HHS Public Access

Author manuscript

Environ Res. Author manuscript; available in PMC 2019 August 01.

Published in final edited form as:

Environ Res. 2018 August ; 165: 330–336. doi:10.1016/j.envres.2018.04.011.

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

Chris C. Lim[1,*], **Richard B. Hayes**[1,2], **Jiyoung Ahn**[1,2], **Yongzhao Shao**[1,2], **Debra T. Silverman**[3], **Rena R. Jones**[3], **Cynthia Garcia**[4], and **George D. Thurston**[1,2]

[1]Department of Environmental Medicine, New York University School of Medicine

[2]Department of Population Health, New York University School of Medicine

[3]Division of Cancer Epidemiology & Genetics, National Cancer Institute, National Institutes of Health

[4]California Air Resources Board, Sacramento, CA

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=3,598) 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 μg/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.

[*]**Corresponding Author**, Chris C. Lim, NYU School of Medicine, Department of Environmental Medicine, 57 Old Forge Rd, Tuxedo Park, NY 10987. 512-913-6114. ccl414@nyu.edu.

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.

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 Foundation, 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).

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 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., 2013a). 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. 2015). 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.

Research Design and Methods

Population

Detailed study and cohort information are presented elsewhere (Thurston et al., 2016). 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.

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 through 2011), 130,384 (23.7%) total participants died, and 3,597 subjects died from diabetes (2.8% of total deaths during the study period).

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 2014), which estimated daily 8-hour 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 x 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-hour 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.

Statistical Methods

Cox proportional hazards models were employed to estimate hazard ratios (HRs) of mortality in relation to ambient air pollution levels (per 10 $\mu g/m^3$ 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 2002–2010, 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

enrollment, cohort participants completed the AARP 124-item FFQ (AARP-FFQ), an early version of the Diet History Questionnaire, to assess dietary intake over the past year. We merged the MyPyramid Equivalents Database, version 1.0, with the AARP food frequency questionnaire data to calculate pyramid equivalents for fruits and vegetables (Reedy et al., 2008).

We also conducted stratified analyses to test for possible effect modification by known individual risk factors: age, sex, race, smoking history, pre-diagnosed health status (heart disease and diabetes), BMI, and diet. Potential effect modification was assessed by including multiplicative interaction terms between the pollutant and covariates of interest in the models, and the likelihood ratio test comparing model fit with and without interaction terms were conducted to test the statistical significance. Also, as further sensitivity analyses, we considered a random effects model at the metropolitan statistical area (MSA) level; without censoring data after people moved; and for $PM_{2.5}$, we also considered an extended Cox model with time-varying and lagged exposures (1 year prior) for the entire follow-up period of years 1995–2011, to evaluate model robustness to choice of exposure metric timeframe. Packages “survival” and “coxme” in R (version 3.4.0) were utilized for analysis.

Results

Detailed cohort characteristics are presented in Table 1; there is only limited variation in pollutant concentrations by participant characteristics, indicating that potential confounding by these variables with air pollution exposure is likely minimal. Average concentrations for $PM_{2.5}$ ranged from 2.8 to 21.2 $\mu g/m^3$, with a mean (SD) of 11.0 (2.7) $\mu g/m^3$; for NO_2 concentration levels ranged from 2.1 to 36.2 ppb, with a mean (SD) of 12.2 (5.5) ppb; and for O_3 concentration levels ranged from 25.5 to 56.5 ppb, with a mean (SD) of 39.5 (4.6) ppb. Annual average $PM_{2.5}$ and NO_2 concentration levels for the years considered in the analysis were highly correlated (R^2=0.72), while $PM_{2.5}$ and O_3 showed weak correlation (R^2=0.10).

After adjusting for both individual- and contextual-level covariates, both $PM_{2.5}$ (HR=1.19; 95% CI: 1.03–1.39) and NO_2 (HR=1.09; 95% CI: 1.01–1.18) were found to be significantly associated with diabetes-related mortality. For O_3, the mortality risk estimates were not significant for either annual (HR=0.96; 95% CI: 0.88–1.04) or summertime (HR=0.98; 95% CI: 0.92–1.03) exposure averages. The time-varying model for $PM_{2.5}$ provided similar results to the full model, and inclusion of MSA-level random effects, those who moved out of ascertainment area, and other comorbidities in the model only marginally changed the effect estimates for the pollutants (Table 2).

The overall exposure-response relationship using splines was plotted, with the best degree of freedom (df=2) selected via Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) values. We observed the significant associations between $PM_{2.5}$ and NO_2 with diabetes-related mortality to be monotonic, and positively linear across the range of concentration levels in the cohort (Figure 1).

Stratified analyses were also conducted for potential effect modifier subgroups. As shown in Table 3, the strength of the $PM_{2.5}$-diabetes mortality association (per 10 μg/m^3) was greater for obese subjects (HR=1.30; 95% CI: 1.05–1.62), compared to overweight (HR=1.13; 95% CI: 0.77–1.65) and normal or underweight subjects (HR=1.07; 95% CI: 0.83–1.40) (*p* interaction=0.04). The strength of the $PM_{2.5}$-diabetes mortality association was also greater in subjects who consumed less than 2.5 pyramid servings of fruits per day (HR=1.28; 95% CI: 1.08–1.53), compared to those who consumed greater amounts (HR=0.93; 95% CI: 0.69–1.27) (*p* interaction=0.01). For NO_2, we largely observed similar patterns to those for $PM_{2.5}$, including evidence of effect modification by level of fruit consumption effects (*p* interaction<0.01).

