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Association between long-term exposure to ambient air pollution and diabetes mortality in the US

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ABSTRACT

Objective: Recent mechanistic and epidemiological evidence implicates air pollution as a potential risk factor for diabetes; however, mortality risks have not been evaluated in a large US cohort assessing exposures to multiple pollutants with detailed consideration of personal risk factors for diabetes.

Research design and methods: We assessed the effects of long-term ambient air pollution exposures on diabetes mortality in the NIH-AARP Diet and Health Study, a cohort of approximately a half million subjects across the contiguous U.S. The cohort, with a follow-up period between 1995 and 2011, was linked to residential census tract estimates for annual mean concentration levels of $PM_{2.5}$, NO_2, and O_3. Associations between the air pollutants and the risk of diabetes mortality (N = 3598) were evaluated using multivariate Cox proportional hazards models adjusted for both individual-level and census-level contextual covariates.

Results: Diabetes mortality was significantly associated with increasing levels of both $PM_{2.5}$ (HR = 1.19; 95% CI: 1.03–1.39 per 10 $\mu g/m^3$) and NO_2 (HR = 1.09; 95% CI: 1.01–1.18 per 10 ppb). The strength of the relationship was robust to alternate exposure assessments and model specifications. We also observed significant effect modification, with elevated mortality risks observed among those with higher BMI and lower levels of fruit consumption.

Conclusions: We found that long-term exposure to $PM_{2.5}$ and NO_2, but not O_3, is related to increased risk of diabetes mortality in the U.S, with attenuation of adverse effects by lower BMI and higher fruit consumption, suggesting that air pollution is involved in the etiology and/or control of diabetes.

1. Introduction

Aging populations, sedentary lifestyles, and calorie-dense diets have contributed to the growing prevalence of diabetes mellitus in both developed and developing countries (Guariguata et al., 2014), posing a serious threat to global public health and welfare. According to the International Diabetes Federation, diabetes affected at least 382 million people worldwide (8.3% prevalence) in 2013, and that number is expected to reach 592 million by the year 2035. Those with diabetes are at elevated risk to develop micro- and macro-vascular diseases throughout their lifetime, substantially reducing their life expectancies (Franco et al., 2007).

Recent evidence implicates ambient air pollution exposure as a potential contributing risk factor for diabetes. Systemic inflammation has a critical role in the etiology of this disease (Donath and Shoelson, 2011; Osborn and Olefsky, 2012), and air pollution has been demonstrated to activate inflammatory mechanisms (Brook et al., 2010). Sun et al. (2009) first provided a basis for the biological mechanism for the air pollution-diabetes relationship in an animal model, revealing that exposure to fine particulate matter increased blood glucose and induced adipose inflammation and insulin resistance. Subsequent studies have elucidated other potential pathophysiologic pathways, including overactivity of the sympathetic nervous system, endothelial dysfunction, and dysregulation of visceral adipose tissue (Rajagopalan and Brook, 2012; Rao et al., 2015).

Epidemiological investigations have also found associations in multiple cohorts between long-term ambient air pollution exposure and diabetes prevalence, incidence, and mortality. Meta-analyses (Park and

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Wang, 2014; Eze et al., 2015) have concluded that the collective evidence from such studies is suggestive of a positive relationship, but that additional studies are still required. Only a few studies have evaluated diabetes mortality: in a group of 2.1 million adults from the 1991 Canadian census mortality follow-up study (CanCHEC), higher long-term $PM_{2.5}$ exposure was associated with increased diabetes mortality (Brook et al., 2013). In the Danish Diet, Cancer, and Health cohort of 52,061 participants, a significant association between long-term NO_2 exposure and mortality was found (Raaschou-Nielsen et al., 2013). In the U.S., an investigation on the association between chronic exposure to $PM_{2.5}$ and multiple cardiovascular mortality outcomes in the American Cancer Society (ACS) cohort also reported a significant association with diabetes mortality (Pope et al., 2014). There exists a need to independently verify and further evaluate this relationship in a large and well-characterized cohort in the U.S., especially with an emphasis on assessment of exposure to multiple pollutants and determination as to whether certain subpopulations are at enhanced risk. Given the recent trend of increasing prevalence of both obesity and diabetes, it is of growing importance to evaluate and quantify the apparent diabetes-related mortality risk contribution from environmental factors, such as air pollution.

In this study, we evaluated the association between long-term exposure to air pollutants ($PM_{2.5}$, NO_2, and O_3) and diabetes-related mortality risk in the NIH-AARP Diet and Health cohort, a U.S study with detailed characterizations of individual-level covariates and census-tract estimates of air pollution concentrations. We also assessed potential effect modification by known personal risk factors.

