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Ambient Air Pollution, Adipokines, and Glucose Homeostasis: The Framingham Heart Study

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Conflicts of interests

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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 5,958 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 hemoglobin A1c which were measured up to twice, and used linear regression models for adiponectin, resistin, and leptin 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 (25^{th} percentile) from a major roadway had 0.28% (95% CI: 0.05%, 0.51%) higher fasting plasma glucose than participants who lived 413 m (75^{th} 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.

Keywords

Air Pollution; Adipokines; Glucose Homeostasis; Epidemiology; Particulate Matter

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 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; Chen et al. 2016b; 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; Chen et al. 2016a; 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 6,574 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 hours, and had at least one measurement of adiponectin, resistin, leptin, fasting glucose, insulin, or HbA1c. Of the 11,638 observations contributed by these 6,574 participants, we first excluded 1,002 (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 5,958 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 geocoded residential addresses, we estimated the distance to the nearest major roadway, which is defined as primary highways with limited-access, primary roads without limited-access, or secondary and connecting roads. The addresses were collected and updated at each examination. For participants who lived far from major roadway, traffic on major roadways is unlikely a primary source of their ambient air pollution exposure, and the air pollution exposure profiles might be different compared to other participants, Thus, we restricted distance analysis to 5,403 participants who lived <1,000 m from the nearest major roadway (Dorans et al. 2016; Li et al. 2017b; Li et al. 2016; Wilker et al. 2015). We later included participants who lived ≥1,000 m from the nearest major roadway in a sensitivity analysis.

2.5 Short-term exposure assessment

We obtained central-site hourly measures of $PM_{2.5}$, BC, and SO_4^{2-} from the Harvard Supersite air pollution monitoring station located on the rooftop of the Francis A. Countway Library of Medicine (5 stories above ground and 50 m from the nearest street) in Boston, Massachusetts. We used a tapered element oscillating microbalance to measure $PM_{2.5}$ and an aethalometer to measure BC. We calculated daily SO_4^{2-} from elemental sulfur measured by X-Ray Fluorescence analysis of the $PM_{2.5}$ filter samples, and used a SO_4^{2-} analyzer on days when X-Ray Fluorescence measurements were unavailable. Detailed measurement methods have been described previously (Kang et al. 2010). Ambient levels of NO_x and O_3 were computed by averaging data collected from local state monitors (three for NO_x and two for O_3) within the Greater Boston area (Ljungman et al. 2014; Mehta et al. 2014) (Figure 1). Temperature and relative humidity were measured at the Boston Logan International Airport Weather Station, 12 km from the central-site (Ljungman et al. 2014). We included 4,116 participants who lived within 50 km from the Supersite for short-term exposure analyses (Li et al. 2017a; Ljungman et al. 2014; Rice et al. 2013).

2.6 Statistical methods

We used linear mixed effects models with participant-specific random intercepts for fasting glucose, insulin, and HOMA-IR to account for repeated measures, and linear regression models for adiponectin, resistin, leptin, and HbA1c, which were measured once. All outcomes were loge-transformed and modeled as continuous variables. Model assumptions were assessed by residual plots and the residuals approximate a normal distribution. We adjusted for age (centered at the mean, age and age^2); sex; body mass index; smoking status (current, former, or never smoker); pack years; alcohol intake (drinks/week; standardized to 0.5 oz (15 ml) alcohol/drink) (Elias et al. 1999); educational attainment (high school or less, some college, and college graduate); physical activity (in tertiles (Kannel and Sorlie 1979)); usual occupation (Li et al. 2016; Loucks et al. 2009); census tract level median household income, median value of owner occupied housing units, and population density; and date of examination visit. Seasonality was accounted for with sine and cosine terms. We added an

exam identifier to models for glucose, insulin, adiponectin, HbA1c, and HOMA-IR. Because the number of participants with missing data on educational attainment, physical activity, or smoking status were small (35 (0.34%) for smoking status, 56 (0.54%) for education status, and 126 (1.21%) for physical activity index), we created missing indicators (binary dummy variable, 1 = if the observation was missing; 0 = if the observation was non-missing) and included in the statistical analyses.

To account for the dispersion pattern of air pollution with increasing distance from a major roadway (Zhou and Levy 2007), we loge transformed distance to the nearest major roadway. We also analyzed the data using categorized distance to a major roadway (<50 m, 50 to <100 m, 100 to <200 m, 200 to <400 m, and 400 to <1,000 m).

We examined the associations for 1- to 7-day moving averages of $PM_{2.5}$, BC, SO_4^{2-}, NO_x, and O_3 using similar statistical models as in the longer-term exposure analyses, and additionally adjusted for 1-day moving average of temperature and relative humidity, and day of the week of the examination date. The 1-day moving average was calculated as the average value from 9:00 am on the day before examination visit to 9:00 am on the day of examination visit (i.e. lag 0). The 2-day moving average was calculated as the mean of lag 0 and lag 1. If missing days were more than 25% of the days for a moving average, we assigned missing to that moving average. Because HbA1c is a measure that reflects average glucose levels over a period of up to 3 months (International Expert Committee 2009), we did not include HbA1c in this analysis.

