Environmental Research 148 (2016) 360–366

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Long term exposure to NO_2 and diabetes incidence in the Black Women's Health Study

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ARTICLE INFO

Article history:
Received 18 January 2016
Received in revised form
22 March 2016
Accepted 18 April 2016

Keywords:
African American
Air pollution
Cohort study
Diabetes
Incidence

ABSTRACT

While laboratory studies show that air pollutants can potentiate insulin resistance, the epidemiologic evidence regarding the association of air pollution with diabetes incidence is conflicting. The purpose of the present study was to assess the association of the traffic-related nitrogen dioxide (NO_2) with the incidence of diabetes in a longitudinal cohort study of African American women. We used Cox proportional hazards models to calculate hazard ratios and 95% confidence intervals (CI) for diabetes associated with exposure to NO_2 among 43,003 participants in the Black Women's Health Study (BWHS). Pollutant levels at participant residential locations were estimated with 1) a land use regression model for participants living in 56 metropolitan areas, and 2) a dispersion model for participants living in 27 of the cities.

From 1995 to 2011, 4387 cases of diabetes occurred. The hazard ratios per interquartile range of NO_2 (9.7 ppb), adjusted for age, metropolitan area, education, vigorous exercise, body mass index, smoking, and diet, were 0.96 (95% CI 0.88–1.06) using the land use regression model estimates and 0.94 (95% CI 0.80, 1.10) using the dispersion model estimates. The present results do not support the hypothesis that exposure to NO_2 contributes to diabetes incidence in African American women.

1. Introduction

In 2012, an estimated 21 million people in the US had diagnosed diabetes, of which 95% was type 2, and approximately 8 million more had undiagnosed diabetes (Centers for Disease Control, 2014).[1] Diabetes doubles the risk of cardiovascular disease incidence and mortality (Go et al., 2013) and is the seventh leading cause of death (Go et al., 2013). The incidence of diabetes has doubled over the past 30 years, rising from 3.6/1000 person-years in 1980 to 7.4/1000 person-years in 2012 (Go et al., 2013; Geiss et al., 2014). Rates are high in black women: in 2010, 15% of black women aged 20 and older had prevalent diabetes compared to 6.2% of white women (Go et al., 2013). While obesity, sedentariness, and other individual-level characteristics are established risk factors for diabetes (Mozaffarian et al., 2009), attention has recently turned to the potential role of air pollution as an etiologic agent. In animal studies, fine particulate matter with aerodynamic diameter $\leq 2.5\ \mu m$ ($PM_{2.5}$) can instigate several metabolic perturbations (e.g., adipocyte and per-vascular fat inflammation, altered adipocytokine expression) that together potentiate the development of insulin resistance and diabetes (Rajagopalan and Brook, 2012). Air pollution has been positively associated with diabetes prevalence (Lockwood, 2002; Brook et al., 2008; Pearson et al., 2010; Eze et al., 2014) and diabetes-related mortality (Li et al., 2014). Whether air pollution contributes to diabetes incidence is an open question which has been addressed in several cohort studies, with conflicting results (Kramer et al., 2010; Puett et al., 2011; Coogan et al., 2012; Park et al., 2015). In a German study (Kramer et al., 2010), significant 15–42% increases in

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[1] Abbreviations: BWHS, Black Women's Health Study; LUR, land use regression; SES, socioeconomic status.

http://dx.doi.org/10.1016/j.envres.2016.04.021
0013-9351/

diabetes incidence were observed per interquartile range (IQR) of NO_2, depending on how NO_2 was estimated. In a Danish cohort, there was a significant 7% increase in diabetes incidence per IQR of NO_2 among women but not among men (Andersen et al., 2012). In the Multiethnic Study of Atherosclerosis, levels of nitrogen oxides (NOx, the sum of NO_2 and NO) were not associated with diabetes incidence (Park et al., 2015). The evidence regarding $PM_{2.5}$ and diabetes incidence is also conflicting, with positive associations observed in some cohorts (Kramer et al., 2010; Chen et al., 2013) and little evidence of associations in other cohorts (Puett et al., 2011).

