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Traffic Exposure in a Population with High Prevalence Type 2 Diabetes - Do Medications Influence Concentrations of C-Reactive Protein?

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Abstract

Type 2 Diabetes (T2D) and particulate air pollution are associated with inflammatory dysregulation. We assessed the modifying effects of diabetes medications on the association of C-reactive protein (CRP), a marker of inflammation, and traffic exposure in adults with T2D (n=379). CRP concentrations were significantly positively associated with residence 100 m of a roadway, >100m and 200m of a roadway and increased traffic density for individuals using insulin. For individuals using oral hypoglycemic medications (OHAs), CRP was significantly negatively associated with residence >100 m - 200 m of a roadway and multiple roadway exposure in an interaction model. Among people with diabetes, individuals on insulin appear to be most vulnerable to the effects of traffic exposure. Disease severity among insulin users may promote the pro-inflammatory response to traffic exposure, though diabetes medications may also modify the response. Possible anti-inflammatory effects of OHAs with traffic exposure merit further evaluation.

Keywords

Residential traffic exposure; C-reactive protein; Type 2 diabetes; Traffic proximity; Traffic density; Puerto Rican; Inflammation

INTRODUCTION

Type 2 diabetes (T2D) development and progression largely involve inflammatory processes (Shoelson et al. 2006). T2D and atherosclerosis, the leading cause of death among people with diabetes, are both diseases associated with considerable vascular dysfunction, in which inflammation plays a central role (Beckman et al. 2002; Libby 2002; Dandona et al. 2004).

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Disclosures

The authors have declared they have no competing interests.

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Several studies have demonstrated that C-reactive protein (CRP), an acute phase protein involved in the innate response to infection is also a physiological marker of systemic inflammation and a well-established risk factor for cardiovascular disease, is associated with hyperglycemia, insulin resistance and T2D (Pickup et al. 1997; Festa et al. 2000). CRP concentrations have also been shown to predict the development of T2D and other insulin disorders (Pradhan et al. 2001; Barzilay et al. 2001; Duncan et al. 2003).

Pollution gradients have been reported around highways and major roads with significant declines with distance in levels of ultrafine particles (UFP) (particulate matter less than 0.1 μ m in aerodynamic diameter), carbon monoxide, black carbon and nitrogen oxides. Chronically elevated UFP exposures such as those likely experienced by residents living near heavily trafficked roadways may lead to long-term or repeated increases in systemic inflammation that promote atherosclerosis (Brugge et al. 2007). Prior studies have shown a pro-inflammatory response to traffic or traffic-related pollutants, i.e., an increase in CRP (Riediker et al. 2004; Ruckerl et al. 2006; Dubowsky et al. 2006; Yue et al. 2007, Delfino et al. 2008; Rioux et al 2010).

Individuals with diabetes appear to be particularly vulnerable to air pollution (Gold 2008) though the effect of diabetes medications on health outcomes has not been examined. In an earlier analysis of the larger cohort of Puerto Rican adults (n=1017), individuals without diabetes had the strongest associations of CRP with traffic exposure (71% difference ; 95% CI 18.4% - 147%) as compared to the other sub-groups examined (BMI and < 30; and persons with T2D) (Rioux et al. 2010a). Though not statistically significant, individuals with diabetes showed a consistently negative association between traffic and the CRP outcome, prompting this examination of the potential modifying effects of diabetes medications on traffic exposure.

Puerto Ricans living in the United States have a disproportionately high prevalence of T2D. Among Puerto Ricans aged 60 and older in Massachusetts, 38% had diabetes relative to 23% of non-Hispanic whites and those with diabetes were more than twice as likely to have elevated glycosylated hemoglobin (> 7%) indicating poor glycolic control (Tucker et al. 2000).

In this study, we examine whether treatments for T2D influence the response to residential traffic exposure, a potential inflammatory stressor. To our knowledge, this is the first study to examine the mediating role of medication use, specifically types of medication including insulin and OHAs, with indicators of traffic exposure.

METHODS

Study design and population

This cross-sectional analysis is part of a longitudinal cohort study on stress, nutrition, aging and chronic health conditions conducted by the Northeastern and Tufts Universities' Center for Population Health and Health Disparities (CPHHD) (Tucker 2005; Tucker et al. 2010). Health status, demographic, and blood and genetic data were collected for more than 1020 older Puerto Rican adults (44 -75 years) recruited primarily through door-to-door enumeration, with additional participants identified randomly during major citywide activities or through referral from community organizations or contact through the media or flyers. Additional details on recruitment have been previously described (Tucker 2010).

From this group, 379 individuals who either reported taking diabetes medications (n=304) or had a fasting glucose concentration $\geq$ 126 mg/dl (n=75), meeting the threshold for the provisional diagnosis of diabetes (ADA, 2006), were included in this study. Selection

criteria did not include traffic considerations but rather were focused on finding older Puerto Ricans who resided within the general study area. Study participants resided primarily in the greater Boston area, with approximately 70 percent present in the various neighborhoods that comprise the urban core of Boston. An additional 8 percent and 10 percent of participants resided in Chelsea and Lawrence, Massachusetts, respectively, two areas of relatively high Puerto Rican populations, with the remainder in surrounding cities and towns.