Parameter estimates were scaled by a factor that approximated the interquartile ranges: 1.5 $\mu g/m^3$ for annual $PM_{2.5}$, −1.9 for distance analysis, which corresponds to contrasting participants who lived 64 m (25^{th} percentile) from a major roadway to those who lived 413 m (75^{th} percentile) away, 5 $\mu g/m^3$ for $PM_{2.5}$, 0.5 $\mu g/m^3$ for BC, 2 $\mu g/m^3$ for SO_4^{2-}, 20 ppb for NO_x, and 15 ppb for O_3.

2.7 Sensitivity analyses

We examined whether associations for annual average $PM_{2.5}$ or roadway proximity differed by median age, sex, educational attainment (high school or less vs. college or higher), obesity status (BMI>30 kg/m^2), or prediabetes status (fasting glucose≥100 mg/dl but <126 mg/dl) by adding interaction terms. Because not all biomarkers were measured across both cohorts, we calculated median age of participants included for each biomarker. We conducted minimally adjusted analyses that only accounted for age, sex, and date of examination. We used 2003–2005 average $PM_{2.5}$ concentrations to assess the impact of using 2003 as the index year, included participants who lived ≥1,000 m from the nearest major roadway to examine the influence of excluding them, and examined the associations for 2003 annual average $PM_{2.5}$ only among participants who lived <1,000 m from the nearest major roadway. We additionally examined the associations within current U.S. Environmental Protection Agency national annual $PM_{2.5}$ standard by excluding observations that had 2003 annual average $PM_{2.5}$ >12 $\mu g/m^3$ (N=1,213) in longer-term exposure analysis, and by excluding observations that had daily $PM_{2.5}$ >35 $\mu g/m^3$ (N=182) in any of the 7 days prior to the examination date for short-term exposure analyses. Furthermore, we assessed whether results were different after restricting short-term exposure analyses to those who

lived within 40 km from the central monitor. Moreover, because NO_x and O_3 were moderately and negatively correlated (r=−0.54, p<0.0001), we conducted a post-hoc sensitivity analysis where we included both NO_x and O_3 in the same model. We restricted the annual $PM_{2.5}$ analyses and proximity analyses to participants who lived within 50 km from the central site; for annual $PM_{2.5}$ analyses, we further adjusted for the difference between the 1-day moving average of central site measured $PM_{2.5}$ and the model-based 2003 annual average $PM_{2.5}$ ($\Delta PM_{2.5}$). Because a different assay was used for insulin in the Third Generation cohort examination 1, we conducted a sensitivity analysis for insulin by excluding participants from examination 1. Last, we conducted analyses only among participants who had two measures for fasting glucose, insulin, and HOMA-IR.

Scaled estimates of the associations (% differences) were reported with 95% confidence intervals (CIs), and we focused on describing the association patterns between air pollutants and the biomarkers. The "% difference" was calculated as "(exp(scaled β) −1)×100%". Analyses were performed using PROC GENMOD and PROC MIXED in SAS 9.4 (SAS Institute, Inc., Cary, NC). Figures were plotted using Stata 13 (StataCorp LP, College Station, TX).

3. Results

Table 1 shows the characteristics of the study sample. The model-based mean 2003 annual average $PM_{2.5}$ concentration at the participant's residential address was 10.6 $\mu g/m^3$ (standard deviation: 1.4 $\mu g/m^3$). Meanwhile, the 2003 annual average $PM_{2.5}$ measured at central site was 11.1 $\mu g/m^3$ (standard deviation: 5.5 $\mu g/m^3$). About one third of the observations were from participants who lived within 100 m from a major roadway. Figure 1 shows the distribution the Framingham Heart Study participants in the Northeastern region, the 2003 annual average $PM_{2.5}$ concentrations, and the locations of the local monitors. Figure 2 shows the distributions of 2003 annual average $PM_{2.5}$ concentration and distance to major roadways. We included box-plots of measured biomarkers in Supplemental Figure A.

3.1 Annual average $PM_{2.5}$ and residential distance to a major roadway

The number of participants and observations in each analysis is listed in Supplemental Table A. Compared to participants who lived 413 m (75^{th} percentile) from a major roadway, participants who lived 64 m (25^{th} percentile) had 0.28% (95% CI: 0.05%, 0.51%) higher glucose, and the association appeared to be driven by the positive association among participants who lived within 50 m from the nearest major roadway (Table 2). There were no clear associations with other biomarkers.

3.2 Short-term air pollution exposure

Characteristics of the 1-day moving averages of each air pollutant measured at the Harvard Supersite and the Spearman correlation coefficients are shown in Supplemental Table B. As shown in Figure 3A, both BC and NO_x were positively associated with fasting glucose across several moving averages, and stronger associations were seen for longer moving averages. We also found positive associations of the 7-day moving average of $PM_{2.5}$ with adiponectin and of SO_4^{2-} with resistin. However, associations between O_3 and glucose were

negative across all moving averages, and so was the 7-day moving average of NO_x with adiponectin. We did not find consistent association patterns for other biomarkers. Plots with 1- to 7-day moving averages of each pollutant are included as Supplemental Figure B.

