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Associations between long-term exposure to air pollution, glycosylated hemoglobin and diabetes

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ABSTRACT

Background: Air pollution exposures have been shown to adversely impact health through a number of biological pathways associated with glucose metabolism. However, few studies have evaluated the associations between air pollution and glycosylated hemoglobin (HbA1c) levels. Further, no studies have evaluated these associations in US populations or investigated whether associations differ in diabetic as compared to non-diabetic populations. To address this knowledge gap, we investigated the associations between airborne fine particulate matter ($PM_{2.5}$) and nitrogen dioxide (NO_2) and HbA1c levels in both diabetic and non-diabetic older Americans. We also examined the impact of $PM_{2.5}$ and NO_2 on prevalent diabetes mellitus (DM) in this cohort.

Methods: We used multilevel logistic and linear regression models to evaluate the association between long-term average air pollutant levels and prevalence of DM and HbA1c levels, respectively, among 4121 older (57+ years) Americans enrolled in the National Social Life, Health, and Aging Project between 2005 and 2011. All models adjusted for age, sex, body mass index, smoking status, race, household income, education level, neighborhood socioeconomic status, geographic region, urbanicity and diabetic medication use. We estimated participant-specific exposures to $PM_{2.5}$ on a six-kilometer grid covering the conterminous U.S. using spatio-temporal models, and to NO_2 using nearest measurements from the Environmental Protection Agency's Air Quality System. HbA1c levels were measured for participants in each of two data collection waves from dried blood spots and log-transformed prior to analysis. Participants were considered diabetic if they had HbA1c values $\geq$ 6.5% or reported taking diabetic medication.

Results: The prevalence of diabetes at study entry was 22.2% (n = 916) and the mean HbA1c was 6.0 ± 1.1%. Mean one-year moving average $PM_{2.5}$ and NO_2 exposures were 10.4 ± 3.0 μg/m^3 and 13.1 ± 7.0 ppb, respectively. An inter-quartile range (IQR, 3.9 μg/m^3) increase in one-year moving average $PM_{2.5}$ was positively associated with increased diabetes prevalence (prevalence odds ratio, POR 1.35, 95% CI: 1.19, 1.53). Similarly, an IQR (8.6 ppb) increase in NO_2 was also significantly associated with diabetes prevalence (POR 1.27, 95% CI: 1.10, 1.48). $PM_{2.5}$ (1.8% ± 0.6%, $p < 0.01$) and NO_2 (2.0% ± 0.7%, $p < 0.01$) exposures were associated with higher HbA1c levels in diabetic participants, while only NO_2 was significantly associated with HbA1c in non-diabetic participants (0.8% ± 0.2%, $p < 0.01$). Significant dose response relationships were identified for both pollutants in diabetic participants and for NO_2 in non-diabetic participants.

Conclusions/interpretations: In a cohort of older men and women in the United States, $PM_{2.5}$ and NO_2 exposures were significantly associated with prevalence of DM and increased HbA1c levels among both non-diabetic and diabetic participants. These associations suggest that air pollution could be a key risk factor for abnormal glucose metabolism and diabetes in the elderly.

1. Introduction

Air pollution exposures have been shown to adversely impact health through a number of biological pathways, including: Oxidative and endoplasmic reticulum stress, systemic and visceral adipose tissue inflammation, and endothelial and mitochondrial dysfunction (Rajagopalan and Brook, 2012; Sun et al., 2009; van Eeden et al., 2001). These pathways have, in turn, been shown to

Abbreviations: DM, type 2 diabetes mellitus; HbA1c, glycosylated hemoglobin; NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter with an aerodynamic diameter of ≤2.5 μm; Ppb, parts per billion.

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contribute to abnormal insulin signaling and/or increased insulin resistance in skeletal muscle, both of which are characteristic of type 2 diabetes mellitus (DM) (Rajagopalan and Brook, 2012; Sun et al., 2009).

While some epidemiologic evidence suggests air pollution may be linked with DM, this evidence is inconsistent. Small positive associations for prevalence of DM have been observed with nitrogen dioxide (NO_2) (Andersen et al., 2012; Brook et al., 2008; Coogan et al., 2012; Eze et al., 2014; Kramer et al., 2010; Park et al., 2015) and fine particulate matter ($PM_{2.5}$) (Chen et al., 2013; Eze et al., 2014; Kramer et al., 2010; Liu et al., 2016; Park et al., 2015; Pearson et al., 2010) while other studies have found no significant associations (Brook et al., 2008; Dijkema et al., 2011; Puett et al., 2011). Associations between air pollution and serum glucose, a measure of glucose homeostasis used to assess diabetes status, have been investigated in a few studies which have reported links between short-term NO_2 exposure and small increases in serum glucose (0.40%, 95% CI: 0.31%, 0.50%) (Sade et al., 2015), with larger associations observed for short-term $PM_{2.5}$ exposures and serum glucose in diabetic individuals (2.93%, 95% CI: 0.35%, 5.59%) (Yitshak Sade et al., 2016). Since serum glucose can vary widely over short periods of time, it is not an ideal outcome measure for assessing the potential effects of long-term pollution exposures. To address this, glycosylated hemoglobin (HbA1c), a marker of long-term glucose control, has been investigated in limited studies (Chuang et al., 2010; Liu et al., 2016; Yitshak Sade et al., 2016). These studies have shown significant increases in HbA1c associated with higher $PM_{2.5}$ exposures in Chinese and Israeli populations, while null associations were observed in a recent German cohort (Wolf et al., 2016). No prior studies of air pollution and HbA1c have been conducted in US populations. To address this gap, we evaluate the association of $PM_{2.5}$ and NO_2 with prevalence of DM and HbA1c levels in a nationally representative cohort of older (57+ years) Americans.