Data collection

Interviews were conducted in the homes of the participants by bilingual interviewers in either English or Spanish, as preferred by the participant. Blood samples were collected in the home by a certified phlebotomist on the day following the home interview, or soon thereafter. Blood samples were returned to the Tufts Nutrition Evaluation Laboratory on the day of collection and were prepared for analysis. CRP was analyzed using the Immulite 1000 immunoassay analyzer (Diagnostic Products Corporation (DPC) Los Angeles, CA). Analytical values above 10 mg/L were repeated. Interviewers recorded medications based on direct observation of the prescription bottles present in the home.

Traffic exposure assessment

Address geo-coordinates were used to characterize residential traffic exposure at the time of the interview and acquisition of blood data. Residential traffic exposure was characterized with respect to proximity to major roadways with at least 20,000 vehicles per day and multi-directional traffic density was characterized in terms of vehicle miles travelled per square mile (VMT/mi²) in each of 130 Traffic Analysis Zones (TAZs) within the study area. ArcGIS software version 9.2 was used to construct 100 meter and 200 meter buffers along roadways of concern and to identify participants who resided within these buffers (*details in* Rioux et al. 2010a and 2010b). TAZ data were obtained from the Central Transportation and Planning Staff of the Boston Region Metropolitan Planning Organization (MPO). A GIS-compatible file with traffic count station positions and measurement data collected by the Massachusetts Highway Department from 1997 – 2006 was used to identify roads of interest (> 20,000 vehicles per day) in the study area. Vehicle counts reflect traffic volumes in both directions.

Three indicators of residential roadway traffic exposure were evaluated: (1) a three- tiered distance gradient (< 100 m; >100 and < 200; and >200 m); (2) number of major roadways (0, 1, or 2+) within 200 m of a residence; and (3) traffic density based on raster-based spatial density analysis. The areas within 100 m or 200 m of either side of a roadway are here referred to as 100 m and 200 m buffers.

Spatial density analysis accounts for the size of a TAZ and calculates the density of traffic levels across adjacent TAZ smoothing the variation between them. Density values represent a running weighted average of vehicle miles travelled within cells 10 by 10 m in diameter calculated over a 1000 meter radius from the center of each TAZ. Three raster-based exposure levels were defined, with level 3 representing the highest traffic density. Study participants were assigned the value for their residence (See Rioux et al. 2010b for additional details). Figure 1 presents the study area and traffic exposure indicators.

Statistical analysis plan

Statistical analysis was performed using PASW (formerly SPSS) version 18.0.0 (July 30, 2009). For univariate and bivariate analyses, mean $\pm$ SD and t-test or ANOVA were used for the variables with normal distribution, and median and Kruskal-Wallis test were used for the variables with a skewed distribution. For categorical variables, the total number of subjects

evaluated and the proportion of patients with events or in that category (%), were estimated. The Chi-Square test was used for bivariate comparisons between categorical variables. CRP was transformed to the natural logarithm (lnCRP) due to its skewness prior to inclusion in multivariate regression analysis.

The association between residential traffic exposure and log-transformed concentrations of lnCRP were evaluated using multivariate linear regression. Results for lnCRP were back-transformed (exponentiated) to reflect the percent difference in CRP concentration for each unit increase in exposure. We began a model building process using step-wise regression and a screening level of $P < 0.10$ to evaluate the full set of explanatory variables presented in Tables 1 and 2. These variables were chosen based on: (1) review of the literature, (2) potential to contribute to pre-existing inflammatory conditions or less than optimal management of such conditions, and (3) observed differences in the blood markers for individuals taking insulin as compared to those taking OHAs. This process resulted in the inclusion of the following set of variables used to adjust the main model for CRP: age, sex, BMI, high-density lipoprotein (HDL), albumin, smoking, waist circumference, statin use, white blood cell count, glucose, glycosylated hemoglobin, insulin concentration, and lymphocytes. We also evaluated a separate model with these same covariates and two socioeconomic factors: attainment of 9th grade education or more, and whether or not total household income was above the 2007 Health and Human Service poverty threshold (HHS, 2007). We evaluated crude models for CRP and each of the traffic indices. The same set of covariates was used in the stratified and interaction models. The two-sided significance level was 0.05.

Because questions regarding acute infections were not included in the interview, men with white blood cell (WBC) concentrations $< 3.9 \times 10^3$ or $> 10.6 \times 10^3$ /mm³ and women with concentrations $< 3.5 \times 10^3$ or $> 11.0 \times 10^3$ /mm³ were eliminated (n=22) from the analyses to control for confounding by infection that could have raised CRP concentrations (Fleming, 1998). One extreme outlier was identified with a CRP value of 127 mg/L, above the 99.9 percentile and nearly twice the next highest value. This case was excluded from the analyses.

Diabetes medications included insulin and OHAs (metformin, sulfonylureas, and glitazones). Building on a prior study (Rioux et al 2010a), we stratified this population into three groups: (1) those using insulin; (2) those using OHAs only; and (3) those not using any diabetes medications, performing separate linear regression analyses on each group. Each of the traffic variables was analyzed in separate regression models against CRP. Indicator variables were used to evaluate the distance gradient (reference level > 200 m); number of roadways near residence (zero as reference level); and the two traffic density approaches (the lowest density levels as reference level).

Models were also developed to assess the interactive effects between traffic exposure and the two main types of diabetes treatment, i.e. use of OHAs only vs. insulin. To better understand the modifying effects of the two types of medication, we also developed an interaction model including all individuals with T2D (excluding those with depressed or elevated WBC counts) with interaction terms created for medication type and each traffic variable, e.g. use of OHAs multiplied by residence > 100 meters to road, use of OHAs multiplied by numbers of roadways within 200 meters. The same terms were created for the interaction of insulin and traffic exposure.