3.3 Sensitivity analyses

The associations of 2003 annual average $PM_{2.5}$ concentration and proximity to major roadways with measured biomarkers did not differ by median age, sex, educational attainment, obesity status, or prediabetes status (Supplemental Tables C and D). Using 2003–2005 annual average $PM_{2.5}$ concentration, including participants who lived ≥1,000 m from major roadways, restricting analyses to participants with both $PM_{2.5}$ and proximity measures, or excluding observations with 2003 annual average $PM_{2.5}$>12 μg/m^3 did not change our results materially (Supplemental Table E). However, if we restrict the analyses to participants who lived within 50 km from the central site, living closer to a major roadway was no longer associated with higher fasting plasma glucose, but with higher leptin levels, and further adjusting for Δ$PM_{2.5}$ did not change the results substantially (Supplemental Table F). Excluding participants from the Third Generation cohort examination 1 did not alter our results for insulin materially. For short-term exposure analyses, restricting to participants who lived within 40 km from the Harvard Supersite or excluding observations that had days with $PM_{2.5}$>35 μg/m^3 in any of the seven days before exam visit did not materially alter our results (Supplemental Figures C and D). The associations of O_3 with glucose were attenuated but remained negative after adjusting for NO_x (Supplemental Figure E). Restricting analyses to participants with two measurements yielded wider 95% CIs but did not alter our results materially (Supplemental Table G and Supplemental Figure F).

4. Discussion

In this large cohort of adults without diabetes, we found positive associations between living closer to a major roadway and higher levels of fasting glucose, after adjusting for demographics, individual- and area-level socioeconomic position, lifestyle factors, time, and seasonality. We further showed that short-term exposure to higher levels of BC and NO_x, both correlates of local traffic-related pollution, were associated with higher levels of fasting glucose.

Reports from controlled animal studies on the associations of exposure to $PM_{2.5}$ and biomarkers of glucose homeostasis or adipokines are mixed (Haberzettl et al. 2016; Sun et al. 2009; Xu et al. 2011; Xu et al. 2010). For example, in Xu et al., mice in the exposed group had higher levels of glucose and HOMA-IR than those in filtered air group, however, the differences were observed among mice fed with normal diet and were very small among those fed with highfat chow (Xu et al. 2010). In Haberzettl et al., among mice fed with high fat chow, there was no difference in levels of glucose, leptin, adiponectin, and resistin between exposed and filtered air group, however, the levels of insulin and HOMA-IR were higher among those exposed (Haberzettl et al. 2016).

A few human studies examined the associations for glucose and insulin together in the same study sample, however, the results were not always in the same direction (Brook et al. 2016; Brook et al. 2013; Chen et al. 2016b; Kim and Hong 2012; Ward-Caviness et al. 2015; Wolf

et al. 2016). Generally, in short-term exposure studies, exposure to air pollution was associated with higher levels of glucose, insulin, or HOMA-IR (Brook et al. 2013; Chen et al. 2016b), whereas in longer-term exposure studies, most of the positive associations were found with glucose but not insulin or HOMA-IR (Chen et al. 2016b; Ward-Caviness et al. 2015; Wolf et al. 2016), however, the positive associations with glucose may be mainly contributed by participants with diabetes or prediabetes (Wolf et al. 2016). In some short-term exposure studies, the associations with glucose or insulin were in different directions across lagged days (Brook et al. 2016; Kim and Hong 2012). In the KORA (Cooperative Health Research in the Region Augsburg, Germany) study, Wolf *et al.* found positive associations of annual average $PM_{2.5}$ with fasting glucose among 2,944 participants but not with insulin, and the associations was attenuated to null after restricting to participants without type 2 diabetes or prediabetes (Wolf et al. 2016). Additionally, annual average NO_x was positively associated with glucose and insulin among participants without type 2 diabetes or prediabetes (Wolf et al. 2016). Ward-Caviness *et al.* studied the associations of distance to roadways with fasting glucose and HOMA-IR in North Carolina and found positive associations of living closer to major roadways with levels of fasting glucose but not with HOMA-IR among 2,124 individuals undergoing cardiac catheterization (Ward-Caviness et al. 2015).

In summary, findings from both controlled animal studies and human studies have three implications. First, even though acute exposures may be associated with higher levels of glucose and insulin, the associations may not be detectable or persist with longer term exposure. Second, markers of traffic such as NO_x and distance to roadways may be better exposure metrics than $PM_{2.5}$, suggesting that other factors associated with near-road exposure may contribute to the observed associations. Third, associations for glucose and insulin may not necessarily be in the same direction among the same study sample. Our findings in the current study are generally consistent with these implications.

Our findings were also similar to those from a large-scale study conducted in Israel, where Sade *et al.* found positive associations between 1- to 3-day averages of nitrogen dioxide and serum glucose among 88,351 participants (Sade et al. 2015). However, the associations between O_3 and fasting glucose were consistently negative across all moving averages in the current study. For chronic exposure analyses, we found that participants who lived closer to a major roadway had higher levels of fasting glucose, which was consistent with findings by Ward-Caviness *et al.* and findings in the KORA study, suggesting an association between traffic-related exposures with fasting glucose.

The magnitude of the association observed between proximity to a major roadway and fasting glucose in the current study is similar to the difference in fasting glucose levels that were associated with 1 standard deviation change in the diet pattern score in a meta-analyses of over 48,000 participants in the CHARGE (Cohorts for Heart and Aging Research in Genomic Epidemiology) consortium (Nettleton et al. 2013), or about 110 cm^3 increase in the visceral adipose tissue volume in men (60 cm^3 in women) in the Framingham Multidetector Computed Tomography Study (Abraham et al. 2015). Furthermore, the 0.28% difference in fasting glucose observed in the current study (about 0.27 mg/dl) was associated with a 4% higher incidence of type 2 diabetes in the Framingham Heart Study (Wilson et al.