An association of air pollutants with diabetes would be of particular importance for African American women, because neighborhoods where African Americans live have higher levels of air pollution, on average, than predominantly white neighborhoods (Downey and Hawkins, 2008). The purpose of the present study was to assess the relation of NO_2 exposure to incidence of type 2 diabetes in a large cohort of African American women, the Black Women's Health Study (BWHS). NO_2 is a good marker of vehicle-related pollutants. A substantial body of evidence suggests that NO_2 is capable of adversely affecting respiratory, cardiovascular and metabolic systems; it is also a key precursor of numerous secondary pollutants with well-documented adverse health effects (U.S. EPA, 2016). We previously reported a positive association of NOx with diabetes incidence among BWHS participants who lived in Los Angeles (Coogan et al., 2012), and no association of $PM_{2.5}$ with diabetes in the overall BWHS cohort (Coogan et al., 2016).

2. Methods

2.1. Study population

The BWHS was established in 1995, when 59,000 black women aged 21 through 69 were recruited mainly from subscribers to Essence magazine, a general readership magazine targeted to black women (Rosenberg et al., 1995). The baseline questionnaire elicited information on demographic and lifestyle factors, reproductive history, and medical conditions. The cohort is followed biennially through mailed and Web-based health questionnaires. All questionnaires are available for viewing at http://www.bu.edu/bwhs/for-researchers/sample-bwhs-questionnaires/. Follow-up of the baseline cohort has been complete for 88% of potential years of follow-up through 2013. The study protocol was approved by the Institutional Review Board of Boston University School of Medicine. Participants indicate consent by completing and returning the questionnaires.

The present analysis includes data from the baseline questionnaire (1995) and eight subsequent follow-up cycles (1997–2011). There were 45,231 women who at baseline lived in any of 56 metropolitan areas in the United States and had complete information on body mass index (BMI). Women excluded because they did not live in the 56 metro areas (n = 11,914) did not differ from the included women in terms of mean age, BMI, or prevalence of diabetes. We further excluded 2228 women with prevalent diabetes at baseline, for a total of 43,003 women in the analytic cohort. Follow-up began at 30 years of age to exclude potential cases of type 1 diabetes.

2.2. Diagnosis of type 2 diabetes

We defined an incident case of type 2 diabetes as self-report of doctor-diagnosed diabetes at age 30 or older during follow-up through 2011. In a validation study, among 227 participants who met these criteria and whose physicians provided data from their medical records, the diagnosis of type 2 diabetes was confirmed in 96% (Krishnan et al., 2010). The incidence of diabetes in BWHS from 1995 through 2013 was 9.5/1000/year. Incidence rates in the National Health Interview Survey for African Americans aged 20–79 were 9.5/1000/year in 1997 and 9.9/1000/year in 1999 (Geiss et al., 2014).

2.3. Estimation of NO_2

For all participant addresses over follow-up that fell in the 56 metro areas, we estimated annual NO_2 levels for the years 2000–2010 at the block group level using a spatiotemporal land use regression (LUR) model. A block group is an area defined by the U.S. Census that includes between 600 and 3000 people. The model is described in detail elsewhere (Novotny et al., 2011). Briefly, the spatial model incorporates year-2006 annual-average NO_2 concentrations at 369 monitoring stations, 81,670 satellite-derived estimates of ground-level NO_2 concentrations, and satellite- and ground-based datasets of land uses. Temporal model incorporates 48,886 monthly-average monitoring station values, which are used to quantify, for each Census block group, local monthly variations relative to the year-2006 spatial LUR. The R^2 for the final spatiotemporal model is 0.80.

We also used a dispersion model to develop a second set of NO_2 estimates for 27 of the metro areas, chosen to include the largest cities and a wide range of pollutant levels. NO_2 levels were estimated for the years 2000–2010 using a combination of line source dispersion modeling of roadway traffic emissions and spatial interpolation of regional background concentrations. Roadway traffic volumes were obtained from the Highway Performance Measurement System for primary and secondary roads for 2012 (http://www.fhwa.dot.gov/policyinformation/hpms.cfm); local roadways were ascertained from the U.S. Census TIGER files (https://www.census.gov/geo/maps-data/data/tiger-line.html), with traffic volumes set to average estimates provided by the Highway Performance Measurement System for urban areas in each state. For each roadway segment, a NO_2 emissions rate was computed by multiplying average daily traffic counts by emissions factors from the U.S. national vehicle emissions inventory, MOVES2014 (http://www.epa.ov/otaq/models/moves/index.htm). A Gaussian line source dispersion model (Benson, 1992) and annual hourly meteorology were used to estimate the dispersion of the roadway emissions at each location. Background NO_2 concentrations were estimated with a spatial semivariogram and kriging model, and were added to the roadway-attributable concentrations to obtain final NO_2 estimates at all participant addresses over follow-up.

