Long-Term Exposure to NO\(_2\) and Ozone and Hypertension Incidence in the Black Women’s Health Study

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**BACKGROUND**
Evidence shows that exposure to air pollutants can increase blood pressure in the short and long term. Some studies show higher levels of hypertension prevalence in areas of high pollution. Few data exist on the association of air pollution with hypertension incidence. The purpose of the present study was to prospectively assess the associations of the traffic-related nitrogen dioxide (NO\(_2\)) and of ozone with the incidence of hypertension in the Black Women’s Health Study (BWHS), a large cohort study of African American women.

**METHODS**
We used Cox proportional hazards models to calculate hazard ratios (HRs) and 95% confidence intervals (CI) for hypertension associated with exposure to NO\(_2\) and ozone among 33,771 BWHS participants. NO\(_2\) and ozone levels at participant residential locations were estimated with validated models.

Studies have documented positive associations of short- and long-term exposure to particulate air pollutants with blood pressure levels.\(^1\)\(^-\)\(^5\) Putative mechanisms include systemic inflammation, oxidative stress, and vascular endothelial injury.\(^6\) Several studies have found positive associations of particulate air pollution\(^7\)\(^-\)\(^8\) and the traffic-related nitrogen oxides\(^9\)\(^-\)\(^10\) (NO\(_2\) or NO\(_x\)) with hypertension prevalence, though others have not.\(^10\)\(^-\)\(^12\) A few studies have assessed the association of particulate air pollution or NO\(_2\) with hypertension incidence, but results are inconsistent.\(^12\)\(^-\)\(^17\) In studies conducted in Asia, elevated ozone was associated with increased blood pressure\(^17\)\(^-\)\(^18\) and with hypertension prevalence.\(^7\) No study to date has assessed ozone in relation to hypertension incidence.

We report here a prospective assessment of associations of NO\(_2\) and ozone with the incidence of hypertension in the Black Women’s Health Study (BWHS). Positive associations would be of particular importance for African American women, among whom the burden of hypertension is high.\(^19\) In addition, due to the legacy of racial segregation in housing, predominantly African American neighborhoods have, on average, higher levels of air pollution than predominantly white neighborhoods.\(^20\) We have previously reported positive associations of fine particulate matter of aerodynamic diameter ≤2.5 µg (PM\(_{2.5}\)) and of NO\(_x\) with hypertension incidence among BWHS residents of Los Angeles.\(^14\) In subsequent analyses in the nationwide BWHS cohort and with longer follow-up, PM\(_{2.5}\) was not associated with hypertension incidence.\(^15\) The present paper extends prior analyses of PM\(_{2.5}\) and NO\(_x\) and hypertension by including the nation-wide cohort and longer follow-up time, and considering ozone in addition to PM\(_{2.5}\) and NO\(_2\).

**RESULTS**
From 1995 to 2011, 9,570 incident cases of hypertension occurred in a total of 348,154 person-years (median follow-up time, 11 years). The multivariable HRs per interquartile range of NO\(_2\) (9.7 ppb) and ozone (6.7 ppb) were 0.92 (95% CI = 0.86, 0.98) and 1.09 (95% CI = 1.00, 1.18).

**CONCLUSIONS**
In this large cohort of African American women, higher ozone levels were associated with an increase in hypertension incidence. Higher NO\(_2\) levels were not associated with greater hypertension incidence; indeed, incidence was lower at higher NO\(_2\) levels.

**Keywords:** African American; air pollution; blood pressure; hypertension; hypertension incidence; women.

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Estimation of air pollutants

We estimated annual NO\textsubscript{2} levels for the years 2000–2010 at the Census block group level using a spatiotemporal land use regression (LUR) model.\textsuperscript{23,24} The spatial model incorporated year-2006 annual-average NO\textsubscript{2} concentrations at 369 monitoring stations, 81,670 satellite-derived estimates of ground-level NO\textsubscript{2} concentrations, and satellite- and ground-based land use datasets. The temporal model incorporated 48,886 monthly average monitoring station values. The \( R^2 \) for the final spatiotemporal model was 0.80.

