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Long-term Exposure to Ambient Air Pollution and Serum Leptin in Older Adults: Results from the MOBILIZE Boston Study

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Abstract

Objective—Long-term exposure to traffic-related air pollution has been linked to increased risk of obesity and diabetes and may be associated with higher serum levels of the adipokine leptin, but this hypothesis has not been previously evaluated in humans.

Methods—In a cohort of older adults, we estimated the association between serum leptin concentrations and two markers of long-term exposure to traffic pollution, adjusting for participant characteristics, temporal trends, socioeconomic factors, and medical history.

Results—An interquartile range increase (0.11 $\mu\text{g}/\text{m}^3$) in annual mean residential black carbon was associated with 12% (95% CI: 3%, 22%) higher leptin levels. Leptin levels were not associated with residential distance to major roadway.

Conclusions—If confirmed, these findings support the emerging evidence suggesting that certain sources of traffic pollution may be associated with adverse cardiometabolic effects.

Keywords

Traffic pollution; epidemiology; metabolic; obesity; diabetes

INTRODUCTION

Ambient fine particulate matter ($\text{PM}_{2.5}$) is a recognized risk factor for cardiovascular morbidity and mortality, and current evidence suggests that traffic-related pollution may be

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especially important (1). The pathophysiologic mechanisms underlying these associations remain incompletely understood, but systemic inflammation, vascular endothelial injury and dysfunction, and progression of atherosclerosis all appear to play key roles. Recent epidemiologic studies suggest that long-term exposure to particulate air pollution or traffic pollution may also be associated with increased risk of diabetes (2–8) as well as higher levels of insulin resistance, hemoglobin A1c and fasting glucose (9–11). A recent clinical study found that exposure to even low levels of PM_{2.5} may reduce metabolic insulin sensitivity (12). Animal toxicological studies also suggest that long-term exposure to particulate matter can induce insulin resistance and mitochondrial dysfunction, inflammation in adipose tissue, and up-regulation of *leptin* gene expression in adipose tissue (13–15).

Leptin is an inflammatory cytokine secreted primarily by adipocytes with pleiotropic effects on appetite, metabolism, neuroendocrine function and immune function (16). Serum leptin levels are highly correlated with body fat content, increase after overeating and decrease during fasting (16). Leptin levels have been positively associated with risk of coronary events (17, 18) and incident diabetes (19, 20).

Given the potential metabolic effects of traffic pollution and the central regulatory role of leptin, it is plausible that long-term exposure to traffic pollution may be associated with higher leptin levels. However, to our knowledge, this hypothesis has not been previously evaluated in an epidemiologic study. Accordingly, we evaluated the cross-sectional association between markers of long-term exposure to traffic pollution and serum leptin in the context of the Maintenance of Balance, Independent Living, Intellect, and Zest in the Elderly (MOBILIZE) Boston Study, a prospective cohort study in older adults.

MATERIALS AND METHODS

Study Design

The MOBILIZE Boston Study is a prospective cohort study of novel risk factors for falls in adults aged ≥65 years (21). Briefly, between 2005 and 2008, we recruited 765 non-institutionalized men and women able to communicate in English and walk twenty feet without assistance, and residing <5 miles from the study clinic. Individuals not planning to reside in the study area for 2 or more years, those with severe vision or hearing impairment, and those with cognitive impairment defined as a Mini-Mental State Examination score of <18 were not eligible to participate. Participant recruitment was based on a simple random sample of persons on town lists within the study area. Upon enrollment, participants completed an in-home interview followed within 4 weeks by an in-clinic evaluation. All participants provided written informed consent and this analysis was approved by the Institutional Review Boards at Hebrew SeniorLife and Brown University.

We collected a non-fasting venous blood sample during the baseline clinic examination and measured serum leptin concentration using a bead-based Multiplex array (HENDO-65K-01, Millipore, Inc., Billerica, MA). We determined leptin concentration on a fitted standard curve (0.1–72 µg/mL) after serum leptin was detected via antibody fluorescent signal on a Luminex plate reader (Biorad Laboratories, Inc., Austin, TX)(22). We assigned half of the

value of limit of detection (LOD, derived from the standard curve) to samples with undetectable leptin concentration.