Discussion

In this analysis, long-term exposure to both $PM_{2.5}$ and NO_2 were found to be significantly associated with increased risk for diabetes mortality in a large, well-characterized U.S. cohort, implicating air pollution exposure as an important modifiable environmental risk factor for diabetes mortality. The strength of the relationship was robust to various model and exposure assessment specifications, and also generally consistent among the observed subgroups, although several subpopulations had significantly elevated risks, notably among those who are obese and consumed lower levels of fruits. The significant NO_2 association is suggestive of a role by traffic-related air pollution, but as tracers for other sources are not available, it was not possible to eliminate other $PM_{2.5}$ sources as possible contributors to the $PM_{2.5}$-diabetes mortality association found here.

The results here further contribute to the body of evidence from numerous investigations thus far that have reported generally positive associations between ambient air pollution exposure and diabetes. $PM_{2.5}$ exposure was related to increased diabetes prevalence in a US-wide ecologic study (Pearson et al., 2012), and the studies that have assessed long-term exposure to $PM_{2.5}$ (Chen et al., 2013; Qi et al., 2018), NO_2 (Andersen et al., 2012), and O_3 (Jerrett et al., 2017; Renzi et al., 2018) in relation to development of diabetes have reported positive findings. Several studies, however, have observed non-significant associations (e.g., Coogan et al., 2016; Eze et al, 2018) with diabetes incidence. Our findings are also consistent with similar prospective cohort studies examining the relationship between air pollution exposure and elevated diabetes mortality risk (Brook et al., 2012; Raaschou-Nielsen et al., 2013; Pope et al., 2015), although such studies did not find evidence of subgroup effect modifications.

Many studies have elucidated biologically plausible pathophysiologic mechanisms of the air pollution-diabetes relationship. Sun et al. (2009) first reported impaired insulin sensitivity, increased visceral adiposity, enhanced systemic inflammation, and impaired vascular endothelial function in mice exposed to $PM_{2.5}$. $PM_{2.5}$ exposure also resulted in impaired energy metabolism, increased inflammation in insulin responsive organs, increased brown adipose inflammation, and imbalances in circulating leptin/adiponectin levels in a genetically susceptible diabetic model (Liu et al., 2014). Recent evidence also suggests that $PM_{2.5}$ exposure induces vascular insulin resistance and inflammation triggered by a mechanism involving pulmonary oxidative stress, suggesting an intermediate step between

exposure and development of systemic insulin resistance (Haberzettle et al., 2016). Other proposed mechanisms include alternations in autonomic balance, exacerbating systemic insulin resistance via overactivity of the sympathetic nervous system (Rajagopalan and Brook, 2012), and activation of hypothalamic-pituitary-adrenal axis (Thomson et al., 2013).

Mechanistic evidence for the relationship between air pollution and diabetes is further supported by epidemiologic studies, largely cross-sectional in design, that examine diabetes precursors. In Germany, long-term exposures to PM_{10} and NO_2 increased homeostatic model assessment (HOMA-IR) levels among children (Thiering et al., 2013), and long-term exposures to PM_{10} and NO_2 were associated with elevated levels of biomarkers of insulin resistance (IR), subclinical inflammation, and adipokines (Wolf et al., 2016). Increased $PM_{2.5}$ exposure was associated with elevated fasting glucose and glycosylated hemoglobin levels in China (Liu et al., 2016), and higher annual average $PM_{2.5}$ exposure was significantly associated with higher fasting glucose, increased homeostatic model assessment (HOMA-IR), and LDL cholesterol, and lower insulin clearance in a cohort of Mexican-American adults at high risk of diabetes (Chen et al., 2016). Among elderly individuals in Korea, short-term NO_2 exposure was associated with elevated HOMA-IR levels, with increased susceptibility for participants carrying risk genotypes in the oxidative stress-related human glutathione S-transferase genes (Kim et al., 2012). In a recent longitudinal study of Los Angeles Latino children, NO_2 exposure negatively affected B-cell function, while higher NO_2 and $PM_{2.5}$ exposures were associated with a faster decline in insulin sensitivity (Alderete et al, 2017). Collectively, the cumulative evidence is generally supportive of a potentially causal association between exposure to air pollutants and diabetes risk, as found here for $PM_{2.5}$ and NO_2, and suggests that air pollution exposure could potentially increase risk of diabetes mortality events by worsening the underlying diabetes disease course or exacerbating glycemic control and insulin resistance.

Of the pollutants considered, we did not observe any statistically significant associations with O_3, in contrast to the recent extended analyses of multiple causes of mortality outcomes in the aforementioned ACS (Turner et al., 2016) and CanCHEC (Crouse et al., 2015) cohorts, which utilized more spatially coarse estimates for O_3 than the analysis conducted here, reported significant positive findings. Both animal and human exposure studies have also implicated insulin resistance in response to ozone exposure; exposure of rats to ozone have been demonstrated to induce whole-body insulin resistance and oxidative stress via production of lung mediators that induce oxidative stress and disrupting insulin-induced signaling and glucose uptake (Vella et al., 2015), while in a recent study where human subjects were exposed to acute O_3 exposures for 2 hours during 15-min on-off exercise, it was found that exposure increased stress hormones and altered peripheral lipid metabolism (Miller et al., 2016). Potential exposure misclassification due to limited exposure assessment (in using more recent years only, 2009–2011) for long-term ozone concentrations in our study, different correlation structures between the co-pollutants across the locations, population differences, and generally lower concentration levels and variability observed for ozone for those in our particular study may be driving the inconsistencies between the cohorts. Both animal and epidemiological studies of ozone exposure in relation to diabetes risk are relatively limited in number, and additional investigations of the ozone-diabetes risk association are warranted.