RESULTS

Study population and demographics

The mean age of study participants was 59 ± 6.9 years and 73 percent were women (Table 1). Thirteen percent reported being employed and 44 percent reported education at or above the 9th grade level. The median CRP concentration of 4.1 mg/L is above the high-risk level of 3.0 mg/L for cardiovascular disease (Pearson et al. 2003). Mean systolic and diastolic blood pressure were 138 ± 18.6 and 80 ± 10.4 , respectively, and a higher percentage of participants had systolic (45% > 140 mmHg) compared to diastolic (12% > 90 mmHg) hypertension. Mean pulse pressure was 59 ± 15 with 70% >50 mmHg, a level associated with adverse cardiovascular outcomes (Haider et al. 2003). Hypertension, defined as systolic blood pressure ≥ 140 or diastolic blood pressure ≥ 90 or taking hypertension medications, was observed in 76 percent of participants. Obesity, defined as body mass index ≥ 30 (kg/m²), was observed in 68 percent of participants.

Eighty percent of the study population was on some form of diabetes medications. Twenty-four percent of study participants used insulin (n=92). Of these, 44 were also on metformin, 24 on glitazones, and 10 on sulfonyureas. Fifty-six percent of participants used OHAs only (n=212). Of these, 198 were on metformin, 117 on sulfonyureas, and 78 were on glitazones. Thirty-six percent of participants on metformin (n=71) were also on sulfonyureas and 21 percent (n=42) were also on glitazones. Twenty-four percent (n=24) of participants who were on sulfonyureas were also on glitazones. Baseline characteristics were not significantly different at the $P < 0.05$ level on the basis of residential distance to roadway.

Comparison of health status and blood markers by medication use and type

In an overall three-way comparison, significant differences were observed between several blood markers, with respect to medication use and type (Table 2). Significant differences in glucose concentration, percent glycosolated hemoglobin, and insulin concentration, all measures of disease severity, and albumin concentrations, were observed between individuals using insulin as compared to OHAs, with indicators further outside the normal range for those on insulin. Significant differences in BMI, glycosolated hemoglobin, albumin, and percent neutrophils and lymphocytes were observed between individuals using insulin as compared to no medication, with indicators further outside the normal range for those on insulin. Significant differences in glucose and insulin concentrations were observed between individuals using OHAs as compared to no diabetes medications, with more elevated concentrations for individuals not using medications. Hypertension was significantly higher among individuals on insulin as compared to all others; reported heart attack and heart disease were greater among those on insulin, but the differences were of borderline significance ($P < 0.075$ and $P < 0.059$, respectively). In general, the health status of individuals on insulin was poorer than that of those on OHAs only.

Medication and traffic interactions

For individuals using insulin, effect estimates for traffic exposure for all models were in the positive direction (Table 3). In the main model, with socioeconomic status (SES) covariates for education and poverty/income levels, CRP was positively and significantly associated with residing ≤ 100 m of a roadway of concern (65% higher CRP concentrations, 95% CI, 3.1 to 164), and between >100 m - ≤ 200 m (81% higher CRP concentrations, 95% CI, 11 to 195), as compared to >200 m, and with the second as compared to reference level of traffic density (60% higher CRP concentrations, 95% CI, 1/2 to 151).

For individuals using only OHAs, effect estimates for traffic exposure for all models were in the negative direction. In the main model with SES covariates, CRP concentrations were

significantly negatively associated only with residing between >100m - 200m of roadway of concern (32% lower CRP concentrations, 95% CI, -51 to -5.2), compared to >200 m. For individuals not on diabetes medications, no consistent pattern was observed in the direction of the effect estimates and none of the traffic indices were significant.

The associations observed in the stratified models between OHAs and traffic exposure and insulin and traffic exposure were confirmed by an interaction model. The interaction model included all persons with diabetes (n=379), all covariates, as well as interaction terms for a subset of the traffic indices: residing 100 m, >100m - 200 m, and number of roadways, each multiplied by the respective coding values for OHAs or insulin use. For individuals using only OHAs, interaction terms were all negative and significant for residing >100m - 200 m ($P < 0.001$), compared to >200 m; residing within 200 m of one roadway ($P = 0.046$) and multiple roadways ($P = 0.007$), as compared to no roadways. For individuals using insulin, interaction terms were all positive and significant for residing 100 m ($P = 0.004$), >100 m - 200 m ($P = 0.007$) and one roadway ($P < 0.001$). Analyses performed using two-way analysis-of-variance (not shown) confirmed these results.

Figures 2a and 2b present the percent differences in CRP for individuals using OHAs or insulin (2a) and those not on medications (2b).

DISCUSSION

This study examined the influence of diabetes medication use and type on the response to residential traffic exposure with respect to concentrations of CRP. CRP concentrations in insulin users were higher with traffic exposure in the stratified model, and were also significant in the interaction model for both distance gradients. The interaction model was designed to compensate for the limitations of sample size apparent in some of the subgroups, e.g. individuals living near 2 or more roadways of concern. CRP concentrations were lower for OHA users across all indices of traffic exposure, though results were more consistently statistically significant in the interaction than in the stratified models. Individuals who were provisionally diagnosed as having diabetes, based on fasting elevated glucose concentrations 126 mg/dl, but who were not on medications, did not show associations with traffic exposure.

