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Ambient ozone and incident diabetes: A prospective analysis in a large cohort of African American women

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ABSTRACT

Background: Ozone is a ubiquitous air pollutant with increasing concentrations in many populous regions. Toxicological studies show that ozone can cause oxidative stress and increase insulin resistance. These pathways may contribute to metabolic changes and diabetes formation. In this paper, we investigate the association between ozone and incident type 2 diabetes in a large cohort of African American women.
Methods: We used Cox proportional hazards models to calculate hazard ratios (HRs) for incident type 2 diabetes associated with exposure to ozone in a cohort of 45,231 African American women living in 56 metropolitan areas across the United States. Ozone levels were estimated using the U.S. EPA Models-3/Community Multiscale Air Quality (CMAQ) predictions fused with ground measurements at a resolution of 12 km for the years 2007–2008.
Results: The HR per interquartile range increment of 6.7 ppb of ozone was 1.18 (95% CI 1.04–1.34) for incident diabetes in adjusted models. This association was unaltered in models that controlled for fine particulate matter with diameter <2.5 μm ($PM_{2.5}$). Associations were modified by nitrogen dioxide (NO_2) levels, such that HRs for ozone levels were larger in areas of lower NO_2.
Conclusions: Our results provide initial evidence of a positive association between O_3 and incident diabetes in African American women. Given the ubiquity of ozone exposure and the importance of diabetes on quality of life and survival, these results may have important implications for the protection of public health.

1. Introduction

Tropospheric ozone (O_3) concentrations have increased by twofold since the 19th century, due largely to growing O_3 precursor emissions associated with human activity (Parrish et al., 2012). O_3 exhibits strong spatial and temporal heterogeneity (Cooper et al., 2014). In the United States nearly 130 million people live in areas that fail to comply with O_3 standards set by the U.S. Environmental Protection Agency (City Rankings - American Lung Association|State of the Air, 2015). While other pollutants have shown marked improvement, ozone has not seen nearly the same decreases in many parts of the United States, particularly in more polluted areas such as Southern California (Gauderman et al., 2015). Higher and worsening concentrations have also been observed in densely populated areas of South and East Asia (Parrish et al., 2012). O_3 is also an important greenhouse gas that contributes substantially to increased radiative forcing and resulting climate change (Intergovernmental Panel on Climate Change (IPCC), 2014). In the troposphere, ozone can elicit a wide range of adverse effects on human health, including: pulmonary dysfunction, hospitalization for respiratory causes, induction and exacerbation of asthma, and premature mortality from several causes, with specific risks observed for diabetic deaths (Berman et al., 2012; Mustafic et al., 2012; US EPA National Center for Environmental Assessment RTPNEMAG & Brown, 2013; Jerrett et al., 2009; Turner et al., 2016).

Growing epidemiological evidence implicates ambient air pollution as a contributor to the development of type 2 diabetes. While toxicological evidence suggests that $PM_{2.5}$ exerts pro-diabetic effects, epidemiological

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data on the association of diabetes with $PM_{2.5}$ exposure is inconsistent (Coogan et al., 2012; Chen et al., 2013; Puett et al., 2011). In addition, some studies have found markers of traffic-related air pollution such as NO_2 to be associated with incident diabetes (Park et al., 2015). Recent meta-analyses reported increased relative risks of type 2 diabetes per 10 μg/m^3 increase in exposure to $PM_{2.5}$: 1.10 (95% CI: 1.02, 1.18) and to NO_2: 1.08 (95% CI: 1.00, 1.17) (Eze et al., 2015). To date, no study has investigated whether ozone is associated with the onset of type 2 diabetes in humans.

Emerging evidence from animal experiments, however, suggests that O_3 exposure may also have the capacity to induce metabolic insulin resistance. Vella et al. (2015) recently demonstrated that rats exposed to O_3 for 16 h (as well as sub-acutely for 4 days at lower levels) developed elevations in fasting glucose levels and whole body insulin resistance (Vella et al., 2015). The insulin resistance was shown to be due to impaired insulin-signaling in muscle tissues as a consequence of oxidative stress-induced endoplasmic reticular stress pathways leading to c-Jun N-terminal kinase (JNK) activation. The investigators also provided evidence that these adverse responses to O_3 inhalation were likely mediated by the formation of pro-oxidative molecules in the pulmonary alveolar fluid capable of translocating into the systemic circulation. Additional studies suggest that O_3 could induce adverse systemic metabolic responses via activation of the sympathetic nervous system, by hypothalamic inflammation, or both (Bass et al., 2013). Hence, O_3 may also work to induce diabetes mellitus through similar pathways as fine particulate matter with diameter <2.5 μm ($PM_{2.5}$) (Rao et al., 2015). Specifically, both pollutants can cause oxidative stress in the lungs, which – if sustained over time – may lead to systemic pro-inflammatory and autonomic responses linked to numerous adverse health effects.

