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Original Contribution

Long-Term Exposure to Air Pollution and Type 2 Diabetes Mellitus in a Multiethnic Cohort

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Although air pollution has been suggested as a possible risk factor for type 2 diabetes mellitus (DM), results from existing epidemiologic studies have been inconsistent. We investigated the associations of prevalence and incidence of DM with long-term exposure to air pollution as estimated using annual average concentrations of particulate matter with an aerodynamic diameter of 2.5 μm or less ($PM_{2.5}$) and nitrogen oxides at baseline (2000) in the Multi-Ethnic Study of Atherosclerosis. All participants were aged 45–84 years at baseline and were recruited from 6 US sites. There were 5,839 participants included in the study of prevalent DM and 5,135 participants without DM at baseline in whom we studied incident DM. After adjustment for potential confounders, we found significant associations of prevalent DM with $PM_{2.5}$ (odds ratio (OR) = 1.09, 95% confidence interval (CI): 1.00, 1.17) and nitrogen oxides (OR = 1.18, 95% CI: 1.01, 1.38) per each interquartile-range increase (2.43 μg/m^3 and 47.1 ppb, respectively). Larger but nonsignificant associations were observed after further adjustment for study site (for $PM_{2.5}$, OR = 1.16, 95% CI: 0.94, 1.42; for nitrogen oxides, OR = 1.29, 95% CI: 0.94, 1.76). No air pollution measures were significantly associated with incident DM over the course of the 9-year follow-up period. Results were partly consistent with a link between long-term exposure to air pollution and the risk of type 2 DM. Additional studies with a longer follow-up time and a greater range of air pollution exposures, including high levels, are warranted to evaluate the hypothesized association.

air pollution; diabetes; nitrogen oxides; particulate matter; prospective cohort study

Abbreviations: BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio; IQR, interquartile range; MESA, Multi-Ethnic Study of Atherosclerosis; NSES, neighborhood socioeconomic status; OR, odds ratio; $PM_{2.5}$, particulate matter with an aerodynamic diameter of 2.5 μm or less; SD, standard deviation.

Type 2 diabetes mellitus (DM) affects 11% of US adults, and the prevalence is double in people 65 years of age or older (1). It has been suggested that more than 90% of adult-onset DM is attributable to modifiable factors, such as lifestyle behaviors and diet (2). Increasing evidence suggests that environmental exposures also contribute to the development of diabetes (3, 4).

Recently, air pollution has been proposed as a risk factor for the development of type 2 DM (5). In a mouse model of diet-induced obesity, 6-month inhalation exposures to high concentrations of particulate matter with an aerodynamic diameter of 2.5 μm or less ($PM_{2.5}$) induced insulin resistance and systemic inflammation and increased visceral adiposity (6). In the same mouse model, exposure to $PM_{2.5}$ for 10 months induced insulin resistance, impaired glucose tolerance, lower circulating levels of adipokines (adiponectin and leptin), and mitochondrial alteration (7). Numerous studies have also shown associations of $PM_{2.5}$ with systemic inflammatory responses and cardiac autonomic dysfunction (8–10), which might lead to diminished insulin action (11, 12).

However, human epidemiologic studies on the relationship between air pollution and DM have yielded inconsistent results (13), with some finding an association (14–16), others finding associations only in subpopulations (17–21), and still

others finding no association (22). Such inconsistencies might be attributed to sociodemographic and geographic differences. More evidence in prospectively followed cohorts is required to determine whether air pollution exposures are causally related to the development of type 2 DM.

We investigated the associations of prevalent and incident DM with individual-level estimates of exposure to $PM_{2.5}$ and nitrogen oxides and residential proximity to major roadways, a proxy of exposure to traffic-related pollution, in the Multi-Ethnic Study of Atherosclerosis (MESA). We also examined effect modification by sex, given that some studies reported a significant association between air pollution and DM only among women (19, 21, 22).

METHODS

Study population

MESA is a prospective cohort study of subclinical and clinical cardiovascular disease. We recruited a total of 6,814 participants comprising 4 racial/ethnic groups (black, white, Chinese, and Hispanic) aged 45–84 years who were free of clinically apparent cardiovascular disease at baseline between July 2000 and August 2002. Participants were enrolled from 6 US sites: Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; New York, New York; and St. Paul, Minnesota. Details of the study design have been published previous (23). The present study included follow-up examinations during 4 different time periods: August 2002 to February 2004 ($n = 6,233$; 91.5%); March 2004 to September 2005 ($n = 5,947$; 87.3%); September 2005 to May 2007 ($n = 5,818$; 85.4%); and April 2010 to February 2012 ($n = 4,716$; 69.2%). For the analysis of prevalent DM at baseline, we excluded participants who were missing data on DM status ($n = 10$), exposure to air pollution ($n = 258$), or covariates ($n = 750$) (numbers in parentheses are not mutually exclusive), yielding a total of 5,839 participants. For the analysis of incident DM, we additionally excluded participants who had DM at baseline ($n = 696$) or who did not attend a follow-up visit ($n = 8$), leaving a total of 5,135 participants. Our study protocol was approved by each study site's institutional review board, and we obtained written informed consent from every participant.