We examined associations using a 3-tiered distance gradient: 100 m, >100 - 200 m, and >200 m. Those at the intermediate distance level showed stronger associations with CRP and traffic relative to those at the closer distance of 100. m. While distance might be assumed to equate with exposure, it is unclear whether exposure to the mix and/or individual components of traffic-related pollution associated with living in closer proximity to high traffic roadways is indeed highest within the 100m, as compared to >100 - 200 m gradient.

Several studies have reported gradients in the concentrations of vehicular emissions near highways, though the magnitude and extent of these gradients is a function of traffic conditions, temperature, relative humidity, topography, wind direction and speed, atmospheric stability, and mixing height (Durant et al. 2010). The majority of roadways in this study were not highways, but rather roadways with between 20,000 – 40,000 vehicles per day. Many of these roads are located in dense urban areas bounded by multi-story buildings that may change pollution dispersion dynamics. In a published study of the larger cohort from which this study of individuals with diabetes was derived, similar trends were reported for the >100 - 200 m distance gradient (Rioux et. al. 2010). A possible explanation is that people living closer to the roadway, at the 100 meter distance may keep windows closed more often than those living in the >100m - 200m distance to minimize

noise and road dust from entering through the windows, thereby reducing their exposures. In addition to pollutant and noise gradients, building type and design and level of activity and time spent at home versus outdoors could also be factors contributing to different exposures and response for those living at varying distances from busy roadways.

For multiple roadways, we examined whether people lived 200 m of one or more roadways. The confidence intervals for the higher exposure and the intermediate exposure overlap though they are quite wide. The upper limits for 2+ roadways were always higher for people on insulin, and the beta value and lower limits were always lower for people on OHAs. While not statistically significant in the main models, most likely due to the limited number of people in our study who resided near 2+ roadways, we believe the trends observed are consistent with our hypothesis that both people on insulin and those on OHAs experience a greater difference in CRP with greater traffic.

As a group, individuals with T2D have been reported to be more susceptible to air pollution, though the mediating effect of diabetes medications on pollution exposures has not been examined. Prior studies asked participants to abstain from taking their diabetes medications for 12-24 hours prior to sample collection (O'Neill et al. 2005 and 2007); did not report on, specifically evaluate, or have access to information on medication use (Ostro et al. 2006; Schneider et al. 2008); or were conducted prior to the introduction of two of the oral medications evaluated here (Zanobetti et al. 2002; Bateson et al. 2004). Sulfonyleureas have been available in the United States since 1954; metformin since 1995; and glitazones since 1997 (Inzucchi et al. 2002).

T2D has been associated with overall obesity, central obesity and waist-to-hip ratio (Shoelson et al. 2006). In Caribbean origin Hispanics, however, diabetes was prevalent even among non-obese individuals, whereas for non-Hispanic white women, the prevalence of diabetes was strongly associated with total and central obesity (Bermudez et al. 2001). A higher prevalence of diabetes among non-obese individuals in this population may partly explain the observable anti-inflammatory response to OHAs, though the mechanism for an enhanced anti-inflammatory response with traffic exposure, and whether this response is representative of the larger population, is unclear.

Mechanisms of action for T2D medications

Diabetes medications compensate when the body can no longer produce adequate amounts, by increasing insulin secretion (sulfonyleureas), increasing insulin sensitivity and decreasing insulin resistance (glitazones), or reducing hepatic glucose production in the presence of insulin (metformin) (Chu et al. 2002; Dandonna 2008). Often, as in this study population, more than one type of pharmacological therapy is used. Among people taking insulin in our population, 32% percent also used OHAs.

At physiologic concentrations, in vitro insulin has been shown to inhibit ICAM-1, an adhesion molecule in the vasculature, and NF- κ B (Dandonna 2008). While insulin has anti-inflammatory effects, the state of insulin resistance, an early and sustained feature of T2D (Bailey 2005), is pro-inflammatory (Hsueh et al. 2004; Shoelson et al. 2007). An advanced state of insulin resistance is often accompanied by arterial dysfunction and macrovascular diseases including atherosclerosis (Beckman et al. 2002; Creager et al. 2003), which may partially explain the higher CRP concentrations observed here for individuals on insulin.

Several mechanisms have been described by which OHAs exert an anti-inflammatory effect. In the population evaluated here, metformin was the most widely used OHA (n=198). Metformin has been termed an insulin sensitizer, though its mechanism of action is primarily the reduction of hepatic glucose production in the presence of insulin (Inzucchi et

al 2002). Insulin sensitizers suppress pro-inflammatory reactive oxygen species, suppress pro-inflammatory genes including the pro-inflammatory transcription factor nuclear factor- $\kappa\beta$ (NF- $\kappa\beta$), restore the anti-inflammatory effect of endogenous insulin and restore normoglycemia (Jiang et al. 1998; Chawla et al. 2001; Mohanty et al. 2004; Ghanim et al. 2006).

Results from clinical trials on the effects of metformin on inflammatory markers including CRP have been equivocal, with some studies reporting decreases with use of metformin (Chu et al. 2002; Haffner et al. 2005; Caballero et al. 2004) and others reporting no significant effects (De Jager et al. 2005; Pradhan et al 2009)

Glitazones, taken by 78 participants, are peroxisome proliferator-activated receptor- γ (PPAR- γ) agonists that exert anti-inflammatory effects at the cellular and molecular level by inhibiting macrophage activation and secretion of cytokines, smooth muscle proliferation and endothelial cell expression of adhesion molecules (Chu et al. 2002; Mohanty et al. 2004; Dandonna et al. 2008). Glitazones also increase insulin sensitivity and decrease insulin resistance.