We measured height, weight, and supine blood pressure, as previously described (23). Participants were classified as normotensive if their blood pressure was <140/90 mmHg, there was no history of hypertension, and they were not receiving medications prescribed for hypertension; controlled hypertensive if blood pressure was <140/90 mmHg and there was a history of hypertension or receiving antihypertensive medication; and uncontrolled hypertensive if blood pressure was ≥140/90 mmHg. Participants were classified as having diabetes mellitus if they reported a past diagnosis of diabetes, reported using any diabetes medications, measured hemoglobin A1c levels were ≥7%, or random glucose measurement was ≥200 mg/dl, and as having hyperlipidemia if total cholesterol was ≥200mg/dl or low-density lipoprotein cholesterol level was ≥130mg/dl or they reported taking lipid-lowering medications.

During the home visit, we obtained detailed information on participant age, race, sex, education, household income, medical history, current medications, physical activity, usual alcohol consumption and smoking history as previously described (21). We used the Physical Activity Scale for the Elderly (PASE), a validated 10-item instrument for assessing physical activity in epidemiological studies of older adults (24). Smoking history was classified as never, past, and current smokers.

Exposure Assessment

We used two complimentary metrics to estimate residential long-term exposure to traffic pollution. First, we used ArcGIS (version 9.2; ESRI, Inc., Redlands, CA) to geocode participant baseline addresses and estimated daily outdoor black carbon levels (a marker of traffic pollution) at each participant's residential address using a validated spatial-temporal land-use regression model, as previously described (25). As in previous studies (26), we averaged residential black carbon over the 365 days preceding each participant assessment to create a metric of long-term exposure to traffic pollution. Second, we calculated the Euclidean distance from residence to the nearest major roadway, defined as roads with US Census Feature Class Code A1 (primary highway with limited access) or A2 (primary road without limited access), as previously described (26). Traffic-related air pollutants are expected to be highest immediately adjacent to a major roadway and then decrease approximately exponentially with increasing distance to major roadway (27, 28).

Statistical Analyses

Serum samples from the baseline visit were available for 680 of the 765 (88.9%) participants. We were able to measure leptin levels in 675 (99.3%) of these samples, of which 16 (2.4%) had values below the LOD and thus were assigned half of the LOD value. We used linear regression to estimate the cross-sectional associations and 95% confidence intervals between log-transformed leptin concentrations and the two markers of long-term exposure to traffic pollution. Results are expressed as the percent difference in serum leptin concentrations associated with differences in annual mean residential black carbon levels or residential distance to the nearest major roadway.

We modeled the association between leptin and annual mean residential black carbon concentration as a continuous variable and checked the validity of this assumption using tertiles of annual mean residential black carbon concentration. We also used natural cubic splines with 3 degrees of freedom to further characterize the functional form of the relationship between annual residential black carbon and leptin. As in our previous analyses (26), we modeled residential distance to major roadway in 5 categories (<100, 100–250, 250–500, 500–1000, >1000 m) and tested for linear trend by assigning the median distance to each category and including the term as a continuous variable in regression models. Additionally, we modeled the association between leptin and the natural logarithm of residential distance to nearest major roadway as a continuous variable. We also modeled the natural logarithm of distance to nearest major roadway as a continuous variable using natural cubic splines with 3 degrees of freedom to further characterize the functional form of the relationship. To minimize the influence of a small number of highly influential points, in a sensitivity analysis we excluded 25 participants with residential distance to major roadway <10 m.