Outcome ascertainment

We measured fasting serum glucose levels in a central laboratory with rate reflectance spectrophotometry using the thin-film adaption of the glucose oxidase method on the Vitros analyzer (Johnson & Johnson Clinical Diagnostics, Inc., Rochester, New York) on samples collected after a 12-hour overnight fast. DM was defined using the American Diabetes Association 2003 criteria (24): use of antidiabetes medication or a fasting glucose level of 126 mg/dL or greater at baseline for the study prevalence or at any follow-up examination for the study of incidence. Almost all of the DM cases in these middle-aged and older adults can be assumed to be type 2 DM. Person-years were computed from baseline to the date of examination at which incident DM was ascertained, loss to follow-up, or the date of the fifth examination, whichever came first.

Assessment of exposure to air pollution

We estimated ambient $PM_{2.5}$ and nitrogen oxides concentrations for each participant over the follow-up period using the hierarchical spatiotemporal model from the Multi-Ethnic Study of Atherosclerosis and Air Pollution. This model, which has been described elsewhere (25, 26), leverages concentrations of $PM_{2.5}$ and nitrogen oxides collected from the US Environmental Protection Agency's Air Quality System, supplemental measurements at the homes and within the communities of MESA participants, and a large suite of spatial covariates, including land use and traffic sources (27). Briefly, the hierarchical model decomposed the space-time field of concentrations into 3 facets: 1) spatially varying long-term averages; 2) spatially varying seasonal and long-term trends; and 3) spatially correlated but temporally independent residuals. Using 2-week average concentrations from each participant's home location at baseline, we computed the annual average concentrations in the calendar year 2000 and applied this data as a proxy measure of long-term exposure because there were high correlations between the estimated $PM_{2.5}$ and nitrogen oxides concentrations in the year 2000 and those at the follow-up examinations. Pearson coefficients for the correlation between baseline and the follow-up $PM_{2.5}$ concentrations ranged from 0.83 to 0.97 (except with examination 5; $r = 0.55$); for nitrogen oxides, they ranged from 0.88 to 0.99 (data not shown). We also computed 365-day average concentrations over the year preceding each examination date for each participant and applied this measure in a sensitivity analysis. We estimated residential proximity to major roadways at each visit, using ArcGIS 9.0 (ESRI, Redlands, California) and the Dynamap road network (TeleAtlas, Menlo Park, California). Participants were considered to live near a roadway if they resided within 100 m of an interstate or US highway (US Census Feature Class Codes A1 or A2) or within 50 m of a state or county highway (code A3) (28).

Other covariates

We obtained sociodemographic, behavioral, and medical data using questionnaires and calibrated devices. Educational attainment was categorized into less than a high school education, high school diploma, some college, and 4 or more years of college. Cigarette smoking and alcohol consumption were categorized into never, former, and current use. We defined family history of DM as positive if the participant had both a diabetic blood relative parent and a diabetic blood-relative sibling. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Physical activity level was assessed as metabolic equivalent task-hours per day for walking, moderate- and vigorous-intensity sports, and conditioning activities reported on a physical activity questionnaire at baseline and at 2 follow-up examinations. Activity was categorized into tertiles (low, <2.8 hours/day; medium, 2.8–6.0 hours/day; high, >6.0 hours/day). Neighborhood socioeconomic status (NSES) index, a summary index of multiple NSES variables that was associated with air pollution exposure in MESA (29), was obtained from the MESA Neighborhood Study, an ancillary study to MESA (30). We collected data on 2 additional scales of neighborhood resources, walking

environment and availability of healthy food, from the MESA Neighborhood Study and investigated them as potential confounders in a sensitivity analysis because of our previous findings that better neighborhood resources were associated with lower risks of obesity and DM (31, 32). We treated cigarette smoking, alcohol use, BMI, and physical activity level as time-varying covariates.