We estimated ozone concentrations from a Bayesian space-time fusion model developed by the US Environmental Protection Agency, which estimates daily 8-hour maximum ozone concentrations for each Census tract centroid.\textsuperscript{25} We averaged these values for the years 2007–2008 to approximate the long-term average at all participant locations over follow-up. Correlations with holdout cross-validation locations for daily predictions ranged from 0.61 to 0.86.\textsuperscript{26} PM\textsubscript{2.5} levels were estimated at participant addresses using a 2-stage modeling strategy that incorporated an LUR model and Bayesian Maximum Entropy (BME) approaches, which has been described in detail elsewhere.\textsuperscript{27} Briefly, the BME method is a spatiotemporal kriging model that was used to interpolate the residuals the LUR model and to optimize the model fit by incorporating epistemic knowledge about the seasonal spatial patterns of pollution variation. The predictions from the LUR model and the BME estimates were combined post hoc. The combined prediction model had a cross-validation \( R^2 \) of 0.79. Because the association of PM\textsubscript{2.5} and hypertension in BWHS has been published previously,\textsuperscript{15} PM\textsubscript{2.5} is included in this analysis only as a covariate. Details of the air pollution estimation methods are given in the online supplementary material.

We examined the within-metro correlations between ozone and NO\textsubscript{2} and between ozone and PM\textsubscript{2.5} and found that the mean correlations were moderately low, and a wide range of correlations among the 56 metro areas included in the study. For ozone and NO\textsubscript{2}, the within-metro Spearman correlation coefficients ranged from −0.95 to 0.21 (mean within-metro correlation = −0.57). For ozone and PM\textsubscript{2.5}, correlation coefficients ranged from −0.80 to 0.37 (mean = −0.29). Based on this empirical assessment, we concluded that there was sufficient independence between ozone and the other pollutants to merit an independent investigation of the ozone effects.

Covariates

Self-reported weight, smoking and alcohol history, and hours/week of vigorous exercise were obtained at baseline and updated on follow-up questionnaires. In 1995 and 2001, we obtained diet data with food frequency questionnaires\textsuperscript{28} and used factor analysis to identify 2 dietary patterns (i.e., high vegetable/fruit intake, high meat/fried food intake).\textsuperscript{29} Height and education were obtained at baseline and education was updated in 2003. Factor analysis was used to create a neighborhood socioeconomic status (SES) score that included 7 census variables (median household income; median housing value; percent of households receiving interest, divided or net rental income; percent of adults aged ≥25 years that completed college; percent of families with children headed by a single female; percent of population living below the poverty line; percent African Americans) and was assigned to each participant address.

Statistical methods

We used Cox proportional hazards models, stratified by age, questionnaire cycle, and metropolitan area to estimate hazard ratios (HR) and 95% confidence intervals (CI) per interquartile range increase of each pollutant (9.7 ppb for NO\textsubscript{2}, 6.7 ppb for ozone). Person-time was calculated from the start of follow-up in 1995 until the occurrence of hypertension, loss to follow-up, death, or end of follow-up, whichever happened first.

Exposures were modeled as the long-term average of NO\textsubscript{2} and ozone at the address where the participant lived in the questionnaire cycle prior to the diagnosis of hypertension. The use of penalized splines did not improve model fit compared with the linear model. We modeled NO\textsubscript{2} and ozone individually, and also in multipollutant models including PM\textsubscript{2.5}.

We present a basic model (model 1) that included age, questionnaire cycle, and metropolitan area. We then added covariates that by themselves changed the coefficient for the pollutant by at least 10% (model 2), including body mass index (weight in kg/height in m\textsuperscript{2}), smoking status, years of education, hours/week vigorous exercise, alcohol consumption, the 2 dietary patterns, and neighborhood SES. Covariates identified in this way were the same for both NO\textsubscript{2} and ozone. We calculated HRs in strata of selected covariates and assessed multiplicative interaction with the likelihood ratio test. All analyses were conducted with SAS version 9.3 (SAS Statistical Institute, Cary, NC).
RESULTS

At baseline, mean levels of NO₂, ozone, and PM₁₀ in the 56-city study area were, respectively, 18.6 ppb (range, 1.0–37.7), 37.4 ppb (range, 25.4–56.4), and 13.9 μg/m³ (range, 3.1–24.2). The Spearman correlation coefficients between the pollutants were as follows: NO₂ and ozone, −0.54; NO₂ and PM₁₀, 0.26; and ozone and PM₁₀, 0.14 (all P < 0.01).