2. Research design and methods

2.1. Population

Detailed study and cohort information are presented elsewhere (Thurston et al., 2015). The NIH-AARP Study was initiated when members of the AARP, 50–71 years of age from six U.S. states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and two metropolitan areas (Atlanta, Georgia, and Detroit, Michigan), responded to a mailed questionnaire in 1995. The NIH-AARP cohort questionnaires elicited information on demographic and anthropometric characteristics, dietary intake, and numerous health-related factors at enrollment. Contextual environment characteristics for the census tract of each of this cohort's participants have also been compiled, allowing us to also incorporate socioeconomic variables at the census-tract level. All participants provided written informed consent before completing the study. The study was approved by the Institutional Review Boards (IRBs) of the National Cancer Institute and New York University School of Medicine.

2.2. Cohort follow-up and mortality ascertainment

Person-years of follow-up were included for each participant from enrollment to the date of death, the end of follow-up (31 December 2011), or the date the participant moved out of the study state or city where s/he lived at enrollment, whichever occurred first. Vital status was ascertained through a periodic linkage of the cohort to the Social Security Administration Death Master File and follow-up searches of the National Death Index Plus for participants who matched to the Social Security Administration Death Master, cancer registry linkage, questionnaire responses, and responses to other mailings. We used the International Classification of Diseases, 9th Revision (ICD-9) and the International Statistical Classification of Diseases, 10th Revision (ICD-10) to define underlying mortality due to diabetes (ICD-9: 250 and ICD-10: E10–E14). Among 566,398 participants enrolled in the NIH-AARP cohort and available for analysis, after exclusions and removing those with missing data the analytic cohort includes 549,735 (97.1% of total cohort) participants with 50,700 (9.2%) self-reported history of diabetes at enrollment. During the follow-up period considered (1995–2011), 130,384 (23.7%) total participants died, and 3597 subjects died from diabetes (2.8% of total deaths during the study period).

2.3. Exposure assessment

Detailed individual residence-level exposure data were considered in these analyses. We employed residential census tract centroid estimates of annual average $PM_{2.5}$ mass exposures available for the years 1980–2010, as derived from a published spatio-temporal prediction model using geographic predictors and extrapolation to predict pre-1999 exposure levels before implementation of nationwide monitoring (Kim et al., 2016). Monthly averages of census tract NO_2 concentrations were also linked, which were estimated based on a national land use regression model using regulatory monitoring (hourly data from 423 monitors) and satellite-based measurements (approximately 4 million measurements, aggregated into annual average values at 81,743) at the census block group level for the years 2000–2010 (Bechle et al., 2015).

We also procured and linked O_3 concentrations derived from an EPA Bayesian space–time downscaling fusion model (US EPA), which estimated daily 8-h maximum O_3 concentrations at the census tract centroid based on National Air Monitoring Stations/State and Local Air Monitoring Stations and CMAQ model data in 12 × 12 km grids for the years 2002–2010. However, for years 2002–2006, O_3 estimates were only available for the eastern part of the U.S. For this reason, daily ozone (O_3) concentrations were obtained for cohort California residents based upon an interpolation of data from monitoring stations in fixed-site Federal Reference Method monitors in the California's State and Local Air Monitoring Network Plan (NAMS/SLAMS) (https://www.arb.ca.gov/aaqm/mldaqsb/amn.htm). Monthly averages of max 8-h O_3 concentrations with ≥ 70% completeness in each month were calculated at monitoring sites. A statewide 250-m gridded pollutant surface using these monthly average concentrations was then developed with inverse distance-weighted (IDW) interpolation, using the Spatial Analyst extension of ArcGIS version 10.3.1 (ESRI, Redlands, CA). The agreement between the EPA model and monitor-based kriging methods were compared for years 2007–2010 when the EPA values become available for California; the correlations between the two approaches were excellent, with R^2 ranging from 0.89 to 0.95.

2.4. Statistical methods

Cox proportional hazards models were employed to estimate hazard ratios (HRs) of mortality in relation to ambient air pollution levels (per 10 μg/m^3 for $PM_{2.5}$; per 10 ppb for NO_2 and O_3), assigning long-term exposure for $PM_{2.5}$, NO_2, O_3 as average annual concentration levels from 2002 to 2010, in order to match the more limited O_3 data availability.

In fully-adjusted multivariate models including individual-level variables, the following covariates were included: age (grouped into 3-year categories), sex, region (6 U.S. states and two cities) as strata; race or ethnic group (Non-Hispanic White; Non-Hispanic Black; Hispanic; Asian, Pacific Islander, or American Indian/Alaskan Native; unknown); level of education (less than high school, some high school, high school completed, post-high school or some college, college and post graduate, unknown); marital status (married, never-married, other, unknown); body-mass index (BMI) (< 18.5 kg/m^2, 18.5- < 25.0, 25.0- < 30.0, 30- < 35, 35+, unknown); alcohol (none, < 1, 1- < 2, 2- < 3, 3- < 5 and 5+ drinks per day); smoking status (never smoker, former smoker of ≤ 1 pack/d, former smoker of > 1 pack/d, current smoker of ≤ 1 pack/d, current smoker of > 1 pack/d, unknown); and diet (total fat consumption, in grams per day; total vegetable and total fruit consumption, in pyramid servings per day), in addition to two contextual characteristics (median census tract household income and percent of census tract population with less than a high school education, based on the 2000 decennial census for the residence at study entry). At study