2007). Moreover, since only a few large scale studies have examined the associations of proximity to major roadways with biomarkers of glucose homeostasis, from a physiological perspective, our findings contribute new evidence to the current literature about the potential underlying mechanism that links air pollution to dysregulated glucose metabolism.

We did not find consistent associations between sustained or short-term exposure to ambient air pollutants and adipokines. Previous human studies and controlled animal studies have reported mixed results. For example, Wang *et al.* found positive associations between annual BC exposure and leptin levels among 675 elderly participants (mean age: 78.1 years), however, distance to roadways was not associated with leptin levels (Wang et al. 2014). In the KORA study, annual average NO_x and nitrogen dioxides were positively associated with leptin (Wolf et al. 2016). On the other hand, controlled animal studies reported that inhalation of $PM_{2.5}$ was associated with lower levels of adiponectin and leptin, and higher levels of resistin (Sun et al. 2009; Xu et al. 2011), suggesting that the physiology of energy metabolism and inflammatory response to air pollution may be different in mice and human.

Several factors may contribute to our findings where higher levels of fasting glucose was associated with living closer to a major roadway but not with higher annual average $PM_{2.5}$ concentration. The $PM_{2.5}$ estimated from the spatial-temporal model is a measure of both near-road and regional particulate matter pollution: it accounts for both particles from traffic and particles transported from distant emission sources. Meanwhile, residential proximity to major roadways is an integrated measure of small and large traffic-related particles, gaseous pollutants, other traffic-related conditions (light, vibration, and noise), or potential psychological stress associated with living closer to major roadways. It is possible that these traffic-related metrics other than air pollution contribute to the associations between living closer to a major roadway and higher levels of fasting glucose.

We unexpectedly observed negative associations between short-term exposure to O_3 and fasting glucose. The reason for this observed association was unclear. O_3 is a strong oxidant that may induce oxidative stress, and exposure to O_3 in controlled animal studies was associated with increased levels of measures of glucose homeostasis (Bass et al. 2013; Miller et al. 2015; Vella et al. 2015). Short-term exposure to O_3 was associated with higher levels of fasting glucose among a group of 560 elderly Koreans (Kim and Hong 2012) but not among 7,578 participants in Taiwan (Chuang et al. 2010). In our study, adjusting for NO_x and O_3 simultaneously led to attenuated associations between O_3 exposure and glucose levels but did not alter the directionality. However, residual confounding, unmeasured confounding, and measurement errors in ozone levels may also contribute to the unexpected negative association pattern.

There are several strengths of our study. The study participants were from large, well-characterized cohorts; physical examinations were conducted following standardized protocols and biomarkers were assessed with quality control. We took advantage of the large sample size and adjusted for covariates including demographics, lifestyles, individual- and area-level measures of socioeconomic position, time, and seasonality. We estimated annual average $PM_{2.5}$ concentration using a spatial-temporal model at a high resolution at participants' self-reported home addresses, and we updated the address information at each

examination visit. Assessments of air pollution and biomarkers were performed independently, and participants from the Framingham Heart Study scheduled their exam visits months in advance. Last, our study was conducted in a region that has ambient air pollution levels in compliance with the current U.S. air quality standards.

We note several limitations of our study. First, participants in the current analyses were middle-aged white individuals with European ancestry. Thus, findings from our study may not be generalizable to populations of different ethnicities or age groups. Second, although we have adjusted for demographics, lifestyle factors, and individual- and area-level measures of socio-economic position, we cannot exclude potential residual confounding, unmeasured confounding, or uncertainty of temporality. Thus, our findings cannot be used for inferring causality. Third, in short-term exposure analyses, we assigned the same air pollution levels measured at a central monitor site to participants who had their examination visits on the same day. The central monitor site is located 20 m above the ground level which is probably higher than usual air pollution monitors but ensures that the nearby buildings do not block the air flow (Brown et al. 2009). In our region, temporal variability contributes to the majority of the variability in shortterm air pollution exposure compared to spatial variability (Lee et al. 2011). A previous study conducted in metropolitan Boston has reported moderate correlations between central-site measured $PM_{2.5}$, elemental carbon, and SO_4^{2-} and outdoor concentrations (Brown et al. 2008). The assignment method may induce a Berkson type of measurement error and decrease statistical power, however, although the results may be attenuated by the non-differential measurement error, we observed positive associations of BC and NO_x with fasting glucose. We assigned the annual average $PM_{2.5}$ concentrations in 2003 to all participants as a surrogate of their sustained exposure. Some biomarkers were measured in Offspring examination 7 (1998–2001) during which the air pollution levels were likely higher, while air pollution levels in the Offspring examination 8 (2005–2008) and Third Generation examination 2 (2008–2011) were likely lower. Because the $PM_{2.5}$ model estimates were only available starting from 2003, we used the 2003–2005 average $PM_{2.5}$ in a sensitivity analysis and the results showed no substantial difference. Furthermore, our conclusions were not changed when we excluded participants whose 2003 annual average $PM_{2.5}$ concentration was above 12 $\mu g/m^3$, a group of participants who were likely exposed to higher levels of $PM_{2.5}$ than other participants over the years. Additionally, we were not able to adjust for dietary patterns of the participants. However, we did adjust for individual-and area-level markers of socioeconomic positions, which may partially account for differences in dietary pattern that are related to place of residence. Last, annual averages of BC and NO_x were not available for the current study. Although our results suggested positive associations between chronic near-road exposure and glucose homeostasis, we cannot assess whether chronic exposure to air pollutants related to near-road exposure such as BC and NO_x were associated with biomarkers of glucose homeostasis.