At baseline, the mean age was 36.8 years, 24% were obese, 48% had ≥16 years of education, 41% were current/past drinkers, 33% were current/past smokers, and 15% reported vigorous physical activity for ≥5 hours/week (Table 1). Compared to women living in the least polluted quintile of ozone, those in the most polluted quintile were less likely to be obese, had more education, were less likely to be current/past smokers or drinkers, less likely to consume a diet high in vegetables and fruit, and less likely to live in poor neighborhoods. In contrast, those in the most polluted quintile of NO₂ were more likely to be current/past smokers and drinkers, had lower levels of education, were more likely to eat a diet high in vegetables and fruit, and were more likely to live in the poorest neighborhoods, than those living in the least polluted quintile. The distribution of covariates over all quintiles of the pollutants are shown in the online Supplementary Material (Supplementary Tables S1 and S2).

From 1995 through 2011, 9,570 women reported incident hypertension. Table 2 shows HRs for hypertension incidence per interquartile range of NO₂ and ozone in single and multi-pollutant models. For ozone, the HR of 1.00 (95% CI = 0.92, 1.08) from the basic model (model 1) increased to 1.09 (95% CI = 0.92, 1.08) in model 2. Neighborhood SES had no material effect on the model 2 HR. When SES was excluded from model 2, the HR was 0.97 (95% CI = 0.86, 1.05) in model 1. The HR for ozone, 1.09 (95% CI = 1.03, 1.25), adjusted for covariates similar to the present analysis. For comparison, we calculated the HR per interquartile range of NO₂ for residents of Los Angeles in the current study: the model 2 HR was 1.13 (95% CI = 0.91, 1.40). It is noteworthy that the HRs for NO₂ for Los Angeles were not confounded by neighborhood SES: when SES was excluded from model 2, the HR for Los Angeles was 1.14 (95% CI = 0.92, 1.40), almost identical to the HR when SES is included. This reflects the fact that the correlation between neighborhood SES and NO₂ levels was low in Los Angeles compared to other cities.

DISCUSSION

In this population of African American women, there was a 9% increase in hypertension incidence per interquartile range of ozone. In contrast, NO₂ was inversely associated with hypertension incidence in multivariate models. In the absence of a plausible biologic rationale, the inverse association may reflect a complex confounding relationship between NO₂ and neighborhood SES. Lower neighborhood SES was strongly and positively associated with NO₂ levels and control for SES may have resulted in over-control for NO₂ level. We have also observed in the BWHS cohort an inverse association of NO₂ with diabetes incidence. Ozone was also correlated with neighborhood SES, but the correlation was weaker and in the opposite direction. The different

We calculated model 2 HRs in strata of covariates (see online Supplementary Table S3). There was no evidence of statistical interaction of either pollutant with any covariate (all P for interaction > 0.05) with the exception of NO₂ and age (P for interaction = 0.01), although age-specific HRs varied but little: age < 40, HR = 0.91 (95% CI = 0.79, 1.05); age 40–54, HR = 0.95 (95% CI = 0.88, 1.03); age ≥ 55, HR = 0.87 (95% CI = 0.77, 0.99).

In previous analyses confined to BWHS participants who lived in Los Angeles (531 cases) and followed from 1995 to 2005, the HR for hypertension incidence per 12.4 ppb NOx was 1.14 (95% CI = 1.03, 1.25), adjusted for covariates similar to the present analysis. For comparison, we calculated the HR per interquartile range of NO₂ for residents of Los Angeles in the current study: the model 2 HR was 1.13 (95% CI = 0.91, 1.40). It is noteworthy that the HRs for NO₂ for Los Angeles were not confounded by neighborhood SES: when SES was excluded from model 2, the HR for Los Angeles was 1.14 (95% CI = 0.92, 1.40), almost identical to the HR when SES is included. This reflects the fact that the correlation between neighborhood SES and NO₂ levels was low in Los Angeles compared to other cities.

