Environment International 111 (2018) 14–22

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Ambient air pollution, adipokines, and glucose homeostasis: The Framingham Heart Study

Wenyuan Li[a,b], Kirsten S. Dorans[a,b,c], Elissa H. Wilker[a,b], Mary B. Rice[d], Itai Kloog[e], Joel D. Schwartz[a,f], Petros Koutrakis[f], Brent A. Coull[g], Diane R. Gold[f,h], James B. Meigs[i], Caroline S. Fox[j,k], Murray A. Mittleman[a,b,*]

[a] Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, United States
[b] Cardiovascular Epidemiology Research Unit, Division of Cardiology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, United States
[c] Department of Epidemiology, Tulane University School of Public Health and Tropical Medicine, New Orleans, LA, United States
[d] Division of Pulmonary, Critical Care and Sleep Medicine, Beth Israel Deaconess Medical Center, Boston, MA, United States
[e] Department of Geography and Environmental Development, Ben-Gurion University of the Negev, Beer Sheva, Israel
[f] Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, MA, United States
[g] Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA, United States
[h] Channing Division of Network Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, United States
[i] Department of Medicine, Harvard Medical School and Division of General Internal Medicine, Massachusetts General Hospital, Boston, MA, United States
[j] National Heart, Lung, and Blood Institute's Framingham Heart Study, Framingham, MA, United States
[k] Division of Intramural Research, National Heart, Lung, and Blood Institute, Bethesda, MD, United States

ARTICLE INFO

Keywords:
Air pollution
Adipokines
Glucose homeostasis
Epidemiology
Particulate matter

ABSTRACT

Objective: To examine associations of proximity to major roadways, sustained exposure to fine particulate matter ($PM_{2.5}$), and acute exposure to ambient air pollutants with adipokines and measures of glucose homeostasis among participants living in the northeastern United States.

Methods: We included 5958 participants from the Framingham Offspring cohort examination cycle 7 (1998–2001) and 8 (2005–2008) and Third Generation cohort examination cycle 1 (2002–2005) and 2 (2008–2011), who did not have type 2 diabetes at the time of examination visit. We calculated 2003 annual average $PM_{2.5}$ at participants' home address, residential distance to the nearest major roadway, and daily $PM_{2.5}$, black carbon (BC), sulfate, nitrogen oxides (NO_x), and ozone concentrations. We used linear mixed effects models for fasting glucose, insulin, and homeostasis model assessment of insulin resistance (HOMA-IR) which were measured up to twice, and used linear regression models for adiponectin, resistin, leptin, and hemoglobin A1c (HbA1c) which were measured only once, adjusting for demographics, socioeconomic position, lifestyle, time, and seasonality.

Results: The mean age was 51 years and 55% were women. Participants who lived 64 m (25th percentile) from a major roadway had 0.28% (95% CI: 0.05%, 0.51%) higher fasting plasma glucose than participants who lived 413 m (75th percentile) away, and the association appeared to be driven by participants who lived within 50 m from a major roadway. Higher exposures to 3- to 7-day moving averages of BC and NO_x were associated with higher glucose whereas the associations for ozone were negative. The associations otherwise were generally null and did not differ by median age, sex, educational attainment, obesity status, or prediabetes status.

Conclusions: Living closer to a major roadway or acute exposure to traffic-related air pollutants were associated with dysregulated glucose homeostasis but not with adipokines among participants from the Framingham Offspring and Third Generation cohorts.