In all models we adjusted for potential confounding by age (natural cubic spline with 3 degrees of freedom), sex, race (white versus other), season (four categories), day of week (4 indicator variables for Monday to Friday), physical activity (linear continuous), alcohol consumption (linear continuous), smoking (never, ever or current), household income (below versus above median), education (no college degree, some or 4-year college, graduate school), and neighborhood socioeconomic status (linear continuous) using two census tract-level variables: percent of population that is non-white and percent of population with college degree or above. In a second model, we additionally adjusted for body mass index (natural cubic spline with 3 degrees of freedom), diabetes mellitus, hypertension (normotension, controlled hypertension, uncontrolled hypertension), and hyperlipidemia. Analyses were performed using R statistical software (R v2.13). A two-sided p value of <0.05 was considered statistically significant.

RESULTS

At baseline, MOBILIZE Boston Study participants were predominantly white and female, with a mean age of 78.1 (SD: 5.4) years (Table 1). Serum leptin concentrations were approximately log-normally distributed, ranging from 0.02 to 105.9 ng/ml with a geometric mean of 4.7 ng/ml and a geometric standard deviation of 3.9 ng/ml.

Annual mean residential black carbon exposure was approximately normally distributed with a mean of 0.37 $\mu\text{g}/\text{m}^3$ and a standard deviation of 0.12 $\mu\text{g}/\text{m}^3$. Participant characteristics varied across tertiles of residential black carbon levels, with participants in the highest exposure category being less likely to be white or have attended graduate school and more likely to have a low household income, hypertension and diabetes mellitus (Table 1).

Serum leptin levels were positively associated with annual mean residential black carbon, reaching statistical significance only in the fully-adjusted model (Table 2). Specifically, in the fully-adjusted model we found 12% (95% CI: 3%, 22%) higher leptin levels associated

with an interquartile range ($0.11 \mu\text{g}/\text{m}^3$) increase in annual mean residential black carbon. When modeling annual mean residential black carbon as a categorical variable, mean leptin levels were 27% (95% CI: 1%, 61%; $p=0.046$) higher in the highest versus lowest tertile of annual mean residential black in the fully-adjusted model, and the linear trend across exposure categories was statistically significant ($P_{\text{trend}} = 0.040$). A fully-adjusted model fit with a natural cubic spline representation of annual mean residential black carbon suggested that this association was approximately linear (Figure 1).

Residential distance to the nearest major roadway varied from near 0 m to just over 3 km, with a median distance of 703 m and 9% of participants living within 100 m of a major roadway. The Pearson correlation between residential distance to major roadway and annual mean residential black carbon was 0.47. We found no evidence of an association between leptin levels and categories of residential distance to nearest major roadway (Table 3). We also found no association between leptin levels and the natural log of residential distance to nearest major roadway, either modeled as a linear continuous variable or using natural cubic splines. Results were similar in sensitivity analyses excluding a small number of potentially high-leverage points.

DISCUSSION

We evaluated the cross-sectional association between serum leptin levels and two markers of long-term exposure to traffic pollution in a cohort of older adults. We found evidence that leptin was associated with annual mean residential black carbon levels, but not with residential distance to nearest major roadway.

While these results may appear contradictory, it is important to note that our two markers of long-term exposure to traffic pollution were only moderately correlated ($r=0.47$) and likely reflect different aspects of residential exposure to traffic pollution. Specifically, residential distance to the nearest major roadway likely reflects exposure to traffic pollution from a combination of automobile and truck traffic moving at higher speeds on interstate highways and larger state highways. On the other hand, our estimates of residential black carbon likely reflect contributions from traffic on a wider range of roadways in the immediate vicinity of each participant's home. Moreover, our black carbon model incorporates information on local meteorology (eg: wind direction, planetary boundary layer height) and regional black carbon levels that vary over time, as well as land use information that does not vary over time. Thus, our predictions of residential black carbon vary over both space and time while measures of distance to nearest major roadway vary spatially, but not over time.