2.4. Ascertainment of covariates

Self-reported height and weight were ascertained at baseline and weight was updated on all follow-up questionnaires. Smoking history, alcohol consumption, and hours per week spent in vigorous exercise were obtained at baseline and updated on follow-up questionnaires. In 1995 and 2001, dietary data was obtained with a 68-item modification of the short form Block-National Cancer Institute food frequency questionnaire (Block et al., 1990). We used factor analysis to identify two dietary patterns, one characterized by high intake of vegetables and fruit and the other by high intake of meat and fried food (Boggs et al., 2011). Information on household income was obtained in 2003, educational attainment in 1995 and 2003, and parental history of diabetes in 1999.

Participants' residential addresses from 1995 through 2009 were geocoded and linked to U.S. Census data at the block group level. We used factor analysis to create a neighborhood socioeconomic status (SES) score that included seven census variables

(median household income; median housing value; % of households receiving interest, dividend or net rental income; % of adults aged ≥25 years that completed college; % of families with children headed by a single female; % of population living below the poverty line; and % African American). Regression coefficients from the factor analysis were used to weight the variables for a combined neighborhood score, with higher scores indicating higher neighborhood SES.

Ozone levels were estimated using the Environmental Protection Agency's Models-3/Community Multiscale Air Quality fused to ground measurements (the "downscaler" model), with a resolution of 12 km for the years 2007–2008 (U.S. EPA, 1999). Daily estimates for 8-h maximum levels at census tract centroids were compiled into annual average concentrations. $PM_{2.5}$ levels were estimated at all residential addresses using a two-stage modeling strategy that incorporated a LUR approach and a Bayesian Maximum Entropy approach, described in detail elsewhere (Beckerman et al., 2013).

2.5. Statistical methods

We used Cox proportional hazards models to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the incidence of diabetes per IQR of NO_2 (9.7 ppb). Person-time was calculated from the start of follow-up in 1995 until the occurrence of diabetes, loss to follow-up, death, or end of follow-up, whichever happened first. NO_2 was modeled as the overall mean of levels estimated for 2000–2010 at all addresses where a participant had lived during follow-up, weighted by time spent at each address (overall mean). This metric accounted for spatial but not temporal variability in NO_2 levels; the overall mean at each location did not vary, regardless of what year a women lived there. To account for temporal trends in NO_2 levels, we used a second metric that was the average of levels estimated before diagnosis, weighted by time spent at each address (temporal mean); this metric varied according to year. For example, the overall mean for an address where a woman lived in 2005 was the average of all available NO_2 levels (2000–2010); the temporal mean for that address in 2005 was the average of NO_2 levels for 2000–2005. Follow-up using the temporal mean was from 2001 to 2011 to coincide with the years for which NO_2 values were estimated. We assessed the proportional hazards assumptions using Schoenfeld residuals. The use of penalized splines did not improve model fit compared with the linear model.

All models were adjusted for age in 1-year intervals, 2-year questionnaire cycle, and metro area (n=56). To a basic model that included only these variables (model 1), we added individual-level covariates that by themselves changed the coefficient for NO_2 by at least 10% (model 2): BMI (weight in kg/height^2 in m) (<25, 25–29, 30–34, 35–39, ≥40), years of education (≤12, 13–15, 16, ≥17), h/week vigorous exercise (none, <5, ≥5), diet pattern as indicated by vegetable/fruit diet pattern score (quintiles) and meat/fried foods diet pattern score (quintiles), and smoking status (never, past, current <15 cigarettes/day, current ≥15 cigarettes/day). We then added neighborhood SES (continuous) (model 3). The addition of ozone and $PM_{2.5}$ to model 3 did not materially change HRs and did not improve model fit, so are not included in the final models.

We conducted analyses stratified by neighborhood SES, BMI, age, education, hypertension, vigorous exercise, western diet score and smoking status. Deviations from multiplicative joint effects were assessed by the likelihood ratio test comparing models with and without interaction terms. We estimated HRs among women who did not move during follow-up. We also estimated HRs separately for women who lived in Los Angeles to compare with results from our previous study (Coogan et al., 2012).