In our assessments of effect modification by individual risk factors, significantly elevated mortality risks associated with $PM_{2.5}$ and NO_2 were indicated among those who are obese, consistent with past epidemiologic studies that observed elevated effects of $PM_{2.5}$ in those with such conditions (Dubowsky et al., 2006; Delfino et al., 2010), suggesting that individuals under a chronic state of inflammation may be more susceptible to pro-inflammatory effects of air pollution exposure. However, we did not observe any effect modification by pre-existing comorbidities, although this may be largely due to their less reliable, self-reported nature in this cohort. We also observed effect modification by diet; significantly decreased mortality risks attributable to air pollution were found among those who consumed higher levels of fruits, potentially due to their high antioxidant content and reduction of systemic oxidative stress, and consistent with past evidence that increasing intake of vegetable and fruit consumption decreases incident diabetes risk (Carter et al., 2010). To our knowledge, there are no prior studies reporting this synergism between dietary habits and air pollution exposure on the risk of diabetes, although a few studies have observed attenuated risk of negative health impacts of air pollution from intake of nutritional supplements with anti-inflammatory properties: for example, omega-3 polyunsaturated fatty acid supplementation prevented heart rate variability decline related to $PM_{2.5}$ exposure (Romeiu et al., 2005), and supplementation with olive oil seemed to protect against the adverse vascular effects of concentrated ambient $PM_{2.5}$ exposure (Tong et al., 2015). As dietary habits and obesity are well-recognized as traditional modifiable risk factors for diabetes, our results suggest that among such individuals, modification of these risk factors (obesity and diet) may additionally reduce diabetes mortality risk attributable to air pollution exposures.

Primary strengths of this study include: the large size of the cohort, long follow-up period (17 years), exposure assessment of multiple pollutants at the census-tract level using latest prediction models, evaluation of time-varying exposures, and availability of information on detailed individual-level risk factors (including diet, BMI, smoking history, and pre-diagnosed health conditions). Our cohort characteristics and study design address some of the limitations noted in past published long-term air pollution exposure-diabetes mortality studies, such as a lack of personal-level information on smoking history or BMI. However, several potential weaknesses also exist in this study; as residence census tract and personal covariates were recorded at baseline and prospective changes in these factors could not be accounted for, except that follow-up was censored when participants moved out of the study region. In addition, we could not differentiate whether the deaths were due to type 1 or type 2 diabetes. Also, our analysis concerned diabetes as an underlying cause of death and did not consider contributory cause to cardiovascular mortality and other diseases to which diabetics are susceptible; nevertheless, the previous studies have found excess mortality whether diabetes was considered as an underlying or contributory cause (Raaschou-Nielsen et al., 2013; Pope et al., 2015). We also did not adjust for exposure to traffic noise, a correlate and potential confounder of traffic-related air pollution, which has been shown to be associated with elevated diabetes risk (Clark et al., 2018; Eze et al., 2017).

In the U.S., approximately 22 million adults (11% prevalence) have diagnosed type 2 diabetes mellitus (T2DM), with the greatest prevalence in people 65 years of age or older (Menke et al., 2015; CDC 2014). Diabetes imposes a sizable burden on U.S. society, with an

estimated total economic cost in 2012 of $245 billion (accounting for 1 in every 10 health care dollars spent), due to increased use of health resources and lost productivity (Yang et al., 2013). Given the ubiquitous nature of ambient air pollution and the risks attributable to exposure, the associated dollar costs and valuations are likely to be substantial. On the other hand, air pollution exposure is a risk factor potentially modifiable by regulatory interventions in lieu of the challenges of societal changes in the public's personal behaviors and diets. Thus, our results contribute to a growing body of evidence suggesting that policies aimed at improving air quality could provide an efficient way to ease the public health and economic burden imposed by diabetes, in the U.S. as well as the developing world. National efforts have been successful thus far in lowering population exposure to air pollutants; remarkably, from 2000 to 2012 the annual average $PM_{2.5}$ concentrations dropped 33% while NO_2 dropped 31% (EPA 2013). Nevertheless, with an aging population, continued abatement efforts and monitoring of associated health effects are needed to maintain and improve on these gains in public health. The significantly elevated mortality risks attributable to $PM_{2.5}$ and NO_2 that were observed among individuals with modifiable risk factors traditionally associated with diabetes also suggest that potential health benefits of lifestyle improvements (e.g. dietary changes) may well be larger than previously reported.

Conclusions

In this study, we found statistically elevated diabetes mortality risk associated with $PM_{2.5}$ and NO_2 in a large prospective U.S. cohort, corroborating past studies, with significant effect modification by BMI and fruit consumption levels. The public health implications our findings are likely even greater in developing nations, where the prevalence of obesity and diabetes as well as air pollution concentration levels are both rising. Additional research is necessary in such locations, where, in addition to the elevated concentration levels, the composition of pollutants (e.g., $PM_{2.5}$ constituents) and population characteristics (e.g., age distribution) likely differ markedly from industrialized countries, where the bulk of past studies have been conducted to date.