5. Conclusions

Our findings suggested positive associations between traffic-related exposures and dysregulated carbohydrate metabolism: living closer to a major roadway or short-term exposure to traffic-related air pollutants were associated with elevated fasting glucose. Few large-scale studies have examined these associations in the United States. Future

longitudinal studies with not only chronic $PM_{2.5}$ assessment but also other traffic-related air pollutants such as BC and NO_x are necessary to confirm or refute our findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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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

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Highlights

- Living closer to a major roadway was associated with higher fasting glucose.
- Annual average $PM_{2.5}$ was not associated with measures of glucose homeostasis.
- Short-term exposure to BC and NO_x were positively associated with fasting glucose.
- Short-term exposure to O_3 was negatively associated with fasting glucose.

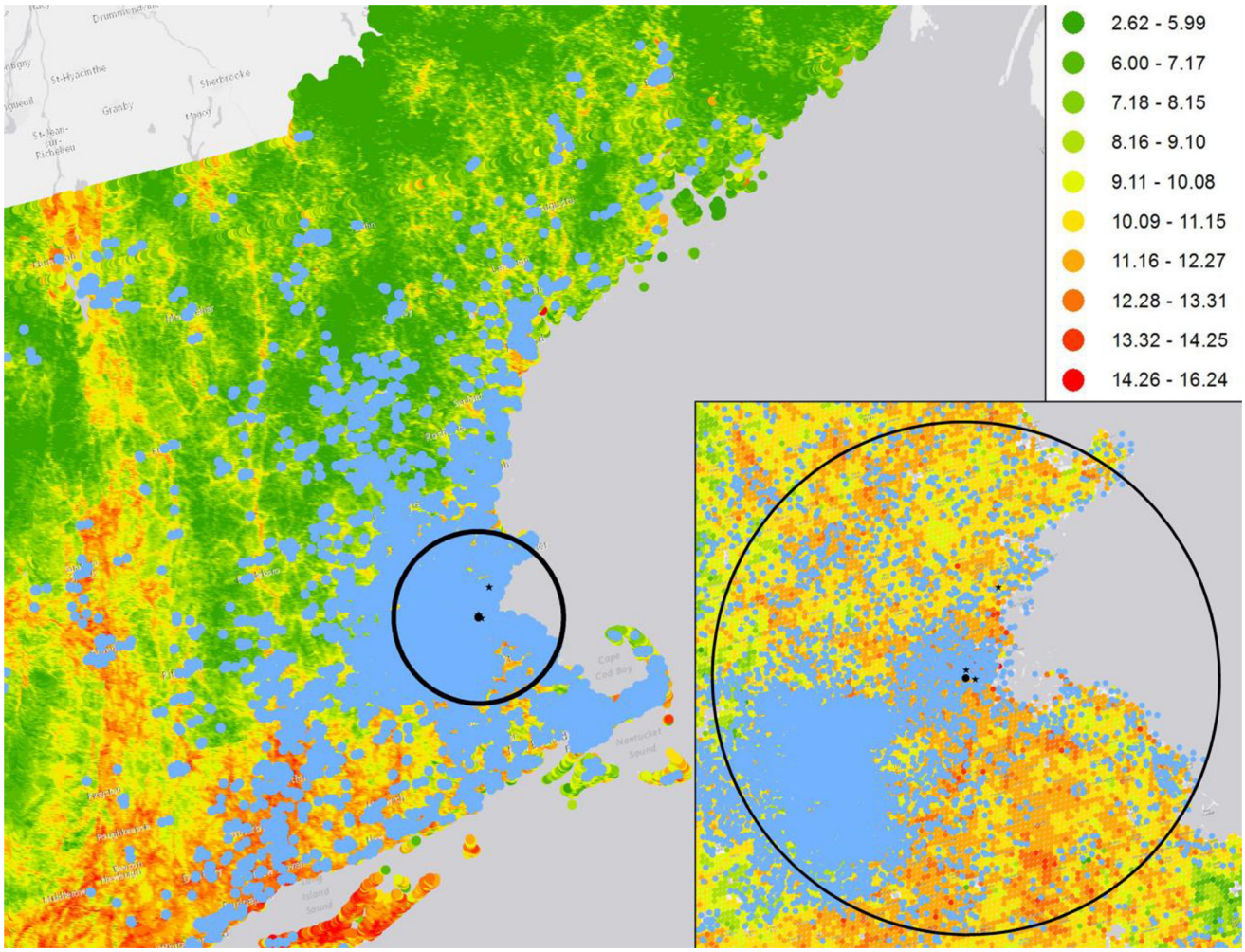

Figure 1.

Map of the study region showing the distribution of the study participants, the model-based 2003 annual average $PM_{2.5}$ concentrations ($\mu g/m^3$), and the locations of Supersite and local state monitors. To protect the confidentiality of the participants, the residential locations on the map were masked by altering the longitude and latitude by a small random amount. Thus, although these locations are representative of the distribution of participants' residential locations, none of them represent actual residential locations of the study participants. Circle indicates the 50 km radius from Supersite. Blue dots: residential locations of the study participants. Black dot: Supersite. Black star: local state monitors.