1. Introduction

Higher exposure to ambient air pollution has been associated with systemic inflammation and oxidative stress, which in turn are potential underlying mechanisms for particle-induced impaired glucose tolerance and insulin resistance (Kodavanti, 2015; Piya et al., 2013; Rajagopalan

Abbreviations: BC, black carbon; HbA1c, hemoglobin A1c; HOMA-IR, homeostasis model assessment of insulin resistance; NO_x, nitrogen oxides; O_3, ozone; $PM_{2.5}$, fine particulate matter; SO_4^{2-}, sulfate

* Corresponding author at: Harvard T.H. Chan School of Public Health, 677 Huntington Ave, Suite 505, Boston, MA 02215, United States.
E-mail address: mmittlem@hsph.harvard.edu (M.A. Mittleman).

https://doi.org/10.1016/j.envint.2017.11.010
Received 29 July 2017; Received in revised form 13 November 2017; Accepted 13 November 2017

and Brook, 2012). Elevated air pollution may also be associated with dysregulated release of a series of peptides or proteins (adipokines) secreted by adipose tissue that regulate carbohydrate metabolism (Piya et al., 2013; Rajagopalan and Brook, 2012). In some (Sun et al., 2009; Xu et al., 2011; Xu et al., 2010) but not all (Haberzettl et al., 2016) controlled animal studies, mice exposed to ambient fine particulate matter ($PM_{2.5}$; particles with aerodynamic diameter ≤ 2.5 μm) were found to have higher levels of resistin, glucose, and insulin, but lower levels of adiponectin and leptin than mice exposed to filtered air. A number of studies have found positive associations between ambient air pollution and prevalence of type 2 diabetes or impaired glucose tolerance in general populations (Eze et al., 2015; Park and Wang, 2014) or women during pregnancy (Fleisch et al., 2014; Fleisch et al., 2016; Lu et al., 2017). However, only a few large-scale studies examined associations between air pollution and blood levels of fasting plasma glucose, insulin, hemoglobin A1c (HbA1c), or adipokines, which are important biomarkers of glucose homeostasis, in communities where air pollution levels are relatively low (Cai et al., 2017; Z. Chen et al., 2016; Honda et al., 2017; O'Donovan et al., 2017; Sade et al., 2016; Sade et al., 2015; Ward-Caviness et al., 2015; Wolf et al., 2016); and many previous human studies have been limited by small sample size, narrow age range, or high levels of ambient air pollution (Brook et al., 2016; Brook et al., 2013; L. Chen et al., 2016; Chuang et al., 2010; Chuang et al., 2011; Kim and Hong, 2012; Liu et al., 2016; Peng et al., 2016; Teichert et al., 2013; Wang et al., 2014).

We studied the associations of annual average $PM_{2.5}$ concentration and residential proximity to the nearest major roadway with blood concentrations of adipokines (adiponectin, resistin, and leptin), fasting glucose, insulin, and HbA1c among participants from the Framingham Offspring and Third Generation cohorts. We calculated homeostasis model assessment of insulin resistance (HOMA-IR), an index that has been used to quantitatively assess insulin resistance and β-cell function (Matthews et al., 1985). We also examined the associations for short-term exposure to $PM_{2.5}$, black carbon (BC), sulfate (SO_4^{2-}), nitrogen oxides (NO_x), and ozone (O_3). Our study extends the scope of current research on the associations between ambient air pollution and measures related to glucose homeostasis by providing findings from a large sample of generally healthy middle-aged adults who lived in the Northeastern U.S., a region with relatively low levels of air pollution.

2. Methods

2.1. Study sample

We included 6574 participants from the Framingham Offspring cohort examination 7 (1998–2001), examination 8 (2005–2008), Third Generation cohort examination 1 (2002–2005), or examination 2 (2008–2011). Detailed selection criteria and design of the two cohorts have been described previously (Kannel et al., 1979; Splansky et al., 2007). To be eligible, participants had to reside in the Northeastern U.S. at the time of examination visits, fasted overnight for at least 8 h, and had at least one measurement of adiponectin, resistin, leptin, fasting glucose, insulin, or HbA1c. Of the 11,638 observations contributed by these 6574 participants, we first excluded 1002 (9%) observations contributed by participants who had diabetes at the time of the examination visits (defined as fasting glucose ≥ 126 mg/dl (American Diabetes Association, 2014) or receiving treatment), and then 247 (2%) observations that had missing data on pack years of smoking, alcohol intake, or body mass index, and leaving a total of 10,389 observations from 5958 participants. Physical examinations were performed at the time of study visits following standardized protocols. Demographics, medication history, smoking history, and alcohol intake were collected using standard questionnaires. Census tract-level socio-economic position data were from the U.S. 2000 census. All participants provided written informed consent, and Institutional Review Boards at Beth Israel Deaconess Medical Center, Massachusetts General Hospital, and Boston University Medical Center approved the study.