Acknowledgments

The study is supported by National Institute of Health NIEHS (1R01ES019584–01A1, R21 ES021194) and NYU NIEHS Center of Excellence (grant ES00260). C.C.L analyzed the data and wrote the manuscript. D.S, R.J, J.A, and Y.S edited the manuscript and contributed to discussion. C.G developed the O_3 dataset for California and edited the manuscript. R.B.H and G.D.T are the main investigators for the study and edited the manuscript.

References

Alderete, Tanya L. Longitudinal associations between ambient air pollution with insulin sensitivity, β-cell function, and adiposity in Los Angeles Latino children. Diabetes. 2017; 66(7):1789–1796. [PubMed: 28137791]

Andersen ZJ, Raaschou-Nielsen O, Ketzel M, Jensen SS, Hvidberg M, Loft S, Sørensen M. Diabetes incidence and long-term exposure to air pollution: A cohort study. Diabetes Care. 2012; 35(1):92–98. [PubMed: 22074722]

Brook RD, Cakmak S, Turner MC, Brook JR, Crouse DL, Peters PA, Burnett RT. Long-Term Fine Particulate Matter Exposure and Mortality From Diabetes in Canada. Diabetes Care. 2013; 36(10): 3313–3320. [PubMed: 23780947]

Brook RD, Jerrett M, Brook JR, Bard RL, Finkelstein MM. The relationship between diabetes mellitus and traffic-related air pollution. J Occup EnvironMed. 2008; 50(1):32–8.

Brook RD, Rajagopalan S, Pope CA, Brook JR, Bhatnagar A, Diez Roux AV, Kaufman JD. Particulate matter air pollution and cardiovascular disease: An update to the scientific statement from the american heart association. Circulation. 2010; 121(21):2331–2378. [PubMed: 20458016]

Carter P, Gray LJ, Troughton J, Khunti K, Davies MJ. Fruit and vegetable intake and incidence of type 2 diabetes mellitus: systematic review and meta-analysis. British Medical Journal. 2010; 341(7772):c4229. [PubMed: 20724400]

Centers for Disease Control and Prevention. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States 2015. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 2015. http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf Accessed October 22, 2015

Clark C, Sbihi H, Tamburic L, Brauer M, Frank LD, Davies HW. Association of long-term exposure to transportation noise and traffic-related air pollution with the incidence of diabetes: A prospective cohort study. Environmental Health Perspectives. 2017; 125(8):1–10. [PubMed: 27384039]

Chen Z, Salam MT, Toledo-Corral C, Watanabe RM, Xiang AH, Buchanan TA, Gilliland FD. Ambient air pollutants have adverse effects on insulin and glucose homeostasis in mexican americans. Diabetes Care. 2016; 39(4):547–554. [PubMed: 26868440]

Crouse DL, Peters PA, Hystad P, Brook JR, van Donkelaar A, Martin RV, Burnett RT. Ambient $PM_{2.5}$, O_3, and NO_2 Exposures and Associations with Mortality over 16 Years of Follow-Up in the Canadian Census Health and Environment Cohort (CanCHEC). Environmental Health Perspectives. 2015; 123(11):1180–1186. [PubMed: 26528712]

Coogan PF, White LF, Yu J, Burnett RT, Marshall JD, Seto E, Jerrett M. Long term exposure to NO_2 and diabetes incidence in the Black Women's Health Study. Environmental Research. 2016; 148(2):360–366. [PubMed: 27124624]

Delfino RJ, Tjoa T, Gillen DL, Staimer N, Polidori A, Arhami M, Longhurst J. Traffic-related air pollution and blood pressure in elderly subjects with coronary artery disease. Epidemiology (Cambridge, Mass). 2010; 21(3)

Dijkema MB, Mallant SF, Gehring U, van den HurkK, Alssema M, van Strien RT, et al. Long-term exposure to traffic-related air pollution and type 2 diabetes prevalence in a cross-sectional screening-study in the Netherlands. Environ Health. 2011; 10:76. [PubMed: 21888674]

Donath MY, Shoelson SE. Type 2 diabetes as an inflammatory disease. Nat Rev Immunol. 2011; 11:98–107. [PubMed: 21233852]

Dubowsky SD, Suh H, Schwartz JD, Coull Ba, Gold DR. Diabetes, obesity, and hypertension may enhance associations between air pollution and markers of systemic inflammation. Environmental Health Perspectives. 2006; 114(7):992–998. [PubMed: 16835049]

Eze IC, Hemkens LG, Bucher HC, Hoffmann B, Schindler C, Künzli N, Probst-Hensch NM. Association between Ambient Air Pollution and Diabetes Mellitus in Europe and North America: Systematic Review and Meta-Analysis. Environmental Health Perspectives. 2015; 123(5):381–389. [PubMed: 25625876]

Eze IC, Foraster M, Schaffner E, Vienneau D, Héritier H, Rudzik F, Probst-Hensch N. Long-term exposure to transportation noise and air pollution in relation to incident diabetes in the SAPALDIA study. International Journal of Epidemiology. 2017; 46(4):1115–1125. [PubMed: 28338949]