Statistical analysis

We used logistic regression models to estimate odds ratios and 95% confidence intervals for the prevalence of DM and Cox proportional hazards models to estimate hazard ratios and 95% confidence intervals for the incidence of DM associated with an interquartile-range (IQR) increase in residential concentrations of $PM_{2.5}$ or nitrogen oxides and for the residential roadway proximity variable. To facilitate comparison with other studies, we also computed odds ratios and hazard ratios for a 10-$\mu g/m^3$ increase in $PM_{2.5}$. All models were adjusted for potential confounding factors that were considered in previous studies (17–20), such as age, sex, race/ethnicity, family history of DM, educational level, cigarette smoking status, alcohol consumption, physical activity level, NSES index, and BMI (model 1). We also evaluated the potential effect of site adjustment (model 2): Site was included as a covariate in logistic regression models but was stratified in Cox models. Residual and unmeasured confounding due to factors that vary across sites could be reduced with adjustment for site. Adjustment for site is essentially equivalent to estimating the association based only on within-site variability in the exposure. We evaluated independent associations of $PM_{2.5}$ and nitrogen oxides with DM by including them in the models simultaneously (multipollutant models). To evaluate effect modification by sex, we applied separate logistic regression and Cox models stratified by sex. Significance (P value) of effect modification by sex was computed from the models that included cross-product terms between sex and all other covariates analogous to the stratified model. Effect modifications by race/ethnicity, educational level, and obesity (BMI $\geq$30) were evaluated in the same manner, but these analyses were considered exploratory because we had no a priori hypotheses.

We conducted several sensitivity analyses to verify whether our results were robust to several alternative model specifications. First, we examined whether the results differed after further adjustment for household income, pack-years of cigarette smoking, waist circumference, hypertension, or neighborhood resources (walking environment and availability of healthy food). Second, we used the 365-day average pollutant concentrations for the year preceding the baseline examination date for each participant as the exposure variables. We also examined $PM_{2.5}$ concentrations estimated using data from the nearest monitoring center. Third, to address residential mobility, we restricted analyses to participants who had lived in baseline home for at least 10 years. Finally, we conducted site-specific logistic and Cox regressions and pooled the estimates using meta-analyses. Heterogeneity of associations was assessed using a χ^2 test with 5 degrees of freedom (6 sites). All analyses were performed in R software, version 2.14 (R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org).

RESULTS

At baseline, 696 of 5,839 participants (11.9%) had DM. During a median of 9 years of follow-up, 622 of 5,135 participants (12.1%) developed DM over the course of 39,102 person-years. Compared with persons without DM, persons with DM at baseline were older (mean age, 64.3 (standard deviation (SD), 9.4) years vs. 61.6 (SD, 10.2) years) and less likely to be female (47.0% vs. 53.3%), whereas age and sex distributions did not differ between the 2 groups (Table 1). Persons with DM at baseline or who developed DM during follow-up had higher BMIs and less favorable neighborhood resources, were more likely to have a family history of DM, and were more likely to be black or Hispanic, less educated, and less physically active. The mean concentrations of $PM_{2.5}$ and nitrogen oxides in the year 2000 were 17.3 (SD, 3.1) $\mu g/m^3$ and 56.5 (SD, 30.1) ppb, respectively, in persons with prevalent DM and 16.7 (SD, 2.8) $\mu g/m^3$ and 49.7 (SD, 27.3) ppb, respectively, in persons without prevalent DM at baseline ($P < 0.001$ for the differences in concentrations between persons with and without prevalent DM at baseline). There was no difference in the mean concentrations of $PM_{2.5}$ and nitrogen oxides between those who did and did not develop DM during follow-up. Approximately 27% of participants were living near major roadways at baseline. $PM_{2.5}$ and nitrogen oxides concentrations were moderately correlated ($r = 0.69$, $P < 0.0001$).

We found significant associations of prevalent DM with $PM_{2.5}$ (OR = 1.09, 95% confidence interval (CI): 1.00, 1.17) and nitrogen oxides (OR = 1.18, 95% CI: 1.01, 1.38) per each IQR increase (2.43 $\mu g/m^3$ and 47.1 ppb, respectively) in model 1, which was adjusted for age, sex, race/ethnicity, family history of DM, educational level, smoking status, alcohol consumption, physical activity level, NSES index, and BMI (Table 2). Larger but nonsignificant associations were observed in model 2, which was further adjusted for study site (for $PM_{2.5}$, OR = 1.16, 95% CI: 0.94, 1.42; for nitrogen oxides, OR = 1.29, 95% CI: 0.94, 1.76). For a 10-$\mu g/m^3$ increase in $PM_{2.5}$, the adjusted odds ratios were 1.40 (95% CI: 1.02, 1.93) in model 1 and 1.82 (95% CI: 0.79, 4.19) in model 2. When both $PM_{2.5}$ and nitrogen oxides were simultaneously included in the model, the odds ratios for both pollutants were reduced and were not statistically significant (Web Table 1, available at http://aje.oxfordjournals.org/). Proximity to major roadways was not associated with prevalent DM in any models (Web Table 2). No significant effect modification by sex was found in the associations between air pollution and prevalent DM (Table 2).