3. Results

NO_2 levels at baseline for the 56 cities in the study area estimated from the LUR model ranged from 1.0 ppb to 37.7 ppb with a mean of 18.6 ppb (SD=6.5). The 25th and 75th percentiles were, respectively, 13.9 ppb and 23.6 ppb. For the 27 cites for which we estimated NO_2 levels with the dispersion model, the estimates ranged from 5.1 ppb to 40.7 ppb, with a mean of 19.2 ppb (SD=5.5); 25th and 75th percentiles were 14.6 ppb and 24.3 ppb, respectively. The distribution of NO_2 across the U.S. and the location of the 56 cities included in the analysis is shown in the Supplementary Material. NO_2 levels fell over time, from a mean of 21.9 ppb in 2000 to 14.8 ppb in 2010 using the LUR model, and from 23.0 ppb to 14.7 ppb using the dispersion model. The Spearman correlation coefficient between the two NO_2 estimates was 0.89.

Age, BMI, level of vigorous exercise, and history of parental diabetes were similar across quintiles of NO_2 (Table 1). Neighborhood SES was the factor most strongly associated with NO_2 exposure: 33% of participants in the lowest quintile of NO_2 resided in the highest SES neighborhoods, whereas only 11% of those in the highest quintile of NO_2 lived in the highest SES neighborhoods. The lowest NO_2 quintile was also characterized by having more participants of higher education and income and fewer participants who smoked.

Over follow-up from 1995 through 2011, 4387 cases of incident diabetes occurred. Table 2 shows the HRs for diabetes for the two exposure metrics (overall mean and temporal mean) and for the two methods of NO_2 estimation (for 56 cities using the LUR estimates and for 27 cities using the dispersion model estimates). In the 56 cities, the model 1 HR using the overall mean was 1.09 (95% CI: 1.00, 1.19). It was reduced to 0.96 (95% CI: 0.88, 1.06) upon addition of covariates in model 2. The model 2 HR using the temporal mean was 0.94 (95% CI: 0.85, 1.04). Additional control for neighborhood SES reduced the overall and temporal mean HRs to 0.90 (95% CI: 0.82, 1.00) and 0.88 (95% CI: 0.79, 0.98), respectively. In the 27 cities, the HRs were similar although slightly smaller than those in the 56 cities.

Table 1
Baseline characteristics according to quintiles of NO_2, Black Women's Health Study participants living in 56 metropolitan areas, 1995[a,b].

	Quintile of NO_2 (range in ppb)				
	1 (1.0–12.9)	2 (13.0–16.3)	3 (16.4–19.9)	4 (20.0–25.0)	5 (25.0–37.7)
Age, mean(SD)	38.7 (9.9)	38.7 (10.3)	39.2 (10.8)	39.0 (10.8)	37.7 (10.9)
BMI, mean (SD)	27.4 (6.2)	27.8 (6.5)	27.9 (6.7)	27.7 (6.5)	27.7 (6.6)
Never smoker, %	69	65	63	63	61
Never drinker, %	60	56	55	55	55
College graduate, %	50	46	45	45	44
Household income > $100,000 (2003), %	16	14	13	13	11
Parental history of diabetes, %	27	26	26	24	25
≥5 h/wk of vigorous exercise, %	13	13	14	13	14
Highest quintile vegetable/fruit diet score, %	17	18	19	19	21
Highest quintile neighborhood SES score, %	33	24	17	15	11

Abbreviations: BMI, body mass index; NO_2, nitrogen dioxide; SD, standard deviation; SES, socioeconomic status.

[a] NO_2 estimates from the land use regression model.
[b] Age-standardized in 5-year increments.

Table 2
Incidence of diabetes per IQR (9.7 ppb) increase in NO_2 using two NO_2 estimation methods, BWHS 1995–2011.

Exposure metric	Cases/person years	Model 1[a] HR (95% CI)	Model 2 HR[b] (95% CI)	Model 3 HR[c] (95% CI)
Using NO_2 estimates from LUR model for 56 cities				
Overall mean	4387/453,221	1.09 (1.00, 1.19)	0.96 (0.88–1.06)	0.90 (0.82, 1.00)
Temporal mean	2813/258,680	1.06 (0.96, 1.17)	0.94 (0.85, 1.04)	0.88 (0.79, 0.98)
Using NO_2 estimates from dispersion model for 27 cities				
Overall mean	3520/365,288	1.05 (0.90, 1.23)	0.94 (0.80, 1.10)	0.89 (0.75, 1.04)
Temporal mean	2242/207,048	1.02 (0.86, 1.21)	0.92 (0.77, 1.09)	0.85 (0.71, 1.02)

[a] Adjusted for age, questionnaire cycle, and metro area.
[b] Model 2 adds BMI (weight in kg/height^2 in m) (<25, 25-29.9, 30–34.9, 35-39.9, ≥ 40), years of education (≤ 12, 13–15, 16, ≥ 17), h/week vigorous exercise (none, <5, ≥ 5), vegetable/fruit diet pattern score (quintiles) and meat/fried foods diet pattern score (quintiles), and smoking status (never, past, <15 cigarettes/day, ≥ 15 cigarettes/day).
[c] Model 3 adds neighborhood SES (continuous) to model 2.