2. Methods

2.1. Population

The National Social Life, Health, and Aging Project (NSHAP) is a prospective, population based probability sample of 4121 older (57+ year), community-dwelling Americans selected from eligible households identified in the Health and Retirement Study (HRS) in 2004 (Waite et al., 2014a,b). The survey over-sampled African-Americans, Latinos, men and the oldest old (75–84 years). In total, 3005 participants were recruited in Wave 1 (2005–2006) and 3377 in Wave 2 (2010–2011). Response rates for each wave were high, with 75% and 74% of individuals selected for Wave 1 and Wave 2 opting to participate, respectively. Of the Wave 2 participants, 2261 also participated in Wave 1, while 744 from Wave 1 were either too sick to participate in Wave 2 or deceased. Additional Wave 2 participants were selected from eligible respondent (n = 907) and non-respondent (n = 209) households originally identified from the HRS probability sample. Participants in each wave underwent in-person interviews to obtain demographic (age, sex, race), social (education level) behavioral (physical activity, tobacco and alcohol use) and health data (history of diagnosed medical conditions and/or medication use), including that on self-reports of physician diagnosed diabetes and use of diabetes and cardiovascular medication. The questions and interview instruments were essentially unchanged between the two waves (Waite et al., 2014a,b). At the time of the interviews, biomeasure data on anthropometrics, cardiovascular and physical health, and blood spots were also collected. The study protocol was approved by the Institutional Review Boards of Northeastern University and the University of Chicago; all participants provided written informed consent.

2.2. Exposure assessment

$PM_{2.5}$ exposure was estimated on a six-kilometer (km) grid covering the United States obtained from spatio-temporal generalized additive mixed models (GAMMs). Models were based on the daily $PM_{2.5}$ mass from 1999 to 2007 as reported previously in Yanosky et al. (Yanosky et al., 2014). Briefly, the U.S. Environmental Protection Agency (EPA) Air Quality System (AQS) database and Interagency Monitoring of Protected Visual Environments (IMPROVE) network provided daily $PM_{2.5}$ data (EPA, 2009; IMPROVE, 2013). Spatio-temporal models were developed incorporating wind speed, temperature and total precipitation as meteorological covariates and county population density, point-source $PM_{2.5}$ emissions density, land use, line-source estimated traffic-related $PM_{2.5}$, and elevation as geospatial covariates. Daily $PM_{2.5}$ estimates were then used to calculate 1–5 year moving average exposure windows. $PM_{2.5}$ estimates were subsequently validated using cross-validation techniques, with a cross-validation R^2 of 0.76 (Yanosky et al., 2014). Exposures were assigned to NSHAP participants based on the grid point closest to their residential address. The distance between each grid centroid-residential address pair varied between 0.05 km and 4.21 km, with a mean distance of 2.23 km.

Exposures to nitrogen dioxide (NO_2) for each NSHAP participant were estimated using measurements from the nearest AQS monitor within 80 km of their residential address (202 individual monitors). Exposure windows of one to five year moving averages from the date of interview were calculated for $PM_{2.5}$ and NO_2. Moving averages were considered valid if $\geq$75% of the daily values within each exposure window were available. For both pollutants, the moving averages were calculated backwards from the date of study enrollment. All NSHAP participants had valid $PM_{2.5}$ measurements for each exposure window, while for NO_2, the number of participants with valid exposures varied by exposure window, ranging between 79.4% of participants having valid NO_2 measures for the five-year exposure window to 81.5% for the one-year exposure window. As estimated exposures and residential addresses were assessed in each wave, changes in residence between waves were accounted for in assigning exposure estimates for both $PM_{2.5}$ and NO_2 models.

2.3. Outcome assessment

HbA1c was collected via dried blood spots on filter paper. HbA1c measurements obtained using dried blood spots have previously been shown to be highly correlated with those obtained using venous blood draws (Lacher et al., 2013; Parkes et al., 1999). For Wave 1, blood spots were analyzed for HbA1c using the Roche Unimate immunoassay and Cobas Inegra Analyzer. For Wave 2, HbA1c assays were conducted using automated ion-exchange high-performance liquid chromatography (IE-HPLC) performed on a Bio-Rad Variant II Hemoglobin Testing System. Both methods are National Glycohemoglobin Standardization Program (NGSP) certified, and between-wave differences in NSHAP HbA1c measurements have been shown to be comparable to those observed in other large, national studies (Gregg et al., 2014).

Blood spot collection was randomized to five out of six Wave 1 participants (N = 2494) (Nallanathan et al., 2008); 389 of the selected participants opted out of the blood spot collection. Wave 1 participants who did and did not provide blood spots did not differ significantly with respect to sex, race/ethnicity, age, educational attainment, income level, or reported physical health (Nallanathan et al., 2008). Due to collection and/or analytic problems, HbA1c measurements were not available for an additional 359 Wave 1 participants. In sum, a total of 1746 Wave 1 participants (70.0%) and 3037 Wave 2 participants (89.9%) had valid HbA1c measurements. A maximum of two measurements was available per participant.