Neither $PM_{2.5}$ concentration nor nitrogen oxides concentration was associated with the incidence of DM over the 9-year follow-up in the entire population (Table 3). We found significant effect modification of the association between nitrogen oxides and incident DM by sex in model 1 (P for interaction = 0.03). In stratified analyses, there was a nonsignificant positive association in women (hazard ratio (HR) = 1.17, 95% CI: 0.95, 1.43) in model 1, whereas a nonsignificant inverse association was seen in men (HR = 0.84, 95% CI: 0.67, 1.06). However, this significant effect modification did not remain in model 2 after adjustment for study site (P for interaction = 0.40). The association between $PM_{2.5}$ and incident DM was not modified by sex. Race/ethnicity, educational level, and obesity did not modify the associations of $PM_{2.5}$ and

Table 1. Characteristics of Study Participants at Baseline Visit by Diabetes Mellitus Status, Multi-Ethnic Study of Atherosclerosis, 2000–2002

Characteristic	DM at Baseline ($n = 5,839$)				DM During Follow-up ($n = 5,135$)[a]			
	Yes ($n = 696$)		No ($n = 5,143$)		Yes ($n = 622$)		No ($n = 4,513$)	
	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%
Age, years	64.3 (9.4)		61.6 (10.2)[b]		61.0 (9.4)		61.7 (10.3)	
BMI[c]	30.5 (5.7)		28.0 (5.3)[b]		31.0 (5.9)		27.6 (5.1)[b]	
Family history of DM		64.2		34.8[b]		48.9		32.9[b]
Female sex		47.0		53.3[d]		52.6		53.4
Race/ethnicity								
White		19.1		43.1[b]		30.9		44.8[b]
Black		37.6		25.5		31.4		24.6
Hispanic		31.0		20.4		26.2		19.6
Chinese		12.2		11.0		11.6		11.0
Educational level								
<High school		28.0		14.4[b]		17.7		13.9[d]
High school diploma		19.7		18.0		19.6		17.8
Some college		28.4		28.9		30.5		28.7
≥4 Years of college		23.9		38.7		32.2		39.6
Smoking status								
Never		50.7		50.3		49.8		50.4
Former		37.1		37.1		38.1		37.0
Current		12.2		12.5		12.1		12.6
Alcohol use								
Never		24.9		19.3[b]		21.4		19.0
Former		35.5		21.6		23.9		21.3
Current		39.7		59.0		53.7		59.7
Physical activity level[e]								
Low (<2.8 hours/day)		39.9		32.6[f]		38.6		33.9[d]
Medium (≤6.0 hours/day)		31.3		33.7		34.7		32.7
High (>6.0 hours/day)		28.7		33.7		26.7		33.4
Study site								
St. Paul, Minnesota		13.9		15.9[b]		13.7		16.2[d]
Forsyth County, North Carolina		14.4		15.9		18.0		15.6
Baltimore, Maryland		14.9		15.0		16.2		14.8
New York, New York		18.3		16.7		18.2		16.5
Chicago, Illinois		12.6		18.7		14.6		19.2
Los Angeles, California		25.9		17.9		19.3		17.7
Neighborhood factors								
NSES index	0.12 (1.15)		−0.35 (1.39)[b]		−0.07 (1.23)		−0.39 (1.41)[b]	
Walking environment	3.84 (0.26)		3.93 (0.31)[b]		3.86 (0.29)		3.94 (0.31)[b]	
Availability of healthy food	3.44 (0.43)		3.50 (0.49)[d]		3.42 (0.46)		3.51 (0.49)[b]	
Air pollution in the year 2000								
$PM_{2.5}$, $\mu g/m^3$	17.3 (3.1)		16.7 (2.8)[f]		16.8 (2.8)		16.7 (2.8)	
Nitrogen oxides, ppb	56.5 (30.1)		49.7 (27.3)[b]		51.3 (29.3)		49.5 (27.0)	
Proximity to a major road		26.7		25.1		24.8		25.2

Abbreviations: BMI, body mass index; DM, diabetes mellitus; NSES, neighborhood socioeconomic status; $PM_{2.5}$, particulate matter with an aerodynamic diameter of 2.5 μm or less; SD, standard deviation.

[a] We excluded 78 subjects with no follow-up data.

[b] $P < 0.0001$.

[c] Weight (kg)/height $(m)^2$.

[d] $P < 0.05$.

[e] Tertile of physical activity which was assessed from metabolic equivalent task-hours per day.

[f] $P < 0.001$.