The variables most responsible for the change between the model 1 and 2 HRs were BMI, followed by smoking. Because some animal data and epidemiologic data in children indicate that air pollution may be positively associated with weight gain (McConnell et al., 2015), and may mediate an association of air pollution and diabetes, we assessed the HRs (using the overall mean) excluding BMI: the model 2 HR was 1.03 (95% CI: 0.94, 1.13) using the LUR NO_2 estimates and it was 0.99 (95% CI: 0.95, 1.16) using the dispersion model NO_2 estimates. Corresponding model 3 HRs, excluding BMI, were 0.91 (95% CI: 0.82, 1.00) and 0.87 (95% CI: 0.74, 1.02).

Neighborhood SES and NO_2 levels were inversely correlated: the Spearman correlation coefficient in the 56 cities combined was -0.24; city-specific correlations ranged from -0.12 (San Francisco) to -0.75 (Trenton, NJ). We calculated HRs in the metro areas where the magnitude of the correlation between NO_2 and neighborhood SES was lowest (Spearman $r<0.25$) and highest ($r\geq 0.40$). These analyses used overall mean NO_2 estimates from the LUR model. In the category of lowest correlation, the model 1 and model 3 HRs were, respectively, 1.10 (95% CI: 0.94, 1.29) and 1.02 (95% CI: 0.87, 1.21). In the category of highest correlation, the model 1 and 3 h were 1.15 (95% CI: 0.99, 1.33) and 0.85 (95% CI: 0.72, 1.00).

Table 3 shows model 2 HRs using the overall mean in strata of covariates, based on NO_2 estimates from the LUR model in the 56 cities. The HRs in the two highest quintiles of neighborhood SES were reduced (quintile 4 HR=0.79 (95% CI: 0.62, 0.99), quintile 5 HR=0.84 (95% CI: 0.66, 1.07)), and the HR in the lowest category of BMI was increased (HR=1.22, 95% CI: 0.83, 1.79). There was, however, no evidence of statistical interaction between NO_2 and neighborhood SES, BMI, age, education, presence of hypertension, level of vigorous exercise, smoking, or diet pattern (all P for interaction >0.05). We calculated HRs among women in the 56 cities who did not move (2078 cases in 185,285 person-years): the model 2 HR using the overall mean was 1.02 (95% CI: 0.88, 1.17) and using the temporal mean it was 1.04 (95% CI: 0.88, 1.22).

In Los Angeles (277 cases/34,070 person-years), using estimates from the LUR model, the model 2 HR using the overall mean was 1.23 (95% CI: 0.87, 1.72). Using estimates from the dispersion model, the model 2 HR was 1.50 (95% CI: 0.90, 2.49). We have previously reported a 25% increase in diabetes incidence (95% CI: 7–46%) per IQR of NOx (12.4 ppb) for BWHS participants who lived in Los Angeles, with follow-up from 1995 to 2005 (183 cases/33,657 person-years) (Coogan et al., 2012). When we duplicate this past analysis, but extend follow-up through 2011 as in the present study, the HR was reduced to 1.18 (95% CI: 1.00–1.38). The prior published results are not strictly comparable to the present results because NOx was used rather than NO_2. Furthermore, NOx was estimated from a LUR model different from that in the present report. In addition, in the prior report NOx was estimated only for 2006, and a slightly different set of covariates were included in the final model. Therefore, to calculate a more comparable HR, we

Table 3
Incidence of diabetes per IQR (9.7 ppb) increase in NO_2 in strata of covariates, NO_2 estimates from LUR in 56 cities, exposure metric=overall mean.