Possible mechanisms of interaction

It is not clear where in the complex and cross-promoting inflammatory network that traffic exposure and diabetes medications intersect. For insulin, it is possible that medication use is a surrogate for the underlying inflammatory conditions associated with advanced T2D, namely atherosclerotic vascular disease, including coronary artery, peripheral arterial, and cerebrovascular disease (Beckman et al. 2002). Individuals with these underlying conditions might be expected to have a greater susceptibility to the inflammatory effects of traffic exposure. Prior evidence supports the interpretation of effect modification of PM_{2.5} exposures or traffic –related exposures by conditions linked to chronic inflammation, including diabetes, obesity and hypertension (Dubowsky et al. 2006). Several studies report that ambient particulates, including diesel exhaust particles and residual oil fly ashes stimulate NF- $\kappa\beta$ and IL-6, (Quay et al. 1998; Shins et al. 2000; Shukla et al. 2000). These studies are consistent with the observed results for individuals on insulin, i.e. increases in CRP with increasing levels of traffic exposure.

As a class, insulin sensitizers, like metformin and glitazones, directly and indirectly suppress pro-inflammatory genes and it is possible that presentation of a pro-inflammatory stressor, i.e. traffic exposure, enhances the anti-inflammatory response, consistent with our findings of reduced CRP with higher traffic exposure. A feed-forward pathway in insulin resistance and atherosclerosis has been described in which activation of NF- $\kappa\beta$ stimulates IL-6 (the cytokine primarily responsible for stimulation of CRP) which further activates NF- $\kappa\beta$ (Shoelson et al 2006). We hypothesize that traffic exposure may stimulate a down-regulation process for those on medications with the anti-inflammatory properties of OHAs.

PPAR- γ agonists including glitazones, have been shown to transrepress certain genes including one mechanism that involves binding coactivators for transcription factor NF- $\kappa\beta$ or directly binding NF- $\kappa\beta$ the end result of which would be inhibition of this pro-inflammatory gene (Zingarelli et al. 2005) and the downstream cytokine (IL-6) and protein (CRP) with which it is associated. Non-steroidal anti-inflammatory drugs such as ibuprofen, fenoprofen, and indomethacin which inhibit cyclo-oxygenase -1 (COX-1) and COX-2 are also PPAR- γ agonists but at higher doses than other PPAR- γ agonists (Zingarelli et al. 2005).

Both in vivo and in vitro studies have demonstrated anti-inflammatory feedback loops involving PPAR- γ . Following exposure to the inflammatory stimuli endotoxin

lipopolysaccharide (LPS), a potent natural ligand of PPAR- γ , 15d-PGJ₂, enhanced suppression of COX-2, that is an enzyme with a key role in inflammation. The authors reported that the PPAR- γ ligand interfered with the NF- κ B signaling pathway from the inflammatory stimuli in a negative feedback loop mediated through PPAR- γ (Inoue et al. 2000). Following induction of polymicrobial sepsis in rats, treatment with a glitazone or the PPAR- γ ligand 15d-PGJ₂ blunted cytokine production and reduced the infiltration of white blood cells into several organs (Zingarelli et al. 2003). The mechanism of action included reduction of NF- κ B.

Factors other than medication

It is important to consider whether the lower CRP with use of OHAs and traffic exposure reported here may be attributable to factors other than diabetes medication. In general, the health status of individuals on insulin was poorer than those not on insulin but on OHAs with respect to fasting glucose concentrations, glycosylated hemoglobin, insulin and albumin concentrations, and percent neutrophils and lymphocytes. All of these factors were included as covariates and only BMI, albumin, and lymphocytes were significantly associated with CRP.

We evaluated lymphocytes, neutrophils and monocytes as outcome variables and observed no consistent associations with any of the traffic indices (analyses not shown). In preliminary analyses (not shown), among individuals using only OHAs, the negative association between traffic and CRP appears to be enhanced for those with BMI<30, though the weight of these results is limited by reductions in sample size with further stratification and subgroup analyses. One possibility, which would require additional evaluation in a larger cohort, is that the anti-inflammatory effect from use of OHAs or the interaction of OHAs and traffic exposure is overwhelmed by the higher circulating CRP in individuals with higher body fat (Yudkin et al. 1999 and 2000; Pandonna et al. 2004).

Studies report that statins, a group of cholesterol-lowering lovastatin (Mevacor), atorvastatin (Lipitor), and rosuvastatin (Crestor), have anti-inflammatory effects (Ridker et al. 1999). In the regression models, statins were associated with significantly lower CRP for individuals taking OHAs only [44% lower CRP for those on statins vs. not (95% CI, -71% - -17%) but not for those on insulin. Taking statins did not change the associations between the traffic indices and CRP concentrations.

Strengths and limitations

While this analysis provides intriguing findings regarding diabetes medications and traffic-related health impacts, the cross-sectional nature of the study, and the use of surrogate rather than direct measures of traffic exposure represent limitations. Small sample size for some of the subgroup analysis was also a limitation, though the interaction model incorporated all cases and generally confirmed the trends observed in the stratified models.