Our spatio-temporal model of residential black carbon has been used in a number of prior Boston-area studies finding associations with increased blood pressure (29), carotid intima-media thickness (30), and markers of endothelial injury and inflammation (31), as well as impaired childhood neurodevelopment (32) and reduced cognitive function in the elderly (33). Several other prior studies have used residential distance to nearest major roadway as a marker of long-term exposure to traffic pollution and found that it is associated with a number of indicators of adverse cardiovascular health including increased risk of myocardial infarction (34), reduced survival after myocardial infarction (35), increased prevalence of

cardiovascular disease (36) and increased left ventricular mass index (37). Of note, prior studies suggest that the effects of traffic pollution may be sensitive to the type of traffic on nearby roadways. For example, Medina-Ramon et al. (38) found that residential proximity to a bus route was associated with decreased survival among heart failure patients, but residential proximity to nearest major roadway was not. However, few prior studies have simultaneously considered both markers of exposure to traffic pollution. Within the context of the MOBILIZE Boston study, we previously found that cognitive function in older adults was associated with residential proximity to major roadways, but the association with mean annual residential black carbon was less pronounced (26). Taken together these results suggest that residential proximity to major roadways and our estimates of residential black carbon likely capture different aspects or components of traffic pollution, each of which may be associated with different outcomes.

Serum levels of leptin, an inflammatory cytokine secreted primarily by adipose tissue, have been correlated with total body fat and associated with incidence rate of heart disease, obesity, and diabetes (16–20). Long-term exposure to ambient air pollution broadly, and traffic pollution specifically, has been associated with increased risk of cardiovascular disease, obesity and diabetes (1–8). If causal, the results of the current study add to the emerging evidence that long-term exposure to at least some aspects of traffic pollution may adversely impact cardiometabolic health.

Our study has some limitations. First, we measured leptin in non-fasting serum samples. Leptin levels are affected by recent food intake, but we do not have information on when or what participants last ate. However, it is likely that the times of the study visit and blood draw, and each participant's fasting status were independent of the long-term exposure to traffic pollution. Second, we measured serum leptin concentration using a bead-based Multiplex assay rather than the conventional Enzyme-Linked Immunosorbent Assay (ELISA). However, validation studies suggest that serum leptin measured by Multiplex assay and ELISA are well correlated (39). Nonetheless, the use of Multiplex assays may have led to some (likely non-differential) misclassification of the outcome, likely biasing our results towards the null hypothesis of no association. Third, we did not have information on residential history of participants prior to study enrollment in the MOBILIZE Boston Study, potentially leading to some exposure misclassification. However, residential mobility in this age group is expected to be low (40), limiting the potential for exposure misclassification. Fourth, our analysis was cross-sectional as serum leptin levels were only measured once upon study enrollment. Thus, we cannot exclude the possibility of reverse causation where those individuals with higher leptin levels may be more likely to reside in areas with higher black carbon levels. Fifth, we had no information on indoor home levels of ambient pollutants nor indoor sources of combustion-derived pollution, potentially leading to either exposure misclassification or residual confounding. Sixth, these results may not be generalizable to other geographic locations with different populations, characteristics or different vehicle fleet and traffic patterns.

On the other hand, strengths of this study include a well-characterized population of community-dwelling older adults. Additionally, at baseline MOBILIZE Boston Study participants were largely representative of older adults in the Boston area in terms of age,

sex, race and ethnicity (21), enhancing the generalizability of our findings to other elderly Boston-area residents.

In summary, we found evidence of an association between serum leptin levels and estimated annual mean residential black carbon concentration, but not residential distance to the nearest major roadway in a cohort of older adults. If confirmed in future studies, our findings support the emerging evidence suggesting that certain sources of traffic pollution may be associated with adverse cardiometabolic effects.

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Figure 1.

Association between serum leptin and annual mean residential black carbon fitted using a natural cubic spline with 3 degrees of freedom. Shaded area within dashed lines represents the 95% confidence interval.

Table 1

Baseline characteristics of 675 participants from the MOBILIZE Boston Study.