Franco OH, Steyerberg EW, Hu FB, Mackenbach J, Nusselder W. Associations of Diabetes Mellitus With Total Life Expectancy and Life Expectancy With and Without Cardiovascular Disease. Archives of Internal Medicine. 2007; 167(11):1145. [PubMed: 17563022]

Guariguata L, Whiting DR, Hambleton I, Beagley J, Linnenkamp U, Shaw JE. Global estimates of diabetes prevalence for 2013 and projections for 2035. Diabetes Research and Clinical Practice. 2014; 103(2):137–149. [PubMed: 24630390]

EPA. Air trends: particulate matter. U.S. Environmental Protection Agency; 2013. http://www.epa.gov/airtrends/pm.html Accessed November 21, 2016

Jerrett M, Brook R, White LF, Burnett RT, Yu J, Su J, Coogan PF. Ambient ozone and incident diabetes: A prospective analysis in a large cohort of African American women. Environment International. 2017:6–11.

Liu C, Bai Y, Xu X, Sun L, Wang A, Wang TY, Rajagopalan S. Exaggerated effects of particulate matter air pollution in genetic type II diabetes mellitus. Particle and Fibre Toxicology. 2014; 11(27):1–14. [PubMed: 24382024]

Liu C, Yang C, Zhao Y, Ma Z, Bi J, Liu Y, Chen R. Associations between long-term exposure to ambient particulate air pollution and type 2 diabetes prevalence, blood glucose and glycosylated hemoglobin levels in China. Environment International. 2016:92–93. 416–421. [PubMed: 26562560]

Menke A, Casagrande S, Geiss L, Cowie CC. Prevalence of and Trends in Diabetes Among Adults in the United States, 1988–2012. Jama. 2015; 314(10):1021–9. [PubMed: 26348752]

Miller DB, Ghio AJ, Karoly ED, Bell LN, Snow SJ, Madden MC, Kodavanti UP. Ozone Exposure Increases Circulating Stress Hormones and Lipid Metabolites in Humans. American Journal of Respiratory and Critical Care Medicine. 2016; 193(12):1382–1391. [PubMed: 26745856]

Osborn O, Olefsky JM. The cellular and signaling networks linking the immune system and metabolism in disease. Nat Med. 2012; 18:363–374. [PubMed: 22395709]

Pearson JF, Bachireddy C, Shyamprasad S, Goldfine AB, Brownstein JS. Association Between Fine Particulate Matter and Diabetes Prevalence in the U.S. Diabetes Care. 2010; 33(10):2196–2201. https://doi.org/10.2337/dc10–0698. [PubMed: 20628090]

Pope CA, Turner MC, Burnett RT, Jerrett M, Gapstur SM, Diver WR, Brook RD. Relationships Between Fine Particulate Air Pollution, Cardiometabolic Disorders, and Cardiovascular Mortality. Circulation Research. 2014; 116(1):108–115. [PubMed: 25348167]

Qiu H, Schooling CM, Sun S, Tsang H, Yang Y, Lee RSY, Tian L. Long-term exposure to fine particulate matter air pollution and type 2 diabetes mellitus in elderly: A cohort study in Hong Kong. Environment international. 2018

Raaschou-Nielsen O, Sørensen M, Ketzel M, Hertel O, Loft S, Tjønneland A, Andersen ZJ. Long-term exposure to traffic-related air pollution and diabetes-associated mortality: A cohort study. Diabetologia. 2013; 56(1):36–46. [PubMed: 22918192]

Rajagopalan S, Brook RD. Air Pollution and Type 2 Diabetes: Mechanistic Insights. Diabetes. 2012; 61(12):3037–3045. [PubMed: 23172950]

Rao X, Montresor-Lopez J, Puett R, Rajagopalan S, Brook RD. Ambient air pollution: an emerging risk factor for diabetes mellitus. Current Diabetes Reports. 2015; 15(6):603. [PubMed: 25894943]

Reedy J, Mitrou PN, Krebs-Smith SM, Wirfalt E, Flood A, Kipnis V, Subar AF. Index-based Dietary Patterns and Risk of Colorectal Cancer: The NIH-AARP Diet and Health Study. American Journal of Epidemiology. 2008; 168(1):38–48. [PubMed: 18525082]

Renzi, Matteo, et al. Air pollution and occurrence of type 2 diabetes in a large cohort study. Environment international. 2018; 112:68–76. [PubMed: 29253730]

Romieu I, Téllez-Rojo MM, Lazo M, Manzano-Patiño A, Cortez-Lugo M, Julien P, Holguin F. Omega-3 fatty acid prevents heart rate variability reductions associated with particulate matter. American Journal of Respiratory and Critical Care Medicine. 2005; 172(12):1534–1540. [PubMed: 16210665]

Thiering E, Cyrys J, Kratzsch J, Meisinger C, Hoffmann B, Berdel D, Heinrich J. Long-term exposure to traffic-related air pollution and insulin resistance in children: Results from the GINIplus and LISAplus birth cohorts. Diabetologia. 2013; 56(8):1696–1704. https://doi.org/10.1007/s00125–013–2925-x. [PubMed: 23666166]

Thomson EM, Vladisavljevic D, Mohottalage S, Kumarathasan P, Vincent R. Mapping acute systemic effects of inhaled particulate matter and ozone: multiorgan gene expression and glucocorticoid activity. Toxicol Sci. 2013; 135:169–181. [PubMed: 23805001]