The selection criteria for the larger longitudinal cohort study conducted by the BPRHS did not initially include traffic considerations. People residing within the evaluated roadway buffers may have very different exposure levels as a result of their exact distance from the road, the location of apartments within a building, the condition of windows, infiltration rates, and ventilation systems within the building. Traffic emissions and traffic-related noise have both been associated with adverse health effects, the relative contribution of each proving difficult to discern (Babish 2006). Topographical features such as trees and other buildings may also reduce traffic impacts within the 200 m buffer. Orientation of homes with respect to roadways was not considered and could influence the magnitude of exposure, with increasing exposures downwind versus crosswind.

People spend different amounts of time at home, reflecting variation in actual residential traffic exposure. Low employment rates (20 percent) among this older population suggest that time spent at home was relatively high, although variation can arise from travel outside the home for purposes other than employment. Prescriptions for and availability of medications were verified during the interview process, though compliance with diabetes medications was not confirmed. Information on length of illness and medication use was not collected.

The strengths of this study include the extent of covariate information on health-related behaviors (smoking, alcohol consumption, physical activity levels) co-morbidities (hypertension, prior heart attack and heart disease) and physiological markers of health status (HDL, LDL, blood pressures, and other markers of inflammation including serum albumin, platelet and white blood cell counts) that could be used to develop and adjust the models and develop a clearer picture of the associations between traffic and the outcome of concern. Extensive information on socioeconomic factors (income/poverty levels, education, health insurance, and other social support factors) were also available and used to develop the final models. Another strength was the comprehensive nature of traffic data, including traffic count statistics on vehicles per day on roads throughout the study area.

CONCLUSIONS

Among people with diabetes, individuals on insulin appear to be more vulnerable to the effects of traffic exposure in terms of increases in CRP concentrations than those on OHAs or not on medications. This response may be a result of their disease severity, the underlying inflammatory conditions associated with advanced T2D in combination with possible interactive effects of insulin medications with traffic exposure. Individuals on OHAs may experience a reduction in CRP concentrations with traffic exposure, possibly from potentiation of the anti-inflammatory effects of OHAs. Further investigations are required to evaluate prospectively whether OHAs confer any protective effects from traffic exposure, as well as any possible impacts on disease progression for diabetes and cardiovascular outcomes in this context.

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Abbreviations

BMI	Body mass index
CRP	C-reactive protein
CPHHD	Center for Population Health and Health Disparities
HDL	High density lipoprotein
IL-6	Interleukin 6
LDL	Low density lipoprotein
lnCRP	Natural log-transformed C-reactive protein
NO₂	Nitrogen dioxide
NO_x	Nitrogen oxides
OHA	Oral hypoglycemic agents
O₃	Ozone
PM_{2.5}	Particulates less than 2.5 microns in aerodynamic diameter
PM₁₀	Particulates less than 10 microns in aerodynamic diameter
Sulfur dioxide	Sulfur dioxide
TAZ	Traffic analysis zone
UFP	Ultrafine particulates (less than 0.1microns in diameter)
VMT/mi²	Vehicle miles travelled per square mile
VOC	Volatile organic chemicals
WBC	White blood cell concentrations

Figure 1.

a: Percent difference in C-reactive protein among individuals using only OHAs and using insulin and 95% CI associated with traffic indices

b: Percent difference in C-reactive protein among individuals using no diabetes medications and 95% CI associated with traffic indices

Figure 2. Percent difference in C-reactive protein among individuals using only OHAs and using insulin (a) and using no diabetes medications (b) and 95% CI associated with traffic indices for complete study group and subgroups

100 = location of residence less than or equal to 100 meters of a roadway with more than 20,000 vehicles per day; >100 - 200 location of residence between 100 and 200 m; 1 roadway = location of residence within 200 m of roadway with more than 20,000 vehicles per day; 2+roadways = location of residence within 200 m of 2 or more of these roadways; DenseLevel2, DenseLevel3 and DenseLevel4 = Raster-based traffic density levels.

Baseline characteristics and proximity to roadways with >20,000 vehicles/day for the Boston Puerto Rican Center for Health and Health Disparities Study Participants with Type 2 Diabetes

Table 1

Characteristics	Total sample n=379	100 meters (n=79)	>100 - 200 meters (n=83)	>200 meters (n=217)	p-Value
<i>Basic descriptive</i>					
Age (years)	59 ± 6.9	59.7	60.6	58.9	0.132
Female sex	275 (73)	59	60	156	0.891
Employed	42 (13)	11	4	27	0.153
Length of residence	7.4 ± 7.4	6.9	7.1	7.6	0.752
Education 9th grade or more	169 (44)	41	28	100	0.053
Below poverty threshold	265 (72)	46	50	124	0.824
Smoking					0.659
never	185 (49)	42	39	104	
past	127 (34)	21	29	77	
current	66 (17)	16	15	35	
Alcohol					0.588
not current	258	54	51	153	
current moderate	101	19	27	55	
current heavy	15	4	4	7	
<i>Health Status</i>					
High density lipoprotein (mg/dl)	42 ± 10.8	44	40	43	0.068
Low density lipoprotein (mg/dl)	98 ± 34.9	99	93	98	0.461
Triglycerides (mg/dl)	177 ± 125	164	197	174	0.209
BMI (kg/m ²)	33.8 ± 6.9	33.6	33.2	34.1	0.621
Systolic BP (mm Hg)	138 ± 18.6	141	139	138	0.382
Diastolic BP (mm Hg)	80 ± 10.4	79.7	79.2	80	0.825
Pulse pressure (mm Hg)	59 ± 15	61.3	59.6	57.5	0.155
Hypertension	320 (85)	67	71	182	0.925
Heart attack (% self-reported)	50 (0.8)	9	12	29	0.841
Heart disease (% self-reported)	74 (20)	14	16	44	0.903
<i>Medications</i>					
Statins	218 (58)	44	50	124	0.83