	Cases/PYs	Model 2 HR (95% CI)*
Neighborhood SES		
Quintile 1	1081/85,569	0.89 (0.67, 1.18)
Quintile 2	934/86,213	0.99 (0.75, 1.29)
Quintile 3	879/88,921	0.95 (0.74, 1.21)
Quintile 4	833/95,834	0.79 (0.62, 0.99)
Quintile 5	660/96,683	0.84 (0.66, 1.07)
Interaction p-value:		0.77
BMI		
<25	298/135,021	1.22 (0.83, 1.79)
25–29	1184/154,702	1.04 (0.86, 1.25)
≥ 30	2905/163,498	0.97 (0.87, 1.10)
Interaction p-value:		0.83
Age		
<40	655/133,509	0.94 (0.75, 1.19)
40–54	2200/224,159	0.97 (0.86, 1.10)
≥ 55	1532/95,553	1.04 (0.89, 1.20)
Interaction p-value:		0.72
Education		
$\leq$ HS	980/71,966	0.98 (0.78, 1.24)
Some college	1476/142,585	0.97 (0.81, 1.16)
College graduate	1926/238,024	0.98 (0.85, 1.13)
Interaction p-value:		0.89
Hypertension		
No	1932/310,669	1.05 (0.91, 1.21)
Yes	2455/142,551	0.91 (0.80, 1.04)
Interaction p-value:		0.19
Vigorous exercise		
<5 h/week	4157/407,886	0.97 (0.88, 1.07)
≥ 5 h/week	187/41,596	0.69 (0.37, 1.27)
Interaction p-value:		0.60
Smoking		
Never	2344/281,409	0.93 (0.81, 1.05)
Past or current	2037/170,892	1.04 (0.90, 1.21)
Interaction p-value:		0.11
Meat/fried food diet pattern score		
Quintile 1	700/87,221	0.90 (0.69, 1.18)
Quintile 2	755/85,892	0.77 (0.60, 1.00)
Quintile 3	814/86,307	1.10 (0.85, 1.42)
Quintile 4	866/86,104	0.98 (0.77, 1.24)
Quintile 5	965/84,832	1.00 (0.80, 1.25)
Interaction p-value:		0.96

* Adjusted for the following, unless the variable is the stratifying variable: age, questionnaire cycle, metro area, BMI (weight in kg/height^2 in m) (<25, 25–29.9, 30–34.9, 35–39.9, ≥ 40), years of education (≤ 12, 13–15, 16, ≥ 17), h/week vigorous exercise (none, <5, ≥ 5), vegetable/fruit diet pattern score (quintiles) and meat/fried foods diet pattern score (quintiles), and smoking status (never, past, <15 cigarettes/day, ≥ 15 cigarettes/day).

assigned year 2006 NO_2 estimates from the prior LUR model to Los Angeles locations in the current analytic cohort, with follow-up from 1995 to 2011. Using those NO_2 estimates, the model 2 HR per 9.7 ppb (IQR in the present report) was 1.15 (95% CI: 0.82–1.61).

4. Discussion

In this large population of African American women, NO_2 levels were not associated with diabetes incidence. Results were consistent regardless of which model was used to estimate NO_2 levels (LUR or dispersion model) and which exposure metric was used (overall mean or temporal mean).

In the current report, the HRs for Los Angeles were higher than for the nationwide cohort. The variation could have occurred by chance. However, prior studies reported larger air pollution effects on mortality in Los Angeles than in national models (Jerrett et al., 2005). There could be a more toxic mixture of air pollution in Los Angeles due to the presence of major port facilities and a relatively higher contribution from traffic and diesel exhaust. We are unable to test this hypothesis directly because the monitoring data needed to predict markers of diesel, such as elemental carbon, are unavailable. Furthermore, in our earlier report from Los Angeles, we reported a statistically significant HR of 1.25 per 12.4 ppb NO_X with follow-up from 1995 to 2005 (Coogan et al., 2012); when we repeated that analysis with follow-up extended to 2011, the HR fell to a nonsignificant 1.18. In the current analysis of NO_2, the HR (based on LUR estimates) was a nonsignificant 1.23. The attenuation in the HRs with the longer follow up may have occurred due to substantial reductions in NO_2 and NOx that occurred during the period from 2006 to 2011, creating potential measurement errors in our exposure estimates. During this period, the California Air Resource Board implemented a comprehensive regulatory program aimed at reducing emissions from ports and on truck routes. Accountability studies of this program showed that large and spatially differentiated reductions in NO_2 and NOx occurred during this period, with the largest reductions occurring along truck routes known as “goods movement corridors”. The proportionately larger reductions along these corridors compared to other busy roads with lower truck volumes or to background residential areas would have created the potential for measurement error in our current exposure estimates because our current models may not have captured the lower emissions from trucks. The differential emissions reductions in specific zones would have imparted a Berkson error structure to the effect estimates (i.e., inflating the standard errors of the HRs). Additional classical error could have occurred due to random changes in other areas outside the goods movement corridors that may have attenuated the estimates toward the null (Molitor et al., 2007; Thomas et al., 1993; Molitor et al., 2006).