Table 1. Baseline characteristics in the BWHS cohort, and in lowest and highest quintiles of pollutants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Entire cohort</th>
<th>Lowest Ozone (25.4–33.5 ppb)</th>
<th>Highest Ozone (41.8–56.4 ppb)</th>
<th>Lowest NO₂ (1.0–12.9 ppb)</th>
<th>Highest NO₂ (25.0–37.7 ppb)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>36.8 (9.7)</td>
<td>36.4 (10.0)</td>
<td>36.6 (9.1)</td>
<td>37.1 (9.3)</td>
<td>35.9 (10.0)</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>27.0 (6.1)</td>
<td>27.0 (6.1)</td>
<td>26.6 (5.8)</td>
<td>26.7 (5.9)</td>
<td>27.0 (6.2)</td>
</tr>
<tr>
<td>BMI ≥ 30 kg/m², %</td>
<td>24</td>
<td>25</td>
<td>22</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>Education ≥ 16 years, %</td>
<td>48</td>
<td>47</td>
<td>49</td>
<td>52</td>
<td>46</td>
</tr>
<tr>
<td>Current/past drinker, %</td>
<td>41</td>
<td>44</td>
<td>39</td>
<td>38</td>
<td>42</td>
</tr>
<tr>
<td>Current/past smoker, %</td>
<td>33</td>
<td>38</td>
<td>28</td>
<td>28</td>
<td>36</td>
</tr>
<tr>
<td>Vigorous exercise ≥5 hours/week, %</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>Highest quintile vegetable/fruit diet pattern, %</td>
<td>19</td>
<td>21</td>
<td>18</td>
<td>17</td>
<td>22</td>
</tr>
<tr>
<td>Lowest quintile neighborhood SES, %</td>
<td>20</td>
<td>27</td>
<td>11</td>
<td>9</td>
<td>27</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; BWHS, Black Women’s Health Study; SES, socioeconomic status.

*At 1995 address.
Table 2. Incidence of hypertension per IQR* in single and multipollutant models

<table>
<thead>
<tr>
<th></th>
<th>Model 1 HR (95% CI)*</th>
<th>Model 2 HR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ozone alone</td>
<td>1.00 (0.92, 1.08)</td>
<td>1.09 (1.00, 1.18)</td>
</tr>
<tr>
<td>Ozone + NO₂</td>
<td>1.02 (0.92, 1.13)</td>
<td>1.04 (0.94, 1.15)</td>
</tr>
<tr>
<td>Ozone + PM₂₅</td>
<td>1.02 (0.94, 1.12)</td>
<td>1.08 (0.99, 1.19)</td>
</tr>
<tr>
<td>Ozone + NO₂ + PM₂₅</td>
<td>1.02 (0.92, 1.13)</td>
<td>1.04 (0.94, 1.15)</td>
</tr>
<tr>
<td>NO₂ alone</td>
<td>1.02 (0.96, 1.08)</td>
<td>0.92 (0.86, 0.98)</td>
</tr>
<tr>
<td>NO₂ + ozone</td>
<td>1.03 (0.96, 1.10)</td>
<td>0.93 (0.87, 1.01)</td>
</tr>
<tr>
<td>NO₂ + PM₂₅</td>
<td>0.99 (0.92, 1.06)</td>
<td>0.90 (0.83, 0.98)</td>
</tr>
<tr>
<td>NO₂ + ozone + PM₂₅</td>
<td>0.99 (0.91, 1.08)</td>
<td>0.91 (0.84, 1.00)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confident interval; HR, hazard ratio; IQR, interquartile range.

*IQR of ozone is 6.7 ppb and of NO₂ is 9.7 ppb.