Characteristics	Total sample n=379	100 meters (n=79)	>100 - 200 meters (n=83)	>200 meters (n=217)	p-Value
Hypertension	289 (76)	61	64	164	0.961
Diabetes medications (any)	304 (80)	60	70	174	0.408
Insulin	92 (24)	20	19	53	0.934
Oral hypoglycemic agents only	212 (56)	40	51	121	0.382
Metformin (a)	198 (52)	41	43	114	0.991
Sulfonylureas (a)	117(31)	20	28	69	0.461
Glitazones (a)	78 (21)	13	21	24	0.374
Non-steroidal anti-inflammatory drugs	128 (34)	27	29	72	0.956
<i>Confirmed conditions</i>					
Obesity (BMI $\geq$ 30)	257 (68)	55	48	154	0.121
<i>Inflammatory Biomarkers</i>					
C-reactive protein (mg/l)	4.1 (0.1 - 69.8)	3.9	4.5	4.1	0.752
Log-transformed C-reactive protein (mg/l)	1.3 $\pm$ 1.1	1.36	1.5	1.4	0.612

Values are no. (%), mean $\pm$ SD, when normally distributed and median (range) when other distribution.

p-values from Pearson chi-square for binary variables and t-test for independent samples for continuous variables.

(a) Includes people also on insulin.

Table 2
Comparison of health status and blood marker levels for all persons with diabetes by medication status

Characteristic	Insulin users (I) (n=92)	OHAs/No Insulin (O) (n=212)	No Diabetes medication (N) (n=75)	Multiple comparison	Overall p -Value	Normal Range	Source
BMI (kg/m ²)	35 ± 6.6	34 ± 7.1	33 ± 6.8		0.401	Underweight: < 18.5 kg/m ² Normal weight: 18.5-24.9 kg/m ² Overweight: 25-29.9 kg/m ² Obesity Class 1: 30-34.9 kg/m ² Obesity Class 2: 35-39.9 kg/m ² Extreme obesity > 40 kg/m ²	NIH, 2000
Waist circumference (cm)	109 ± 15	106 ± 15	104 ± 14		0.073	?102 cm in men and ?88 cm in women	NIH, 2000
Glucose (mg/dl)	175 ± 82	147 ± 60	172 ± 66	a. c.	0.001	< 126 mg/dl	ADA, 2006
Glycosolated hemoglobin (%)	9.4 ± 2.0	8.3 ± 1.8	7.7 ± 1.9	a. b.	<0.001	Normal 4-6 %, Treatment goals: < 7%	ADA, 2004
Homocysteine (umoles/l)	9.2 ± 3.9	9.3 ± 3.6	9.0 ± 5.7		0.893	Desirable levels (Ubbink 2001): μmol/L. Elevated Males: > 11.4 μmol/L Females: > 10.4 μmol/L	Pfeiffer et al. 2005
High density lipoprotein (mg/dl)	43.2 ± 11.0	41.9 ± 10.4	43.7 ± 11.6		0.363	>40 mg/dl	(EPDET, 2002)
Low density lipoprotein (mg/dl)	96.2 ± 32.9	96.2 ± 35.5	103.2 ± 35.8		0.316	Optimal: < 100 mg/dL	(EPDET, 2002)
Triglycerides (mg/dl)	188 ± 152	170 ± 99.5	182 ± 151		0.485	Normal: < 150 mg/dL	(EPDET, 2002)
C-reactive protein (mg/l)	6.1 ± 7.8	6.9 ± 7.3	8.7 ± 11.6		0.081	< 1.0 mg/l low risk of cardiovascular disease; 1.0 - 3.0 average risk; > 3.0 high risk	Pearson et al. 2003
Ln-transformed CRP	1.46 ± 1.0	1.2 ± 1.1	1.49 ± 1.2		0.104		
Insulin levels (μU/ml)	26 ± 22	18 ± 16	31 ± 30	a. c.	<0.001	Insulin resistance: > 20.7 μIU/ml	Stern et al. 2005
Albumin (g/dl)	4.11 ± 0.41	4.27 ± 0.28	4.22 ± 0.30	a. b.	0.001	3.8-5.4 g/dL for males and 3.8-5.3 g/dL for females	Visser et al. 2005

Characteristic	Insulin users (I) (n=92)	OHAs/No Insulin (O) (n=212)	No Diabetes medication (N) (n=75)	Multiple comparison	Overall <i>p</i> -Value	Normal Range	Source
White blood cell count (10 ³ cells/ μl)	7.1 ± 1.6	6.9 ± 1.6	6.8 ± 1.5		0.316	See text	
Neutrophils (% of white blood cells)	57 ± 8.5	54 ± 9.8	52 ± 10	b.	0.009	40% to 60% of the white blood cells	MedlinePlus 2010
Lymphocytes (% of white blood cells)	34 ± 7.7	36 ± 8.9	38 ± 9.9	b.	0.004	20% to 40% of the white blood cells	MedlinePlus 2010
Hypertension (%)	90	86	75	b, c.	0.015		
Heart attack (self-reported)	19	12	8	a, b.	0.075		
Heart disease (self-reported)	27	18	13	a, b.	0.059		

Values are mean ± SD or percentages where noted. *p*-Values are derived from one-way ANOVA for continuous variables and Pearson chi-square for binary variables. Multiple (Bonferroni) comparison: Insulin (I), OHAs (O), No meds (N). Significant at *p* < 0.05; I vs O = a; I vs N = b; N vs O = c.