Characteristics	All (n=675)	Annual Mean Residential Black Carbon ($\mu\text{g}/\text{m}^3$)		
		0.33 (n=223)	0.33–0.39 (n=223)	>0.39 (n=224)
Age, years, mean $\pm$ SD ^a	78.1 $\pm$ 5.4	78.3 $\pm$ 5.2	78.0 $\pm$ 5.6	78.0 $\pm$ 5.5
Male, %	37.3	37.2	35.9	38.8
White, %	79.0	96.4	78.9	61.1
Education, %				
High school or less	32.9	21.1	39.5	38.8
College or vocational school	35.1	42.2	30.0	32.1
Graduate school	31.9	36.8	30.0	29.0
Household income \$35,000, %	54.7	42.2	57.4	64.3
Body mass index, kg/m^3 , mean $\pm$ SD	27.3 $\pm$ 5.1	27.4 $\pm$ 4.9	26.9 $\pm$ 4.9	27.7 $\pm$ 5.5
Alcohol consumption, drinks/day, mean $\pm$ SD	0.9 $\pm$ 1.0	1.0 $\pm$ 0.8	0.9 $\pm$ 0.9	0.9 $\pm$ 1.2
Smoking History, %				
Never	42.1	39.0	47.1	41.1
Past	53.0	56.5	47.5	54.0
Current	4.7	4.0	5.4	4.9
Hypertension, %	78.1	76.2	77.6	80.4
Diabetes mellitus, %	19.0	14.8	17.0	24.6
Hyperlipidemia, %	49.3	49.8	49.3	49.1
Leptin, ng/ml , mean $\pm$ SD	9.2 $\pm$ 11.0	7.9 $\pm$ 9.6	9.2 $\pm$ 11.5	10.6 $\pm$ 11.7
Annual black carbon, $\mu\text{g}/\text{m}^3$, mean $\pm$ SD	0.37 $\pm$ 0.12	0.27 $\pm$ 0.04	0.36 $\pm$ 0.02	0.50 $\pm$ 0.12

^aSD=standard deviation

Cross-sectional association between annual mean residential black carbon and percent difference (95% confidence interval) in serum leptin levels among participants from the MOBILIZE Boston Study

Table 2

Annual Mean Residential Black Carbon (µg/m ³)				
	Continuous ^a	0.33	0.33–0.39	>0.39
Model 1 ^b	8% (–1%, 19%)	1.0 (Ref)	–9% (–29%, 16%)	20% (–8%, 55%)
Model 2 ^c	12% (3%, 22%)	1.0 (Ref)	–1% (–20%, 24%)	27% (1%, 61%)

^aExpressed as the % difference in leptin levels for an interquartile range (0.11 µg/m³) shift in annual mean residential black carbon;

^bAdjusted for age, sex, race, season, day of week, smoking, alcohol consumption, physical activity, household income, education and neighborhood socioeconomic status.

^cAdditionally adjusted for body mass index, diabetes mellitus, hypertension, and hyperlipidemia.

Table 3
Cross-sectional association between residential distance to nearest major roadway and percent difference (95% confidence interval) in serum leptin levels among participants from the MOBILIZE Boston Study

	Residential Distance to the Nearest Major Roadway					P _{trend}	Log Distance ^a
	<100 m (n=61)	100–250 m (n=74)	250–500 m (n=119)	500–1000 m (n=198)	>1000 m (n=215)		
Model 1 ^b	7% (–26%, 55%)	–25% (–47%, 4%)	–12% (–34%, 18%)	–23% (–40%, –1%)	1.0 (Ref)	0.94	10% (–10%, 35%)
Model 2 ^c	1% (–28%, 42%)	–28% (–47%, –3%)	–3% (–25%, 26%)	–17% (–34%, 3%)	1.0 (Ref)	0.64	4% (–13%, 25%)

^aExpressed as the % difference in leptin levels comparing participants living 50 vs 1000m from a major roadway;
^badjusted for age, sex, race, season, day of week, smoking, alcohol consumption, physical activity, household income, education and neighborhood socioeconomic status.
^c additionally adjusted for body mass index, diabetes mellitus, hypertension, and hyperlipidemia.