Based on the evidence from animal models and analogous findings on other common air pollutants, we hypothesized that ozone could contribute to the development of diabetes. We assessed this hypothesis in a large cohort of African American women.

2. Methods

2.1. Study population

In 1995, the Black Women's Health Study (BWHS) began when 59,000 black women aged 21 through 69 were recruited largely though subscribers to Essence magazine, a publication targeted to black women (Rosenberg et al., 1995). A baseline questionnaire solicited information on demographics, medical conditions, reproductive history, and lifestyle factors. Follow up occurred biennially with Web-based and mailed health questionnaires. Follow-up of the baseline cohort has been completed for 88% of potential years of follow-up through 2011. The Institutional Review Board of Boston University School of Medicine approved the study protocol. Participants indicate consent by completing and returning the questionnaires.

Here we used data from the baseline questionnaire (1995) and eight subsequent follow-up cycles (1997–2011), provided by 45,231 women who lived in any of 56 U.S. metropolitan areas and who had complete body mass index (BMI) information at baseline. Those excluded because they did not live in the 56 metro areas ($n = 11.914$) did not differ statistically from the women included in terms of mean age, prevalence of diabetes or BMI. Follow up started at 30 years of age to exclude potential cases of type 1 diabetes, regardless of whether the age at enrollment was <30. For example, a woman who was 28 at enrollment in 1995 would not add to follow up time until 1997 when she turned 30. We excluded 2228 women with prevalent diabetes at baseline, which left a total of 43,003 women for analysis.

2.2. Diagnosis of diabetes

Incident cases of type 2 diabetes were ascertained by self-report of doctor-diagnosed diabetes at age 30 or older during follow-up. A validation study among 227 participants who met the ascertainment criteria confirmed type 2 diabetes in 96% of the women based on the data from their medical records or provided by their physicians (Krishnan et al., 2010).

2.3. Ascertainment of covariates

Self-reported data on alcohol consumption, smoking history, hours per week spent in vigorous activity, and weight and height (used to calculate BMI, weight in kg/height in m^2) were obtained at baseline. All except height were updated with biennial follow-up questionnaires. Dietary data were obtained in 1995 and 2001 using a food frequency questionnaire modified from the 68-item short form Block-National Cancer Institute instrument (Block et al., 1990). We used factor analysis to identify two dietary patterns, one characterized by high intake of meat and fried food and the other by high intake of fruits and vegetables (Boggs et al., 2011). Educational attainment, household income, and parental history of diabetes were reported on various follow-up questionnaires.

We geocoded residential mailing addresses from 1995 to 2009 using TeleAtlas Road coverage as the reference layer. Geocoded addresses were then linked to U.S. Census data (block group level). Using factor analysis, we developed a neighborhood socioeconomic status (SES) score based on census variables indicating wealth, education, and income as described in detail elsewhere (Coogan et al., 2015).

2.4. Estimation of ozone

We estimated O_3 concentrations from a Bayesian space-time fusion model known as the Downscaler, which was developed by the U.S. Environmental Protection Agency (Berrocal et al., 2012). The model estimates daily 8-hour maximum O_3 concentrations for each census tract centroid in the contiguous United States. The model fuses data from the ground-based monitoring network with Community Model for Air Quality (CMAQ) model estimates with output on 12 * 12 km grids. We extracted daily estimates and averaged these for the years 2007–2008 to approximate the long-term average at all residential locations reported by BWHS participants over follow-up.

The Downscaler model underwent several validation steps (Berrocal et al., 2012). In brief, maps of the model output were produced for sub-regions of the United States and compared quantitatively and visually to monitoring locations, which showed the spatial patterns of predictions were largely consistent with monitored levels. The model performance was also assessed using the predictive mean absolute error (PMAE) of the space-time prediction, which showed the Downscaler outperformed either ordinary kriging models or CMAQ models alone. Correlations with hold-out cross-validation locations for daily predictions ranged from 0.61–0.86. These validation analyses suggested that the model predicted ambient ozone concentrations well.

2.5. Estimation of $PM_{2.5}$

We used a hybrid modeling approach to estimate ambient $PM_{2.5}$ for the years 1999–2008 at all participant residential addresses. Methods have been described in detail elsewhere (Beckerman et al., 2013). Briefly, we employed a two-stage modeling strategy that incorporated a land use regression (LUR) approach and a Bayesian Maximum Entropy (BME) approach. The model used data on traffic density and green space as fixed predictors. Validation of the final LUR-BME model in the cross-validation dataset showed strong agreement between observed and predicted $PM_{2.5}$ levels with no evidence of bias; the cross-validation $R^2 \sim 0.79$.