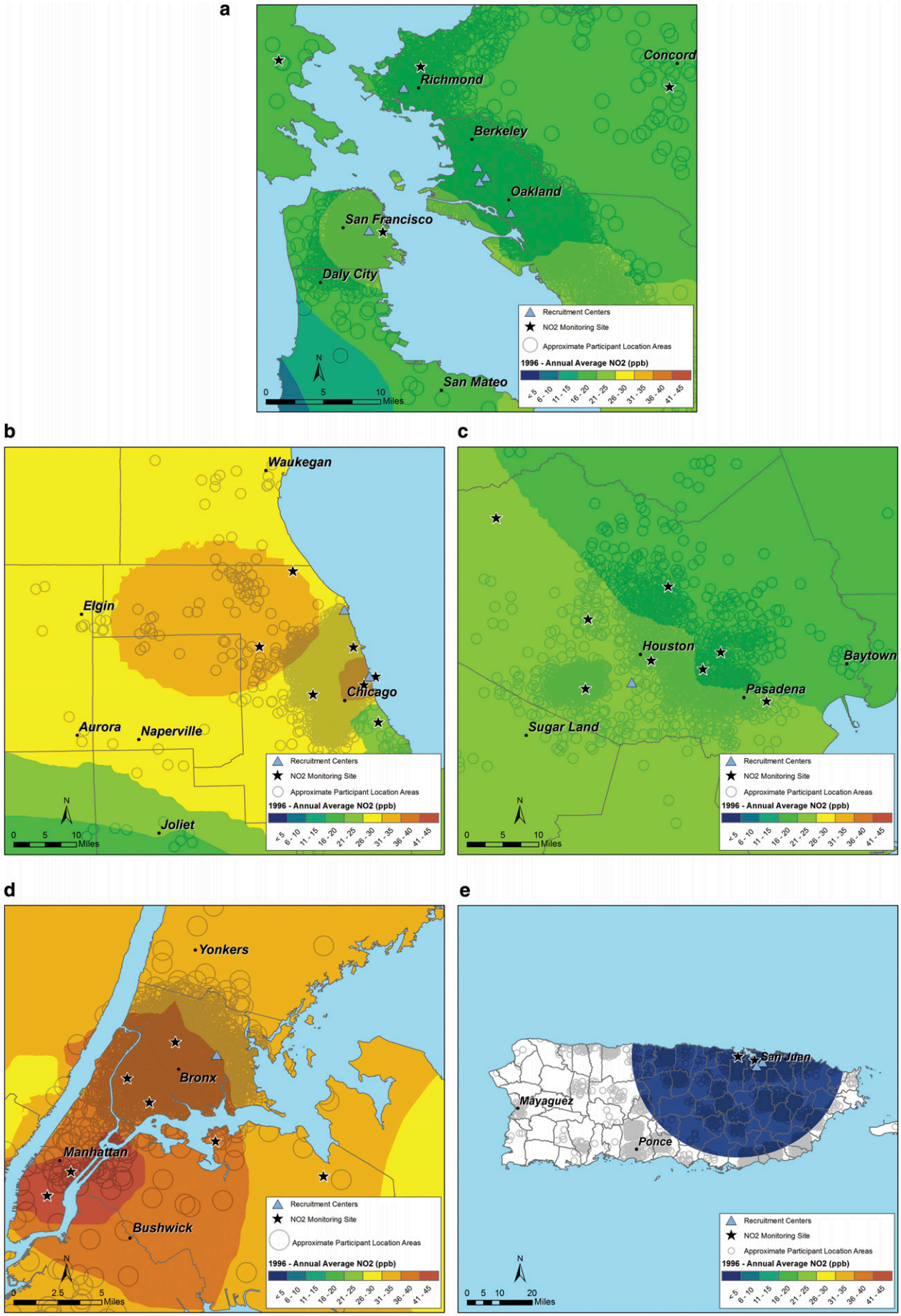
a
Concord
Richmond
Berkeley
Oakland
San Francisco
Daly City
San Mateo
Recruitment Centers
NO2 Monitoring Site
Approximate Participant Location Areas
1996 - Annual Average NO2 (ppb)
< 5
6 - 10
11 - 15
16 - 20
21 - 25
26 - 30
31 - 35
36 - 40
41 - 45
N
0 5 10 Miles
b
Waukegan
Elgin
Chicago
Aurora
Naperville
Joliet
c
Houston
Baytown
Pasadena
Sugar Land
d
Yonkers
Bronx
Manhattan
Bushwick
0 2.5 5 Miles
e
San Juan
Mayaguez
Ponce
0 5 10 20 Miles