Thurston GD, Ahn J, Cromar KR, Shao Y, Reynolds HR, Jerrett M, Hayes RB. Ambient Particulate Matter Air Pollution Exposure and Mortality in the NIH-AARP Diet and Health Cohort. Environmental Health Perspectives. 2015; 124(4):484–490. [PubMed: 26370657]

Tong H, Rappold AG, Caughey M, Hinderliter AL, Bassett M, Montilla T, Samet JM. Dietary supplementation with olive oil or fish oil and vascular effects of concentrated ambient particulate matter exposure in human volunteers. Environmental Health Perspectives. 2015; 123(11):1173–1179. https://doi.org/10.1289/ehp.1408988. [PubMed: 25933197]

Turner MC, Jerrett M, Pope CA III, Krewski D, Gapstur SM, Diver RW, Burnett RT. Long-Term Ozone Exposure and Mortality in a Large Prospective Study. American Journal of Respiratory and Critical Care Medicine. 2015; 64(6):897–905.

Vella RE, Pillon NJ, Zarrouki B, Croze ML, Koppe L, Guichardant M, Soulage CO. Ozone exposure triggers insulin resistance through muscle c-Jun N-terminal kinase activation. Diabetes. 2015; 64(3):1011–1024. [PubMed: 25277399]

Wang B, Xu D, Jing Z, Liu D, Yan S, Wang Y. Effect of long-term exposure to air pollution on type 2 diabetes mellitus risk: a systemic review and meta-analysis of cohort studies. European Journal of Endocrinology / European Federation of Endocrine Societies. 2014; 171(5):R173–82.

Wolf K, Popp A, Schneider A, Breitner S, Hampel R, Rathmann W, Peters A. Association Between Long-Term Exposure to Air Pollution and Biomarkers Related to Insulin Resistance, Subclinical Inflammation and Adipokines. Diabetes. 2016 Nov.65

Yang W, Dall TM, Halder P, Gallo P, Kowal SL, Hogan PF, Petersen M. Economic costs of diabetes in the U.S. in 2012. Diabetes Care. 2013; 36(4):1033–1046. [PubMed: 23468086]

U.S. Environmental Protection Agency. Fused air quality surfaces using downscaling tool for predicting daily air pollution [accessed 2016 Nov 2]. Available from: http://www.epa.gov/air-research/fused-air-quality-surfaces-using-downscaling-tool-predicting-daily-air-pollution

Highlights

- The NIH-AARP Diet and Health Study, a prospective cohort with more than a half million participants and a follow-up period of 17 years, was linked with latest prediction models for $PM_{2.5}$, NO_2, and O_3
- Long-term exposures to PM2.5 and NO2 are significantly associated with elevated diabetes mortality risk
- The associations were significantly modified by BMI and total fruit consumption