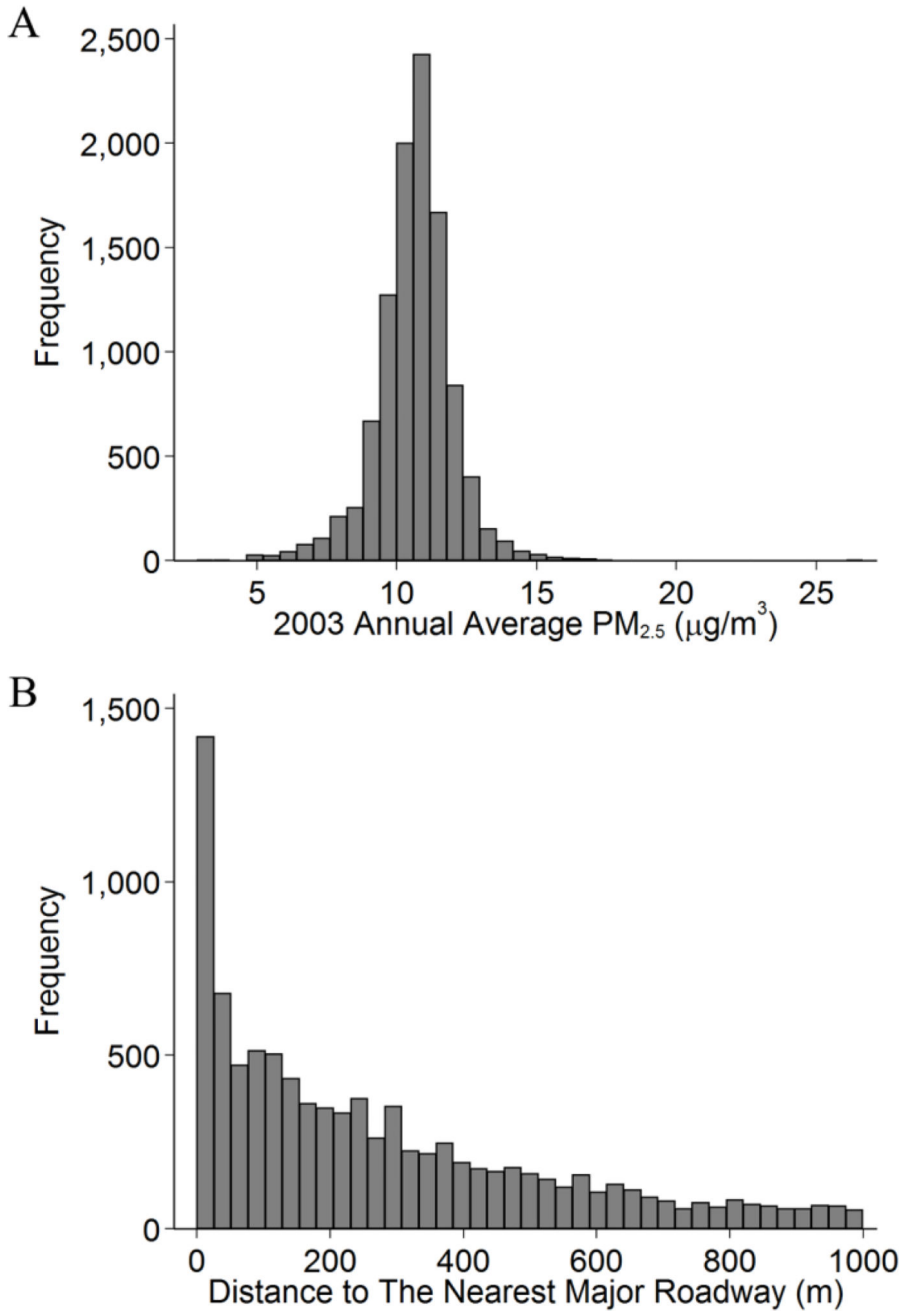

Figure 2.

Histograms of A) 2003 Annual Average Fine Particulate Matter ($PM_{2.5}$) and B) Distance to Major Roadways Among 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). There were 5,958 participants (10,389 observations) with 2003 annual $PM_{2.5}$, and 5,403 participants (9,264 observations) with proximity measurements.