Figure 1. (*a*) NO_2 exposure in 1996 (median birth year) for the San Francisco Bay Area. 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 the nearby urban centers. *Solid stars* represent the location of monitoring sites. *Blue triangles* represent recruitment centers. NO_2 = nitrogen dioxide. (*b–e*) NO_2 exposure in 1996 in Chicago (*b*), Houston (*c*), New York (*d*), and Puerto Rico (*e*).

In addition, 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 nominally positive associations that were broadly consistent with one another, with little between-study heterogeneity (I^2 for the first year and first 3 yr of life were 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 interregional differences.

Because 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 with 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, whereas 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 whether 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 body weight 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 before 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 that should be acknowledged. Many prior studies have used $PM_{2.5}$ as another indicator of traffic-related pollution, though a meta-analysis reported nonsignificant 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 with other pollutants. Thus, the nonsignificant 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, because we did not have the ability to measure air pollution by personal air sampling. Although more accurate methods for measuring pollution are available by directly

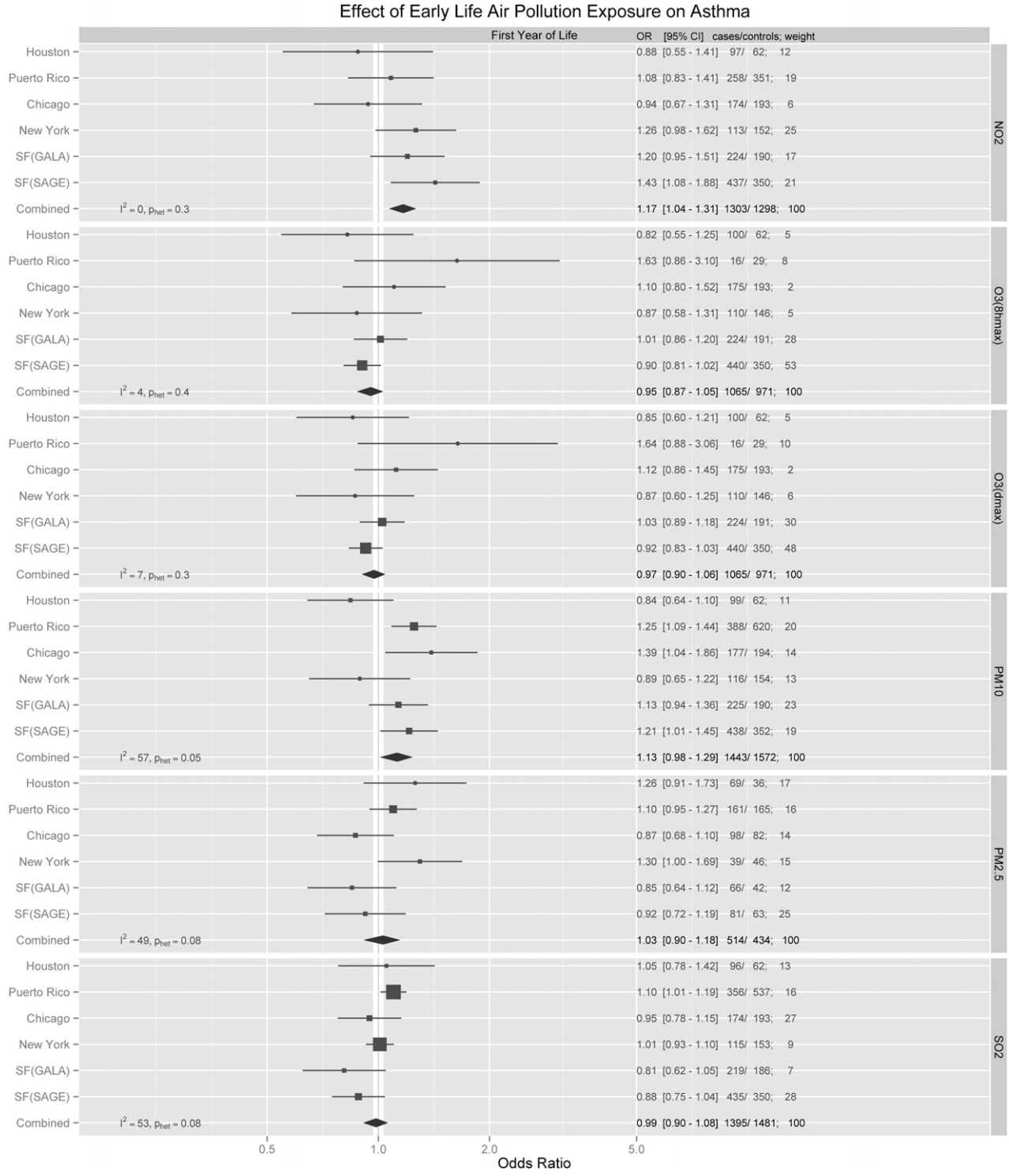

Figure 2. Adjusted region-specific and summary odds ratio (OR) estimates for all pollutants during the first year of life. Region-specific analyses were adjusted for age, SES, income, and race/ethnicity, and then pooled using a random-effects model. For NO_2 and O_3 (1-h max, 8-h max), ORs were calculated for every 5-ppb change. For PM_{10}, ORs were calculated for every 5-$\mu g/m^3$ change. For $PM_{2.5}$, ORs were calculated for every 1-$\mu g/m^3$ change. For SO_2, ORs were calculated for every 1-ppb change. CI = confidence interval; GALA = Genes–environments and Admixture in Latino Americans; NO_2 = nitrogen dioxide; O_3 = ozone; OR = odds ratio; $PM_{2.5}$ = particulate matter < 2.5 μm in diameter; PM_{10} = particulate matter < 10 μm in diameter; ppb = parts per billion; SAGE = Study of African Americans, Asthma, Genes, and Environments; SO_2 = sulfur dioxide.

monitoring pollutants at a residence or school (17, 32), it is often infeasible to sample continuously throughout the year by 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,