Three other prospective studies have assessed NO_2 or NOx and diabetes incidence (Park et al., 2015; Andersen et al., 2012; Kramer et al.,. 2010). In 9 years of follow-up in the Multiethnic Study of Atherosclerosis (Park et al., 2015), the HR per IQR of NOx (47.1 ppb) was 1.20 (95% CI: 0.80, 1.80) for women and 0.91 (95% CI 0.59–1.42) for men, adjusted for a range of individual-level risk factors, neighborhood SES, and study site. In 10 years of follow-up of a large Danish cohort (Andersen et al., 2012), the multivariable HR per IQR increase in NO_2 (4.9 $\mu g/m^3$) was 1.04 (95% CI: 1.00, 1.08). HRs were higher among women (HR=1.07: 95% CI 1.01, 1.13), never smokers (HR=1.12, 95% CI: 1.05, 1.20), and physically active people (HR=1.10, 95% CI: 1.03, 1.16). In 22 years of follow-up in a study in the Ruhr area of Germany, the HR for diabetes per IQR of NO_2 estimated with an LUR model (15 $\mu g/m^3$) was 1.31 (95% CI: 1.01, 1.70), adjusted for BMI, education, and indoor sources of air pollution (Kramer et al., 2010). Several other studies have assessed the association of particulate matter with diabetes incidence, with inconsistent results. In the German study cited above (Kramer et al., 2010) and in a large Canadian study (Chen et al., 2013), levels of particulate matter were associated with significant 16% and 11% increases, respectively, in incidence per 10 $\mu g/m^3$ increase in pollutant levels. In a second German study, levels of overall particulate matter were not associated with diabetes incidence, but there was a nonsignificant 36% increase in incidence per 1 $\mu g/m^3$ increase in traffic-specific particulate matter (Weinmayr et al., 2015). In contrast, no significant associations between $PM_{2.5}$ and diabetes incidence were observed in the Nurse's Health Study (Puett et al., 2011), the Health Professionals Follow-up Study (Puett et al., 2011), the Multi-Ethnic Study of Atherosclerosis (Park et al., 2015), or in the BWHS (Coogan et al., 2016).

The hypothesis that particulate matter and ozone could increase the risk for diabetes is mechanistically plausible, as recently reviewed elsewhere (Rao et al., 2015). In experimental studies, traffic-related fine and ultrafine particles and ozone have proven capable of triggering inflammation, oxidative stress, and the biological pathways that promote metabolic insulin resistance (Rajagopalan and Brook, 2012; Brook et al., 2013; Vella et al. 2015). NO_2 can induce similar inflammatory responses to those of particulate matter and ozone (U.S. EPA, 2016; Hesterberg et al., 2009), but we are aware of no toxicological studies that have directly investigated whether NO_2 promotes metabolic insulin resistance. Therefore, in the prior epidemiological studies showing positive associations of NO_2 and diabetes incidence, NO_2 may have served as a proxy for traffic-related fine and ultrafine particles.

The prevalence of overweight and obesity is high in African American women (Go et al., 2013) and is high in the BWHS. Obesity is one of the strongest risk factors for diabetes (Krishnan et al., 2007). Although there was no statistically significant interaction between NO_2 and BMI, the HR was highest (1.22) among women with BMI < 25. Similarly, in a prior report from BWHS, there was no association between $PM_{2.5}$ and diabetes in the overall cohort (HR=0.99, 95% CI 0.90, 1.09), but the HR was nonsignificantly increased in women with BMI < 25 (HR=1.36, 95% CI 0.91–2.04) (Coogan et al., 2016). Based on prior studies (Kramer et al., 2010; Andersen et al., 2012; Chen et al., 2013), the magnitude of any association of air pollution with diabetes incidence is expected to be modest, and modest associations can be difficult to observe in high risk groups, such as obese women.