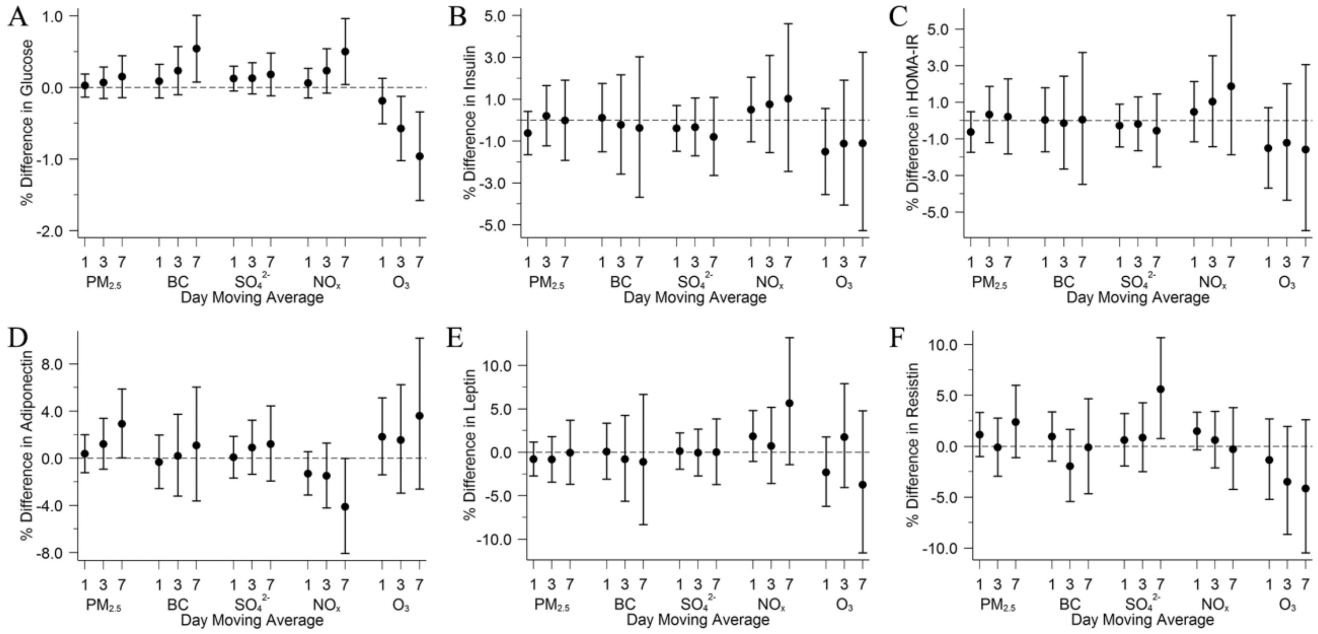

Figure 3.

Associations of 1-, 3-, and 7-Day Moving Averages of Air Pollutants With A) Fasting Glucose, B) Insulin, C) HOMA-IR, D) Adiponectin, E) Leptin, and F) Resistin Among 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). Models were adjusted for centered age, (centered age)^2, sex, body mass index, smoking status, pack years, alcohol intake, educational attainment, physical activity, census tract median household income, census tract median value of owner occupied housing units, census tract population density, usual occupation, date of examination visit, sine and cosine season, day of week, temperature, and relative humidity. An exam identifier was added for glucose, insulin, HOMA-IR, and adiponectin. Results were scaled to 5 μg/m^3 for fine particulate matter ($PM_{2.5}$), 0.5 μg/m^3 for black carbon (BC), 2 μg/m^3 for sulfate (SO_4^{2-}), 20 ppb for nitrogen oxides (NO_x), and 15 ppb for ozone (O_3). Error bars indicate the 95% confidence intervals.

Table 1

Summary Statistics for the 10,389 Observations (5,958 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).

Characteristics	Offspring cohort Mean(SD) or N[%]		Third Generation cohort Mean(SD) or N[%]	
Examination cycle	7	8	1	2
No. of participants	2,415	1,925	3,281	2,768
Age, years	60.4 (9.5)	65.7 (9.0)	39.8 (8.7)	46.1 (8.5)
Women	1,332 [55.2]	1,093 [56.8]	1,793 [54.7]	1,510 [54.6]
BMI, kg/m^2	27.8 (5.1)	27.8 (5.1)	26.8 (5.4)	27.7 (5.5)
Alcohol, drinks/week	5.2 (7.7)	4.6 (7.1)	4.8 (7.1)	4.8 (6.7)
Smoking status[a]				
Non-smoker	893 [37.0]	742 [38.6]	1,862 [56.8]	1,621 [58.6]
Former smoker	1,187 [49.2]	966 [50.2]	835 [25.5]	821 [29.7]
Current smoker	335 [13.9]	182 [9.5]	584 [17.8]	326 [11.8]
Pack year	16.9 (22.2)	15.4 (21.0)	6.7 (11.4)	6.8 (12.0)
Educational attainment[b]				
High school or less	788 [32.6]	571 [29.7]	541 [16.5]	406 [14.7]
Some college	729 [30.2]	599 [31.1]	1,063 [32.4]	845 [30.5]
College graduate	852 [35.3]	753 [39.1]	1,670 [50.9]	1,516 [54.8]
Fasting plasma glucose[c,d,e], mg/dl	97.0 (9.7)	99.9 (9.1)	92.6 (8.4)	93.3 (8.7)
Insulin[c,d,e], pmol/l	–	57.9 (33.8)	27.0 (13.0)	55.7 (31.5)
HOMA-IR[c,d,e]	–	2.1 (1.3)	1.0 (0.5)	1.8 (1.1)
HbA1c[c,e], %	–	5.5 (0.3)	–	5.4 (0.3)
Adiponectin[c,e], μg/ml	8.8 (5.4)	–	7.2 (4.8)	–
Leptin[c,e], ng/ml	–	–	7.3 (7.7)	–
Resistin[c,e], ng/ml	12.8 (5.1)	–	–	–
2003 annual average $PM_{2.5}$, μg/m^3	10.6 (1.3)	10.6 (1.3)	10.7 (1.5)	10.6 (1.5)
Distance to a major roadway[f], m	264 (244)	268 (249)	268 (252)	283 (259)
Distance category[f]				
<50 m	521 [23.6]	415 [23.9]	624 [21.6]	514 [21.1]
50-<100 m	203 [9.2]	161 [9.3]	331 [11.4]	255 [10.5]
100-<200 m	385 [17.5]	292 [16.8]	529 [18.3]	418 [17.2]
200-<400 m	551 [25.0]	430 [24.8]	666 [23.0]	555 [22.8]
400-<1,000 m	544 [24.7]	437 [25.2]	744 [25.7]	689 [28.3]

Abbreviation: HOMA-IR, homeostasis model assessment of insulin resistance; HbA1c, hemoglobin A1c; $PM_{2.5}$, fine particulate matter; SD, standard deviation.