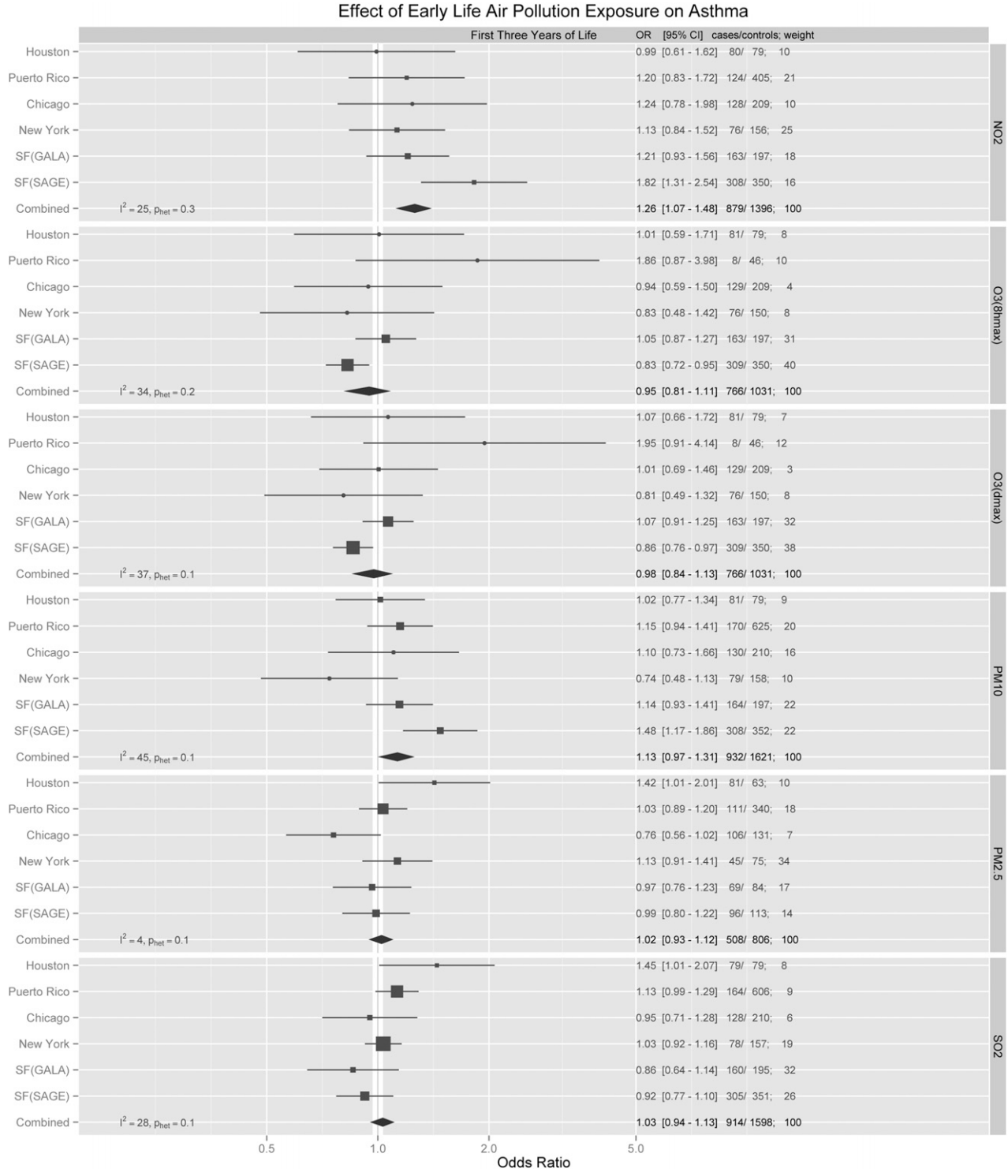

Figure 3. Adjusted region-specific and summary odds ratio (OR) estimates for all pollutants during the first 3 years of life. Region-specific analyses adjusted for age, SES, income, and race/ethnicity, and then pooled using a random-effects model. For NO_2 and O_3 (1-h max, 8-h max), ORs were calculated for every 5-ppb change. For PM_{10}, ORs were calculated for every 5-$\mu g/m^3$ change. For $PM_{2.5}$, ORs were calculated for every 1-$\mu g/m^3$ change. For SO_2, ORs were calculated for every 1-ppb change. CI = confidence interval; GALA = Genes–environments and Admixture in Latino Americans; NO_2 = nitrogen dioxide; O_3 = ozone; OR = odds ratio; $PM_{2.5}$ = particulate matter < 2.5 μm in diameter; PM_{10} = particulate matter < 10 μm in diameter; ppb = parts per billion; SAGE = Study of African Americans, Asthma, Genes, and Environments; SES = socioeconomic status; SO_2 = sulfur dioxide.

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. Although we would have liked to stratify by atopic or nonatopic asthma, we did not have skin-prick testing results for 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 attempted to establish a 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 year and first 3 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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