Table 2. Odds Ratios for the Prevalence of Diabetes Mellitus at Baseline per Each Interquartile-Range Increase[a] in Concentrations of Air Pollutants Among Study Participants ($n = 5,839$), Multi-Ethnic Study of Atherosclerosis, 2000–2002

Pollutant and Model	All		Men		Women		*P* for Interaction[b]
	OR	95% CI	OR	95% CI	OR	95% CI	
$PM_{2.5}$							
Model 1[c]	1.09	1.00, 1.17[d]	1.04	0.94, 1.16	1.14	1.02, 1.28[d]	0.27
Model 2[e]	1.16	0.94, 1.42	1.31	0.98, 1.74	1.04	0.78, 1.39	0.27
Nitrogen oxides							
Model 1[c]	1.18	1.01, 1.38[d]	1.07	0.85, 1.33	1.33	1.06, 1.66[d]	0.17
Model 2[e]	1.29	0.94, 1.76	1.40	0.89, 2.20	1.21	0.79, 1.87	0.65

Abbreviations: CI, confidence interval; OR, odds ratio; $PM_{2.5}$, particulate matter with an aerodynamic diameter of 2.5 μm or less.

[a] The interquartile range was 2.43 μg/m^3 for $PM_{2.5}$ and 47.1 ppb for nitrogen oxides.

[b] *P* value for the interaction term between sex and the air pollutant.

[c] Model 1 was adjusted for sex (except in the stratified analyses by sex), age, race/ethnicity, family history of diabetes mellitus, educational level, smoking status, alcohol consumption, physical activity level, neighborhood socioeconomic status index, and body mass index.

[d] $P < 0.05$.

[e] Model 2 was adjusted for all of the variables in model 1 and study site.

nitrogen oxides with either DM incidence or prevalence (data not shown).

Figure 1 shows site-specific analyses. For prevalent DM, Chicago and Los Angeles showed positive associations with both $PM_{2.5}$ and nitrogen oxides, whereas Baltimore showed inverse associations. For incident DM, Chicago, Los Angeles, and New York showed positive associations, whereas St. Paul, Forsyth County, and Baltimore had inverse associations, which resulted in an overall null association. Chicago was the only site where significant positive associations were found both cross-sectionally and prospectively (for prevalent DM and $PM_{2.5}$, OR =1.80, 95% CI: 1.10, 2.92; for incident DM and $PM_{2.5}$, HR = 1.55, 95% CI: 1.03, 2.32; and for incident DM and nitrogen oxides, HR = 3.64, 95% CI: 1.12, 11.8). There was statistical evidence of significant heterogeneity in the hazard ratio estimates in relation to nitrogen oxides across the sites ($P = 0.035$).

In sensitivity analyses, additional adjustment for household income, waist circumference, pack-years of smoking, hypertension, or walking environment did not change the results (Web Table 3). The strength of the association between nitrogen oxides and incident DM increased after adjustment for availability of healthy food, although the association

Table 3. Hazard Ratios for the Incidence of Diabetes Mellitus per Each Interquartile-Range Increase[a] in Concentrations of Air Pollutants Among Study Participants ($n = 5,135$), Multi-Ethnic Study of Atherosclerosis, 2000–2012

Pollutant and Model	All		Men		Women		*P* for Interaction[b]
	OR	95% CI	OR	95% CI	OR	95% CI	
$PM_{2.5}$							
Model 1[c]	1.02	0.95, 1.10	1.00	0.90, 1.11	1.04	0.94, 1.16	0.56
Model 2[d]	1.05	0.87, 1.26	1.00	0.75, 1.32	1.10	0.85, 1.41	0.71
Nitrogen oxides							
Model 1[c]	1.00	0.86, 1.16	0.84	0.67, 1.06	1.17	0.95, 1.43	0.03
Model 2[d]	1.04	0.77, 1.40	0.91	0.59, 1.42	1.20	0.80, 1.80[e]	0.40

Abbreviations: CI, confidence interval; OR, odds ratio; $PM_{2.5}$, particulate matter with an aerodynamic diameter of 2.5 μm or less.

[a] The interquartile range was 2.43 μg/m^3 for $PM_{2.5}$ and 47.1 ppb for nitrogen oxides.

[b] *P* value for the interaction term between sex and the air pollutant.

[c] Model 1 was adjusted for sex (except in the stratified analyses by sex), age, race/ethnicity, family history of diabetes mellitus, educational level, smoking status, alcohol consumption, physical activity level, neighborhood socioeconomic status index, and body mass index.

[d] Model 2 was adjusted for all of the variables in model 1 and study site.

[e] $P < 0.1$.