[a] 35 (1.8%) participants in the Offspring cohort examination cycle 8 were missing smoking status and were assigned missing indicators.

[b] 46 (1.9%), 2 (0.1%), 7 (0.2%), and 1 (0.04%) participants in examination cycle 7, 8, 1, and 2, respectively, were missing educational attainment data and were assigned missing indicators.

[c] The total number of available observations for fasting glucose, insulin, HOMA-IR, HbA1c, adiponectin, leptin, and resistin are 10,389, 7,657, 7,657, 4,690, 5,282, 3,266, and 2,030, respectively.

[d] 4,431 participants had two measurements of fasting glucose, 2,379 participants had two measurements of insulin and HOMA-IR.

[e] Geometric mean and standard deviation.

[f] Calculated based on participants who lived < 1,000 m from the nearest major roadway. 211 (8.7%), 190 (9.9%), 387 (11.8%), and 337 (12.2%) participants in examination cycle 7, 8, 1, and 2, respectively, lived ≥1,000 m from the nearest major roadway and were excluded in proximity analyses.

Table 2

Associations of the 2003 Annual Average Fine Particulate Matter ($PM_{2.5}$) Concentrations and Residential Proximity to Major Roadways With Adipokines and Biomarkers of Glucose Homeostasis Among 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) [a].

	Fasting Plasma Glucose		**HBA1c**		**Adiponectin**		**Resistin**	
	% Difference	**95% CI**	**% Difference**	**95% CI**	**% Difference**	**95% CI**	**% Difference**	**95% CI**
2003 annual $PM_{2.5}$ [b]	−0.08	−0.28, 0.12	−0.05	−0.22, 0.12	−0.30	−1.98, 1.41	−2.15	−4.19, − 0.07
Living closer to major roadways [c,d]	0.28	0.05, 0.51	0.03	−0.17, 0.22	−0.73	−2.68, 1.26	2.20	−0.09, 4.54
Distance categories [c]								
<50	0.72	0.19, 1.26	0.05	−0.40, 0.50	−1.15	−5.60, 3.51	3.83	−1.28, 9.21
50-<100	0.22	−0.44, 0.89	0.19	−0.39, 0.77	2.10	−3.66, 8.21	−1.30	−7.72, 5.58
100-<200	−0.03	−0.58, 0.53	0.36	−0.13, 0.85	−0.44	−5.16, 4.52	4.69	−0.85, 10.54
200-<400	0.24	−0.27, 0.76	0.06	−0.38, 0.50	0.24	−4.12, 4.81	0.09	−4.68, 5.09
400-<1,000	0 (REF)		0 (REF)		0 (REF)		0 (REF)	

	Insulin		HOMA-IR		Leptin	
	% Difference	95% CI	% Difference	95% CI	% Difference	95% CI
2003 annual $PM_{2.5}$ [b]	−0.73	−1.90, 0.44	−0.81	−2.05, 0.45	0.19	−1.94, 2.38
Living closer to major roadways [c,d]	0.60	−0.76, 1.99	0.85	−0.62, 2.33	1.46	−1.12, 4.12
Distance categories [c]						
<50 m	1.13	−2.05, 4.42	1.59	−1.82, 5.13	2.22	−3.86, 8.67
50-<100 m	−3.02	−6.83, 0.95	−3.04	−7.11, 1.20	−1.67	−8.76, 5.96
100-<200 m	−1.85	−5.13, 1.55	−1.92	−5.43, 1.72	−4.82	−10.72, 1.48
200-<400 m	−0.62	−3.67, 2.54	−0.61	−3.87, 2.77	−4.22	9.74,1.63
400-<1,000 m	0 (REF)		0 (REF)		0 (REF)	

Abbreviation: CI, confidence interval; $PM_{2.5}$, fine particulate matter; HBA1c, hemoglobin A1c; HOMA-IR, homeostasis model assessment of insulin resistance.

[a] Models were adjusted for centered age, (centered age)^2, sex, body mass index, smoking status, pack years, alcohol intake, educational attainment, physical activity, census tract median household income, census tract median value of owner occupied housing units, census tract population density, usual occupation, date of examination visit, and sine and cosine season. An exam identifier was added for fasting glucose, insulin, HOMA-IR, HBA1c, and adiponectin.

[b] Results were scaled to equivalent to 1.5 μg/m^3 higher in $PM_{2.5}$ concentrations.

[c] Analysis was restricted to participants who lived within 1,000 m from major roadways.

[d] Results were scaled to comparing participants who lived 64 m (25th percentile) from major roadways to those who lived 413 m (75th percentile) away.

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