Strengths of the study include the prospective study design, the large sample size and long follow-up. While diabetes was self-reported, a validation study in BWHS demonstrated a high degree of accuracy of self-report (Krishnan et al., 2010). The analytic cohort was limited to women age 30 and over which increased the likelihood that the cases diagnosed during follow-up were type 2 diabetes. We also were able to control for a wide range of potential confounders. Undiagnosed diabetes may have biased HRs to the null. It is not feasible in a large national cohort like BWHS to assess undiagnosed diabetes. However, virtually all BWHS participants had health insurance and access to regular care; in 2011, 78% reported that their blood sugar had been checked in the past 2 years. According to NHANES data 1999–2002, the prevalence of undiagnosed diabetes among non-Hispanic black women aged 20 and older was 3.8% (95% CI 2.4–6.1%) (Cowie et al., 2006). To assess undiagnosed diabetes in the BWHS, we assayed HbA1C levels in a sample of 1873 participants who had given a blood sample and had never reported diabetes; 6.4% had HbA1c levels of 6.5% (47.5 mmol/mol) or higher, suggesting that they may have indeed had diabetes. It is unlikely that this level of misclassification would result in substantial bias.

NO_2 and neighborhood SES were inversely correlated, and the addition of neighborhood SES reduced HRs to below 1.0. Among metro areas where the correlation between NO_2 and SES was

lowest, the fully adjusted HR was 1.02, whereas in the areas where the correlation was highest, the HR was 0.85. HRs were also < 1.0 in the two highest quintiles of neighborhood SES. These results suggest that there is a complex confounding relation between NO_2 and neighborhood SES and that it is difficult to completely control for it.

We had two sets of NO_2 estimates. The LUR estimates were at a scale $\sim$10 km grids and assigned to the block group of participant residences. Among the $\sim$32,000 block groups in the 56 cities where BWHS participants lived, the average NO_2 concentration coefficient of variability for blocks in a block group was 6%, suggesting that spatial averaging to the level of the block group, rather than the block, introduced only minor loss of information. As regards stability of LUR estimates over time, estimates from LUR models for a particular year or years are relatively stable, and can validly be applied several years backwards and forwards (Eeftens et al., 2011). The fact that HRs were very similar using the LUR and dispersion model estimates argues for validity of the findings.

Both models had the potential for over-smoothing due to dependence on a sparse network of 369 government monitoring sites, most of which are located away from traffic sources due to siting criteria. It is therefore likely that both estimates were unable to capture completely the fine-scale variation that occurs around major roadways and highways, and there was likely to be underestimation in areas that had high levels of NO_2, which would bias results toward the null. The dispersion model also relied on a nationally available dataset of traffic coverage that did not have estimates of traffic flows for all roadways. The imputation needed to fill in these missing data points might also have led to less variation than we would observe with extensive field measurements, again potentially leading to underestimates in areas of high exposure and a bias toward the null.

The annual average NO_2 concentration across the U.S. has decreased by 48% from 1990 to 2012 (EPA, 2013). One of our exposure metrics, the overall mean, did not account for temporal trends. However, the relative spatial distribution of NO_2 has been stable over time. In addition, HRs estimated with a second exposure measure that incorporated temporal trends (temporal mean) were similar to HRs based on the overall mean.

A limitation is that pollutant levels were estimated only at each woman's residential location. We did not have exposure measures based on personal monitoring devices, nor did we have information on indoor air quality. However, time-activity studies show that Americans spend on average 67% of their time at home, (Leech et al., 2002) and most studies of long-term exposure to air pollution have relied on ambient outdoor measurements modeled at the home location, including those that have documented associations of air pollution with increased mortality and cardiovascular outcomes (Krewski et al., 2005).

5. Conclusions

The present results do not support the hypothesis that exposure to ambient NO_2 contributes to an increased incidence of diabetes in African American women. In fact, when the model was adjusted for neighborhood SES, there was a suggestion of a decrease in incidence per IQR increase in NO_2. We suspect that these weak inverse associations may be due to confounding by neighborhood SES which may not be fully controlled simply by adjusting for or stratifying on quintile of neighborhood SES.

Acknowledgements

We thank Matthew Bechle of the Department of Civil, Environmental, and Geo-Engineering, University of Minnesota, for his assistance with the LUR NO_2 estimates.

Grant support/Acknowledgments

This study was supported by grants from the National Institute of Environmental Health Sciences (ES019573) and the National Cancer Institute (UM1CA164974 and CA058420). The funding sources had no involvement in study design; collection, analysis, and interpretation of data; writing the paper; or in the decision to submit for publication. The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

The Institutional Review Board of Boston University School of Medicine approved this research.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.envres.2016.04.021.

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