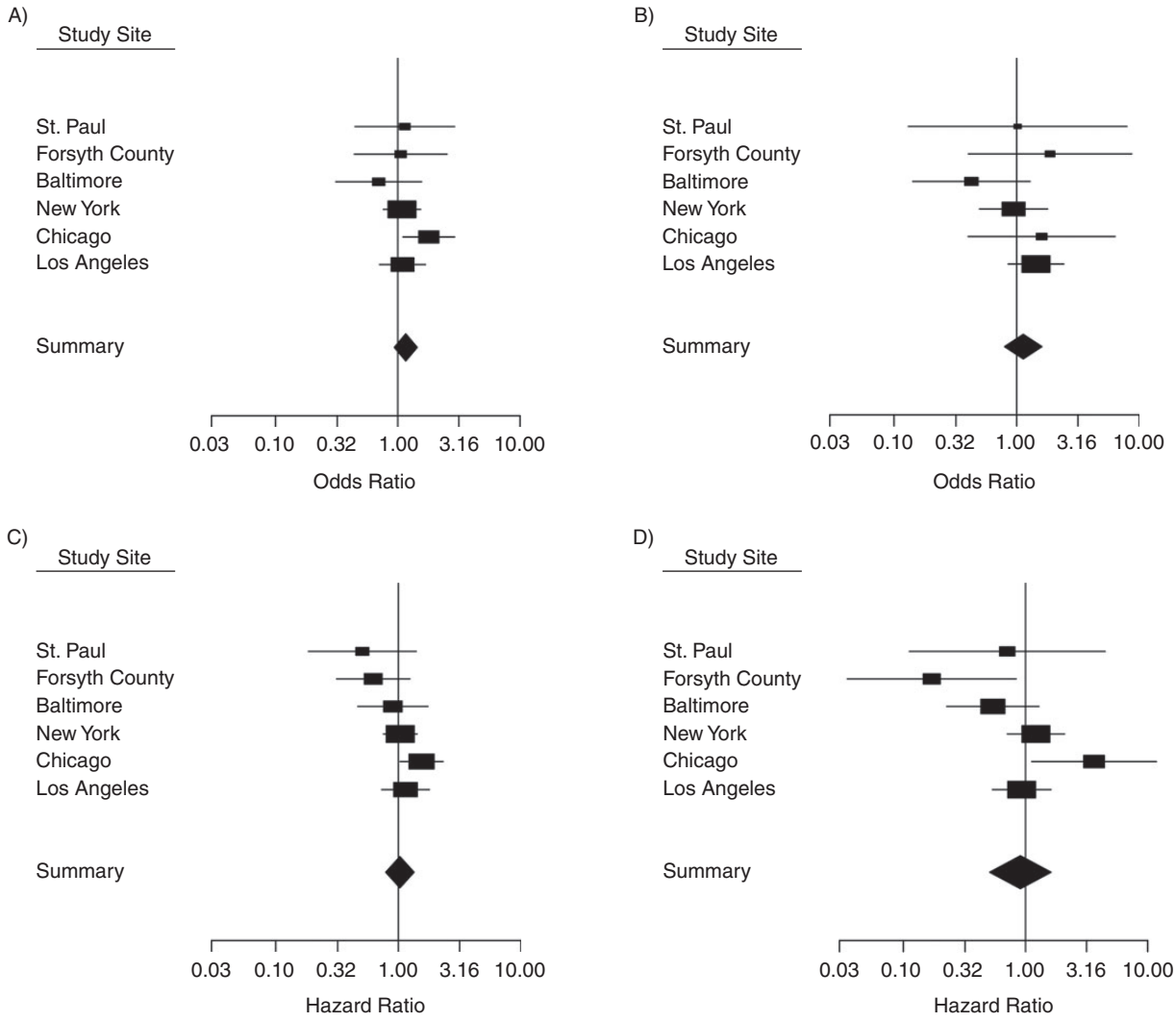

Figure 1. Site-specific and pooled summary estimates (odds ratios for prevalent diabetes mellitus and hazard ratios for incident diabetes mellitus), Multi-Ethnic Study of Atherosclerosis, 2000–2012. The study sites were Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; New York, New York; and St. Paul, Minnesota. A) Prevalence of diabetes mellitus in relation to concentrations of particulate matter with an aerodynamic diameter of 2.5 μm or less. B) Prevalence of diabetes mellitus in relation to nitrogen oxides concentrations. C) Incidence of diabetes mellitus in relation to concentrations of particulate matter with an aerodynamic diameter of 2.5 μm or less. D) Incidence of diabetes mellitus in relation to nitrogen oxides. All analyses were adjusted for sex, age, race/ethnicity, family history of diabetes mellitus, educational level, smoking status, alcohol consumption, physical activity level, neighborhood socioeconomic status index, and body mass index.

remained not statistically significant (HR = 1.12, 95% CI: 0.94, 1.34) (Web Table 3). The overall results were similar when we examined the annual average concentrations preceding the baseline examination date and baseline $PM_{2.5}$ concentrations estimated from the nearest monitoring site (Web Table 4). When the analyses were restricted to participants who had lived in their current home for more than 10 years, the results seemed to be robust (Web Table 5).