Table 3

Percent difference and 95% confidence intervals in C-reactive protein associated with traffic indices stratified by medication use.

Medication type	Crude model				Main model ^a				Main + SES			
	(n)	Coeff	95% CI	p-Value	Coeff	95% CI	p-Value	Coeff	95% CI	p-Value	Coeff	95% CI
Individuals Using Insulin (n=91)												
3-Tiered gradient												
100 m	20	79.0	33.0	265.5	0.003	60.0	1.7	151.9	0.042	65.0	3.1	164.3
>100 - 200 m	19	120.3	6.8	199.5	0.027	73.7	9.3	175.7	0.020	81.3	11.0	195.9
Number of roadways												
1 roadway	31	98.8	28.4	207.7	0.002	74.4	19.2	155.2	0.005	79.5	19.7	169.1
2+ roadways	8	100.6	-3.6	317.5	0.062	38.0	-27.2	161.7	0.320	49.2	-23.8	192.4
Traffic Density												
Level 2	46	35.1	-16.1	117.5	0.212	53.0	-1.7	138.2	0.059	60.0	1.2	150.9
Level 3	16	37.4	-26.7	157.5	0.317	35.3	-21.3	132.3	0.270	46.1	-16.8	156.3
Individuals Using Only OHAs (n=209)												
3-Tiered gradient												
100 m	40	-27.8	-51.8	8.2	0.114	-15.5	-39.9	19.0	0.333	-15.7	-40.8	20.0
>100 - 200 m	51	-39.0	-57.9	-11.7	0.009	-32.8	-51.0	-7.7	0.014	-32.1	-51.4	-5.2
Number of roadways												
1 roadway	80	-34.1	-52.1	-9.3	0.011	-23.0	-41.8	1.8	0.066	-22.7	-42.2	3.5
2+ roadways	11	-35.9	-68.2	28.9	0.210	-38.6	-65.5	9.3	0.097	-36.4	-64.7	14.7
Traffic Density												
Level 2	97	11.9	-20.5	57.5	0.519	0.7	-24.9	35.0	0.965	-3.3	-28.6	30.7
Level 3	39	-28.3	-53.8	11.4	0.139	-22.3	-46.4	12.5	0.181	-22.6	-47.2	13.3
Individuals Not Using Medications (n=75)												
3-Tiered gradient												
100 m	19	32.7	-38.9	188.1	0.47	50.1	-35.5	249.0	0.34	59.5	-31.7	272.5
>100 - 200 m	13	-44.3	-71.7	9.3	0.088	-42.8	-71.8	16.2	0.12	-46.8	-74.7	12.1
Number of roadways												
1 roadway	28	-28.0	-60.7	32.0	0.284	-29.5	-62.2	31.5	0.266	-31.9	-64.3	29.7

Medication type	Crude model					Main model ^a					Main + SES		
	(n)	Coeff	95% CI	p-Value	Coeff	95% CI	p-Value	Coeff	95% CI	p-Value			
Individuals Using Insulin (n=91)													
2+ roadways	4	53.4	-58.3 465.2	0.514	186.3	-22.2 952.8	0.111	250.4	-6.2 1210.5	0.062			
Traffic Density													
Level 2	41	-9.5	-51.8 69.6	0.752	16.9	-39.9 127.5	0.64	4.7	-45.9 102.4	0.89			
Level 3	8	51.1	-45.2 316.2	0.42	79.3	-41.4 449.6	0.30	103.6	-25.5 456.8	0.162			

^aMain model adjusted for age, gender*, bmi*,[†] hdl*, albumin*, smoking, waist circumference, statin use*, white blood cell count*, glycosolated hemoglobin[†], glucose, insulin levels[†], lymphocytes*, SES factors include poverty/income ratio and education[†]

* Significant (p<0.05) for OHA models.

[†] Significant (P<0.05) for insulin models. Reference levels were: > 200 m for the 3-tiered gradient; 0 (roads) for number of roadways 200 m of a residence; and level 1 for density level.

Table 4

Significance of Interaction terms for medication use and traffic exposure.

Model	All diabetes cases (n=370)	
	OHAs × traffic interaction terms	β p -Value
OHAs × 100 m		-0.211 0.427
OHAs × >100m - 200 m		-0.939 <0.001
OHAs × 1 roadway		-0.450 0.046
OHAs × 2 or more roadways		-1.134 0.007
Insulin × traffic interaction terms		
Insulin × 100 m		0.814 0.004
Insulin × >100m - 200 m		0.814 0.007
Insulin × 1 roadway		0.915 <0.001
Insulin × 2 or more roadways		0.470 0.291

Models adjusted for same covariates as main model +SES.

Reference levels were: > 200 m for 100m and >100m - 200 m ; 0 (roadways) for number of roadways 200 m of a residence.