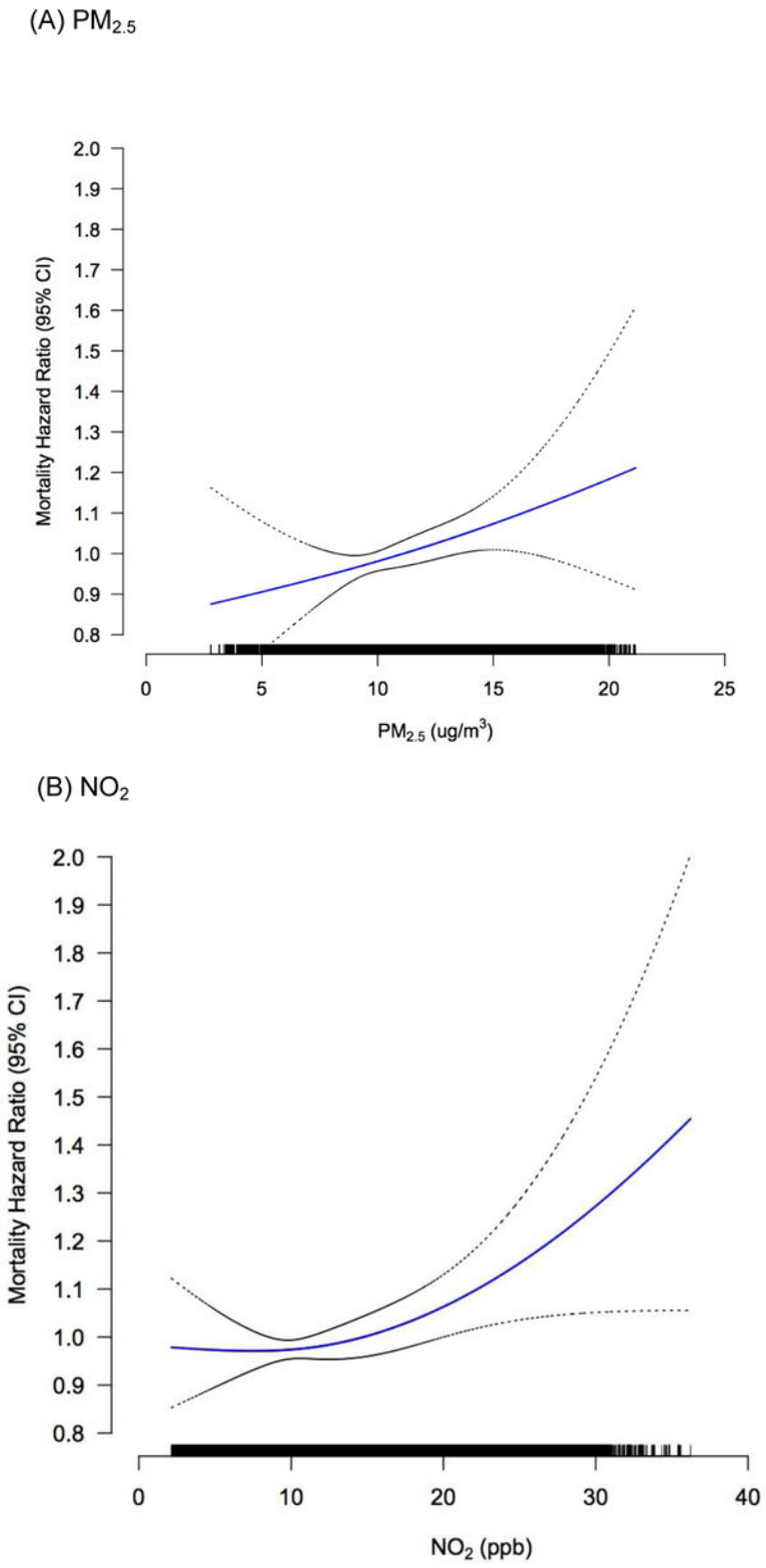

Figure 1.

Concentration-response curves (solid lines) and 95% CIs (dashed lines) relative to the effect at mean concentration, based on natural spline models with 2 degrees of freedom, for

standard Cox models adjusted for individual-level and contextual covariates. The tick marks on the x-axis identify the distribution of observations according to air pollutant concentrations.

Table 1

Descriptive Statistics for the NIH-AARP Cohort

	N (%)	$PM_{2.5}$	NO_2	O_3
Age				
>=65	202,135 (36.8)	10.9 (2.8)	12.0 (5.6)	39.5 (4.6)
<65	347,600 (63.2)	11.1 (2.7)	12.3 (5.5)	39.5 (4.6)
Sex				
Male	324,654 (59.1)	11.0 (2.7)	12.0 (5.4)	39.5 (4.5)
Female	225,081 (40.9)	11.1 (2.8)	12.4 (5.6)	39.4 (4.7)
Race				
White	501,428 (91.2)	10.9 (2.7)	11.9 (5.4)	39.6 (4.5)
Black	21,576 (3.9)	12.3 (2.4)	15.3 (5.9)	38.2 (4.4)
Hispanic	10,228 (1.9)	11.4 (3.5)	14.8 (7.0)	38.8 (5.4)
Asian, Pacific Islander, or American Indian/Alaskan Native	8,878 (1.6)	11.9 (3.0)	15.7 (6.5)	38.0 (5.7)
Education				
Less than high school	33,311 (6.1)	11.0 (2.7)	11.9 (5.7)	39.5 (4.2)
Some high school	107,547 (19.6)	11.1 (2.6)	12.0 (5.4)	39.4 (4.1)
12 years or high school completed	53,834 (9.8)	10.9 (2.7)	11.6 (5.4)	39.6 (4.3)
post-high school or some college	127,430 (23.2)	11.0 (2.9)	12.3 (5.7)	39.7 (4.9)
college and post graduate	211,024 (38.4)	11.1 (2.7)	12.5 (5.4)	39.3 (4.7)
BMI				
<18.5	4,661 (0.8)	11.0 (2.7)	12.0 (5.7)	39.7 (4.7)
18.5–25	184,722 (33.6)	10.9 (2.7)	12.2 (5.6)	39.4 (4.7)
25–30	227,220 (41.3)	10.9 (2.7)	12.1 (5.5)	39.5 (4.6)
30–35	84,420 (15.4)	11.1 (2.7)	12.2 (5.5)	39.5 (4.5)
>35	33,894 (6.2)	11.2 (2.7)	12.6 (5.6)	39.3 (4.5)
Marital				
Married	374,223 (68.1)	10.9 (2.7)	11.8 (5.4)	39.7 (4.5)
	144,330	11.1	12.7	39.2
	(26.2)	(2.8)	(5.7)	(4.7)
Other	26,636 (4.8)	11.6 (2.7)	14.2 (6.1)	38.3 (4.9)
Smoking				
Never	191,283 (34.8)	11.2 (2.7)	12.4 (5.5)	39.5 (4.6)
Less than a pack, 1+ year quit	146,124 (26.6)	11.0 (2.7)	12.2 (5.5)	39.4 (4.6)
More than a pack, 1+ year quit	115,543 (21.0)	10.8 (2.7)	11.8 (5.5)	39.6 (4.5)
Less than a pack, stopped less than a year/current	48,927 (8.9)	11.1 (2.7)	12.4 (5.7)	39.4 (4.6)
More than a pack, stopped less than a year or		10.9	11.7	39.6
current	26,858 (4.9)	(2.8)	(5.6)	(4.5)
Alcohol Drinks Per Day				
0	136,107 (24.8)	11.2 (2.7)	11.9 (5.7)	39.9 (4.6)
<1	287,101 (52.2)	11.1 (2.7)	12.5 (5.5)	39.5 (4.6)
1–2	62,140 (11.3)	10.8 (2.7)	12.1 (5.4)	39.3 (4.8)