DISCUSSION

In the present large, community-based, multiethnic prospective study, higher long-term exposures to $PM_{2.5}$ and nitrogen oxides estimated as the annual averages in the year 2000 were significantly associated with prevalent DM at baseline. We found larger but less significant associations after adjustment for study site, which suggests that air pollution might have stronger within-site associations with prevalent DM. In contrast, long-term exposure to air pollution was not associated with the development of DM over a 9-year follow-up period. Significant effect modification by sex of the association between nitrogen oxides and incident DM was observed, with an inverse association in men and a positive association in women. No significant association was found between proximity to roadways and either prevalent or incident DM. Our sensitivity analyses suggest that the observed associations are robust to or might

be stronger with adjustment for neighborhood resources, such as walking environment and availability of healthy food.

Associations of air pollution exposures with prevalent and incident DM were generally larger after adjustment for study site. Also, the standard errors became wider, as expected, because power was lost because of a reduction in the overall variability in our exposure estimates after adjustment for site. Certain previous studies in this population (33) and other multisite studies (34) have also indicated that the associations were strengthened after accounting for site. Because adjustment for site results in estimates that rely exclusively on within-site variability, stronger associations can be found after adjustment for site if the within-site associations are bigger than the between-site associations. This appeared true in our study, especially in the case prevalent DM, because larger associations were found after adjustment for study site. Although $PM_{2.5}$ concentrations are typically relatively homogeneous over large geographic areas (35, 36), $PM_{2.5}$ concentrations in our data showed large within-site variations that were comparable to between-site variations, especially in Chicago (range, 12.6–27.9 μg/m^3) and Los Angeles (17.2–26.0 μg/m^3), the sites where odds ratios were positive and higher (for Chicago, OR = 1.80, 95% CI: 1.10, 2.92; for Los Angeles, OR = 1.09, 95% CI: 0.71, 1.69). Relatively large within-site variations in nitrogen oxides concentrations were also found in Chicago (range, 22.6–69.8 ppb) and Los Angeles (15.9–136 ppb), where odds ratios were positive and higher (for Chicago, OR = 1.60, 95% CI: 0.40, 6.36; for Los Angeles, OR = 1.44, 95% CI: 0.85, 2.42). Interestingly, adjustment for study site differentially influenced the associations with prevalent DM by sex: The magnitudes of the odds ratio for the associations of both $PM_{2.5}$ and nitrogen oxides with prevalent DM increased in men after adjustment for study site but decreased in women (Table 2). This suggests that confounding factors associated with site might be differentially distributed by sex, although a similar pattern was not observed with incident DM. In summary, the models without adjustment for site provide estimates of associations based on both within-site and between-site variability, whereas the models with adjustment for site rely exclusively on within-site variability. Therefore, measures of associations derived from models adjusted for site cannot be confounded by site-specific factors.

Animal studies have suggested that there are biological mechanisms that connect air pollution exposure with insulin resistance and type 2 DM (5, 37). Long-term exposure to fine particulate matter might induce impaired glucose tolerance (7), increase macrophage levels and inflammation in visceral adipose tissue (6), induce endoplasmic reticulum stress in the liver and lungs (38), and alter mitochondrial functions and brown adipose tissue functions (39). Our cross-sectional findings support this hypothesis. However, our prospective findings do not support the hypothesis that long-term exposure to air pollution is associated with incident DM.

Previous epidemiologic studies on the association between long-term exposure to air pollution and incident DM have had mixed findings (13). A study conducted in 1,775 women from West Germany found significant positive associations between the annual average traffic-related air pollution concentration in 1990 and the incidence of type 2 DM between 1990 and 2006 (HRs ranged from 1.15 for particulate matter or nitrogen dioxide concentrations estimated from a traffic emission inventory to 1.42 for nitrogen dioxide concentration estimated using land-use regression) (20). In the Black Women's Health Study conducted in Los Angeles (n = 3,992), every IQR increase in the annual average concentration of nitrogen oxides (12.4 ppb) was associated with a 25% higher risk of incident type 2 DM over a mean follow-up of 10 years (95% CI: 1.07, 1.46) (17). In a study of 62,012 residents in Ontario, Canada, a 10-μg/m^3 increase in $PM_{2.5}$ concentration was associated with an 11% higher risk of incident DM (14). In the Danish Diet, Cancer, and Health Cohort Study (n = 51,818 subjects with 9.7 years of follow-up), Andersen et al. (18) found no associations of various measures of traffic-related air pollution with DM (defined as hospital admission for diabetes or use of medication or blood glucose tests); however, they did find a significant association when the analysis was restricted to confirmed cases of DM, although the magnitude of the association was small (per each 4.9-μg/m^3 increase in nitrogen dioxide, HR = 1.04, 95% CI: 1.00, 1.08). Another large study (n = 88,460) conducted in 2 prospective cohorts from the Nurses' Health Study and the Health Professional Follow-Up Study found no significant associations of the 1989 annual average concentrations of particulate matter with an aerodynamic diameter of 10 μm or less and $PM_{2.5}$ with incident DM between 1989 and 2002 (19).