As noted, in previous analyses confined to BWHS participants in Los Angeles, NOx and hypertension incidence were positively associated (HR = 1.14). The current HR for NO₂ in Los Angeles residents was similar (HR = 1.13) to the prior result for NOx, although they are not directly comparable. As noted, neighborhood SES did not confound the HRs for NO₂ in Los Angeles as it did in the overall study, reflecting the weaker association between neighborhood SES and NO₂ levels in Los Angeles compared to most other cities in the study area. The higher HR in Los Angeles compared to in the overall cohort (HR = 0.92) likely reflects this difference in confounding by neighborhood SES; it could also have occurred by chance.

The hypothesis that exposure to air pollutants could increase the risk for hypertension is biologically plausible, although most evidence pertains to PM₂₅ rather than gaseous pollutants. Substantial evidence supports the hypothesis that PM₂₅ inhalation is capable of increasing continuously measured blood pressure over both the short- (1–7 days) and long-term (1 year). Putative mechanisms include sympathetic nervous system activation, endothelial dysfunction, and vasoconstriction, along with chronic vascular oxidative stress, inflammation, and remodeling. Animal experiments have corroborated the relevance of these underlying pathways and have further uncovered a role for hypothalamic inflammation in the genesis of chronic hypertension induced by long-term PM₂₅ exposure. In contrast, the available human exposure studies do not consistently show an impact of gaseous pollutants, including NO₂, on cardiovascular function or blood pressure. While a few studies have shown cross-sectional positive associations between ozone and blood pressure, most controlled human exposure studies do not support a direct role for ozone in raising blood pressure.

There was no association of NOx with hypertension incidence in a Danish cohort, although slight inverse associations with measured blood pressure and hypertension prevalence were observed at baseline. In that same study, however, the risk for incident hypertension for women who lived within 50 meters of a major road (compared to more than 50 meters) was 1.13 (95% CI = 0.97, 1.32). Distance to roadways is a surrogate for exposure to vehicle-related pollution. Similarly, in the Women's Health Initiative, the HR for incident hypertension for women who lived within 50 meters of a major roadway (compared to >1,000 meters) was 1.13 (95% CI = 1.00, 1.28) for trend = 0.013). No prior studies have assessed NO₂ or ozone specifically in relation to hypertension incidence.

Strengths of the present study include the prospective study design, data on many potential confounders, large number of outcomes, and long follow-up. A limitation is the fact that hypertension was self-reported. While our validation study demonstrated a high degree of accuracy of self-report among women who reported hypertension, we could not estimate the prevalence of undiagnosed hypertension among women who did not report hypertension. Data from the National Health and Nutrition Examination Survey (2007–2010) indicate that approximately 6% of US adults have undiagnosed hypertension. While we cannot exclude the possibility that undiagnosed hypertension may have introduced some degree of bias, the fact that virtually all BWHS participants had health insurance and access to regular care suggests that any such bias would be minimal.

While our use of hypertension incidence as an outcome was a strength, our study may have been limited by the fact that changes in a binary outcome like incidence or prevalence may be more difficult to detect than changes in a continuous parameter like directly measured blood pressure. For example, in the Sister Study, NO₂ levels were positively associated with measured systolic blood pressure, but not with hypertension prevalence. Small but clinically important blood pressure elevations may occur without an individual crossing the threshold to overt hypertension. Thus our study was limited by lack of blood pressure measures.

The use of national statistical models to predict exposures was a study strength; both models had high R² values and low error and bias. Both models, however, relied partially on government monitoring data, which is sparse in some areas. This could have led to some over-smoothing of the exposure estimates, especially if there are idiosyncratic local sources, yielding exposure misclassification. The analysis was limited by the fact that air pollution levels were estimated only at residential locations. We lacked information on key microenvironments (e.g., exposures in transit and at the workplace).
In conclusion, in the present study, higher ozone levels were associated with an increase in hypertension incidence. There was no evidence of higher incidence of hypertension associated with higher NO\textsubscript{2} levels; indeed, incidence was lower at higher exposure levels.

**SUPPLEMENTARY MATERIAL**

Supplementary data are available at American Journal of Hypertension online.

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**DISCLOSURE**

The authors declared no conflict of interest.

**REFERENCES**