	N (%)	$PM_{2.5}$	NO_2	O_3
2–3	20,778 (3.8)	10.7 (2.7)	12.1 (5.5)	39.2 (4.9)
3–5	20,078 (3.7)	10.7 (2.7)	11.7 (5.4)	39.5 (4.7)
5+	23,531 (4.3)	10.6 (2.8)	11.7 (5.6)	39.4 (4.7)
Vegetable Consumption, Pyramid Servings Per Day				
1st Quartile	136,176 (24.8)	11.0 (2.7)	12.0 (5.6)	39.5 (4.4)
2nd Quartile	137,359 (24.9)	11.0 (2.7)	12.0 (5.6)	39.5 (4.5)
3rd Quartile	137,870 (25.1)	11.0 (2.7)	12.0 (5.6)	39.5 (4.6)
4th Quartile	138,330 (25.2)	11.0 (2.7)	12.6 (5.6)	39.4 (4.7)
Fruit Consumption, Pyramid Servings Per Day				
1st Quartile	136,632 (24.9)	10.9 (2.7)	11.9 (5.5)	39.5 (4.2)
2nd Quartile	137,435 (25.0)	11.0 (2.7)	12.0 (5.4)	39.5 (4.3)
3rd Quartile	137,745 (25.0)	11.0 (2.7)	12.2 (5.5)	39.4 (4.4)
4th Quartile	137,923 (25.1)	11.1 (2.8)	12.7 (5.6)	39.3 (4.5)
Fat Consumption, Grams Per Day				
1st Quartile	138,972 (25.3)	11.0 (2.7)	12.5 (5.6)	39.2 (4.7)
2nd Quartile	138,327 (25.2)	11.0 (2.7)	12.3 (5.5)	39.4 (4.6)
3rd Quartile	137,087 (24.9)	11.0 (2.7)	12.1 (5.5)	39.6 (4.5)
4th Quartile	135,329 (24.6)	11.0 (2.7)	12.0 (5.5	39.7 (4.5)

Table 2

Diabetes Mortality HRs (per 10 μg/m^3 for $PM_{2.5}$; per 10 ppb for NO_2 and O_3) by model specifications

		$PM_{2.5}$		NO_2		O_3	
		HR	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
Model 1	Age, Sex, Location Only	1.59	1.36–1.86	1.25	1.16–1.35	1.01	0.93–1.09
Model 2	Full Model	1.19	1.03–1.39	1.09	1.01–1.18	0.96	0.88–1.04
Model 3	M2 + Comorbidity	1.22	1.05–1.42	1.10	1.02–1.18	0.96	0.88–1.04
Model 4	M2 + Random Effects	1.23	1.03–1.47	1.10	1.01–1.19	0.93	0.84–1.03
Model 5	Without censoring movers	1.21	1.03–1.43	1.09	1.01–1.18	0.96	0.88–1.04
Model 6	Time-varying Exposure	1.18	1.03–1.36				

*Adjusted for age, sex, and location as strata; and race, BMI, education, smoking, and marriage at individual-level; and median income and % with high school education at census-tract level

Table 3

Diabetes Mortality HRs by category of selected risk factors

		$PM_{2.5}$			NO_2		
		HR	**95% CI**	**p-val**	**HR**	**95% CI**	**p-val**
Age	>65	1.28	1.04–1.58	0.12	1.15	1.04–1.27	0.57
	<65	1.09	0.87–1.38		1.04	0.93–1.17	
Sex	Female	1.03	0.79–1.34	0.37	0.96	0.84–1.10	0.07
	Male	1.28	1.07–1.55		1.17	1.06–1.29	
Race	White	1.10	0.93–1.30	0.09	1.10	1.01–1.20	0.96
	Other	1.61	1.04–2.49		0.83	0.60–1.15	
BMI	Obese	1.30	1.05–1.62	0.04	1.08	0.97–1.20	0.51
	Overweight	1.13	0.77–1.65		1.13	0.99–1.29	
	Normal	1.07	0.83–1.40		1.08	0.89–1.30	
Smoke	Ever	1.22	1.02–1.47	0.37	1.10	1.00–1.21	0.91
	Never	1.19	0.90–1.58		1.10	1.01–1.20	
Vegetable	>2.5 pyramid servings/day	1.38	1.05–1.82	0.93	1.13	0.99–1.30	0.79
	<=2.5 pyramid servings/day	1.11	0.93–1.34		1.11	1.02–1.20	
Fruits	>2.5 pyramid servings/day	0.93	0.69–1.27	0.01	0.93	0.79–1.09	<0.01
	<=2.5 pyramid servings/day	1.28	1.08–1.53		1.17	1.08–1.27	
Fat	>100 g/day	1.13	0.83–1.54	0.89	1.13	0.96–1.32	0.21
	<=100 g/day	1.20	1.01–1.43		1.07	0.99–1.17	
Pre-Heart	Yes	1.23	0.94–1.61	0.72	1.10	0.96–1.26	0.55
	No	1.21	1.00–1.45		1.11	1.01–1.22	
Pre-Diabetes	Yes	1.14	0.95–1.37	0.77	1.07	0.98–1.17	0.82
	No	1.23	0.92–1.64		1.07	0.92–1.23	

*Adjusted for age, sex, and location as strata; and race, BMI, education, smoking, and marriage at individual-level; and median income and % with high school education at census-tract level