It is unclear why exposure to air pollution was associated with prevalent but not incident DM in our study. One possible explanation is that persons who were more susceptible to DM had already developed DM before baseline. Individuals who were free of diabetes at baseline could be relatively healthier and less susceptible to the potential effects air pollution. Interestingly, higher age, which is a well-established risk factor for type 2 DM, was also associated with prevalent but not incident DM (Table 1). At baseline, the prevalence of DM was higher in men than in women (13.3% vs. 10.7%), whereas the incidence of DM was comparable between men and women (12.3% vs. 12.0%) (data not shown). On the other hand, the 9-year follow-up time might not have been long enough to capture the long-term, effects of air pollution on the development of DM. Another possible reason is that air pollution concentrations during the study period were not high enough to increase the risk of developing DM. Over the past several decades, air quality in the United States has improved: The annual average $PM_{2.5}$ concentrations dropped 33% from 2000 to 2012, and concentrations of particulate matter with an aerodynamic diameter of 10 μm or less dropped 39% from 1990 to 2012 (40). A similar improvement was observed in our study sites between 2000 and 2012 (data not shown). Therefore, we might have low power to detect associations of incident DM with those low levels of air pollution. To the extent that exposures at baseline are correlated with similarly patterned but higher exposures in the past, our cross-sectional results could reflect the effects of prior exposures when air pollution concentrations were much higher.

Our finding of a stronger association between nitrogen oxides and incident DM in women is in agreement with previous findings (18, 19, 21), although it is difficult to interpret the inverse association in men. It is unclear why women might be more susceptible to air pollution in relation to DM. Brook

et al. (21) conducted a cross-sectional study in Hamilton and Toronto, Canada ($n = 7,634$) and reported a significant association between nitrogen dioxide concentration and prevalent DM in women (for each ppb increase in nitrogen dioxide, which is equivalent to an OR of 1.17 for an IQR increase of 4 ppb, OR = 1.04, 95% CI: 1.00, 1.08) but not in men. Puett et al. (19) did not find a significant association when they examined data from the Nurses' Health Study (women) and the Health Professional Follow-Up Study (men) together, but they did observe a significant association between roadway proximity and incident DM in the Nurses' Health Study alone. The Danish Diet, Cancer, and Health Cohort Study also found a statistically significant association between nitrogen dioxide and confirmed DM only among women (18). Both sex-related biological differences (e.g., hormone-dependent physiological response) and socially determined sex differences (e.g., differential activity pattern and related exposure measurement accuracy) (41) might account for the observed difference between the sexes.

Our study has numerous strengths, including a large, prospective cohort with multicity and multiethnic groups in whom we examined both prevalent and incident DM that was objectively identified via medication use and fasting glucose levels; the quality of the fine-scale intra-urban modeling of air pollution exposure assessment; and high-quality covariate assessments. Nonetheless, this study has several limitations that need to be considered. Our exposure measures were based on annual averages from the year 2000, and we assumed that the exposures were time constant. An alternative approach could involve using time-varying $PM_{2.5}$ and nitrogen oxides concentrations estimated at each visit, which might capture subsequent exposures (after baseline) that could be more relevant to disease risk. Given the high correlations between baseline and follow-up visit concentrations, the present study was able to contrast the rank order of pollution exposures but could not properly capture the impact of improved air quality (reduced ambient concentrations) on the risk of DM.

In conclusion, our study provides evidence that supports the association between long-term exposure to air pollution and the prevalence of DM. However, our results do not support the hypothesis that long-term exposure to air pollution is associated with incidence of DM, although short follow-up times and low exposure concentrations during the follow-up period might have limited our ability to detect an association. Much higher concentrations of air pollution have been reported in recently urbanized cities in Asia and Latin America (42, 43), where type 2 DM is an increasing public health concern. Given that the prevalence of type 2 DM is increasing worldwide and that people are exposed to a wide range of fine particulate concentrations, additional large studies with longer follow-up and a greater range in air pollution concentrations, including high levels, are warranted to evaluate the hypothesized association.

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