2.2. Biomarker assessment

Blood samples were collected after an overnight fast. Fresh plasma samples were used for fasting glucose assessment, and blood samples for other biomarkers were stored at −80 °C until assay. Detailed assessment methods have been described elsewhere (Lee et al., 2016; McManus et al., 2012; Meigs et al., 2002). Briefly, fasting glucose was measured by the hexokinase method twice in each cohort; HbA1c was measured by turbidimetric immunoassay in Offspring cohort examination 8 and Third Generation cohort examination 2; insulin was evaluated by commercially available enzyme-linked immunosorbent assay kits from Linco Research (St. Charles, MO) in Third Generation cohort examination 1, and Roche reagents (R&D Systems, Minneapolis, MN) in Offspring cohort examination 8 and Third Generation cohort examination 2. Adiponectin, leptin, and resistin were measured using enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN): adiponectin was measured in Offspring cohort examination 7 and Third Generation cohort examination 1; resistin was measured in Offspring cohort examination 7; and leptin was measured in Third Generation cohort examination 1. HOMA-IR was calculated as [fasting glucose (mmol/l) × insulin (μU/ml)] / 22.5 (Matthews et al., 1985).

The average intra-assay coefficient of variation (CV) was 2%–3% for fasting glucose and insulin, 4% for adiponectin, 9% for resistin, and 3% for leptin (Demissie et al., 2006; Ho et al., 2017; Thanassoulis et al., 2012). Additional information can be found at https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000007.v29.p10.

2.3. Annual average concentration of $PM_{2.5}$

We geocoded participants' residential addresses using ArcGIS software and used a hybrid spatial-temporal model to estimate $PM_{2.5}$ concentration at residential address (Kloog et al., 2014). The model uses satellite-based aerosol optical depth, a measure of particle abundance in the atmospheric column, to estimate daily $PM_{2.5}$ at a resolution of 1×1 km^2. It improved $PM_{2.5}$ estimation by utilizing data from spatial predictors (such as population density and traffic density) and temporal predictors (such as meteorological parameters), as described in detail in our previous work (Kloog et al., 2014; Li et al., 2016).

Briefly, we first regressed ground $PM_{2.5}$ concentration against satellite-based aerosol optical depth, adjusting for land use terms and meteorological predictors. We addressed non-random missingness of daily aerosol optical depth data by using inverse probability weighting. When compared to observed values, predictions from this model have an excellent mean out-of-sample R^2 of 0.88 and little bias (slope = 0.99) (Kloog et al., 2014). Second, we predicted $PM_{2.5}$ concentration in 1×1 km^2 if the grid cells only had aerosol optical depth measurement. Third, if the grid cells did not have aerosol optical depth measurement, we used a generalized additive model with spatial smoothing, the mean of nearby monitors, and a cell-specific random intercept to impute $PM_{2.5}$ estimates (overall mean out-of-sample $R^2 = 0.88$) (Kloog et al., 2014). Last, we took the differences between monitor-assessed $PM_{2.5}$ and predicted $PM_{2.5}$ for each cell and regressed them against monitor-specific spatial and temporal variables to generate localized daily predictions. We then added this localized daily prediction to the grid cell prediction to generate an address-specific $PM_{2.5}$ prediction. We used the 2003 annual average $PM_{2.5}$ concentration for all participants (Dorans et al., 2016; Li et al., 2016; Wilker et al., 2015).

2.4. Residential proximity to the nearest major roadway

In the current study, we used distance to a major roadway as a surrogate measure for traffic-related air pollution. Based on the