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Medication type modifies inflammatory response to traffic exposure in a population with type 2 diabetes

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Abstract

The association between residential traffic exposure and change in C-reactive protein over 2-years was evaluated using multivariate linear regression including interaction models for traffic and diabetes medication use/type (insulin vs. oral hypoglycemic agents (OHAs)).

The study population was Puerto Rican adults (n = 356) residing in greater Boston with type 2 diabetes. Traffic was characterized as proximity to roads with >20,000 weekday traffic volumes, and multi-directional traffic density.

Increases in CRP concentration were significantly associated with residence 100 m of a roadway (p = 0.009) or near multiple roadways (p < 0.001), vs. further away, for individuals using insulin in stratified models, with consistent results in interaction models (p = 0.071 and p = 0.002).

As)HAs)HCRP was significantly lower with highest traffic density exposure in stratified (p = 0.03) and interaction models (p = 0.024) for individuals using OHAs.

Individuals on insulin experienced increased CRP concentrations with traffic exposure over a 2-year study period, while those using OHAs did not experience increases.

Keywords

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

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Author contributions

C.L.R. conceived and designed the analysis, analyzed and interpreted the data, wrote the manuscript; M.M. designed the analysis, interpreted the data, contributed to the discussion, reviewed and approved of the manuscript; K.T. contributed data, reviewed and approved of the manuscript; D.B. interpreted the data, reviewed and approved of the manuscript.

Disclosures

The authors have declared they have no competing interests.

1. Introduction

Several large cohort studies have examined the role of fine particulate pollution in incident type 2 diabetes (Chen et al., 2013) including traffic-related pollution assessed as nitrogen dioxide (NO₂, likely a marker for locally elevated particulate matter), traffic load in vehicles per day, roadway proximity or some combination thereof (Andersen et al., 2012; Coogan et al., 2012; Puett et al., 2011; Krämer et al., 2010). With one exception (Andersen et al., 2012), most of these studies found an association with incident type 2 diabetes and at least one of the traffic indicators examined. One study showed that NO₂ and traffic loads near residence were significantly associated with type 2 diabetes mortality (Raaschou-Nielsen et al., 2013). The impact of traffic-related pollution on type 2 diabetes progression and mortality may be underestimated here, and in general, as co-morbidities related to type 2 diabetes rather than type 2 diabetes are often coded as cause of death (Peters, 2012; Fuller et al., 1983).

C-reactive protein (CRP) concentration has been shown to predict the development of type 2 diabetes and other insulin disorders (Hu et al., 2004; Pradhan et al., 2001; Barzilay et al., 2001; Duncan et al., 2003). Prior studies have reported a pro-inflammatory association with traffic or traffic-related pollutants, i.e., an increase in CRP (Riediker et al., 2004; Rückerl et al., 2006; Dubowsky et al., 2006; Yue et al., 2007; Delfino et al., 2008; Rioux et al., 2010a, 2011; Brugge et al., 2013).

Our study participants are part of a larger cohort of Puerto Ricans living in the Boston, MA area who were found to have a disproportionately high prevalence of type 2 diabetes. An earlier study among Puerto Ricans aged 60 and older in MA showed that 38% had type 2 diabetes, relative to 23% of neighborhood based non-Hispanic whites; and that those with type 2 diabetes were more than twice as likely to have elevated glycosylated hemoglobin (>7%) indicating poor glycemic control (Tucker et al., 2000). We previously reported two cross-sectional analyses in this larger population (Rioux et al., 2010a, 2011). In the first, with 1017 Puerto Rican adults, individuals with type 2 diabetes who were exposed to high traffic patterns had higher CRP than those less exposed (Rioux et al., 2010a). A subsequent analysis of only those people with type 2 diabetes reported significantly elevated CRP in association with traffic exposures for individuals taking insulin (n = 92), and unexpectedly, significantly lower CRP in association with traffic exposure among those taking OHAs (n = 209), primarily metformin (n = 192) (Rioux et al., 2011). These studies suggest an enhanced adverse response to pro-inflammatory stressors for individuals taking insulin. This adverse response may be associated with disease severity, disease duration, or, possibly, the interactive effects of insulin with traffic exposure. The studies also raise the question of whether OHAs are protective against pro-inflammatory stressors. In this longitudinal analysis, we aimed to test whether, consistent with cross-sectional results, medications for type 2 diabetes were associated with change in the inflammatory response to residential traffic exposure over a 2 year follow-up period, and whether this varied by type of medication used. To our knowledge, this is the first longitudinal study to examine the modifying role of type 2 diabetes medication type with indicators of traffic exposure.

2. Materials and methods

2.1. Study design and population

This analysis is part of a longitudinal cohort study on stress, nutrition, aging and chronic health conditions conducted by the University of Massachusetts at Lowell, Northeastern and Tufts Universities' Center for Population Health and Health Disparities (CPHHD). Baseline health status, demographic, and blood and genetic data were collected for 1505 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. This recruitment has been previously described (Tucker et al., 2010). Here we evaluate those participants with type 2 diabetes at baseline for whom two-year follow-up data were collected and who lived at the same address over the two-year follow-up period to insure consistency in exposure.

Because questions regarding acute infections were not included in the interview, men with white blood cell (WBC) concentration $<3.9 \times 10^3$ or $>10.6 \times 10^3/\text{mm}^3$ and women with concentration $<3.5 \times 10^3$ or $>11.0 \times 10^3/\text{mm}^3$ were excluded ($n = 59$) from our analyses to control for confounding by infection that could have raised their CRP concentration (Fleming et al., 1998). From the remaining group 356 individuals either reported taking type 2 diabetes medications ($n = 288$) or had a fasting glucose concentration $\geq 126 \text{ mg/dl}$ ($n = 68$), meeting the threshold for the provisional diagnosis of type 2 diabetes (American Type 2 diabetes Association, 2006), and were included in this study. Selection criteria did not include traffic considerations but were focused on those who resided within the general study area. Study participants resided primarily in the greater Boston area, with approximately 70 percent present in neighborhoods that comprise the urban core of Boston. An additional 8 percent and 10 percent of participants resided in Chelsea and Lawrence, MA, respectively, two areas of relatively high Puerto Rican concentration, with the remainder in surrounding cities and towns.

2.2. Data collection

Details on data collection were previously reported (Tucker et al., 2010; Rioux et al., 2011). 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.

2.3. Traffic exposure assessment

Address geo-coordinates were used to characterize residential traffic exposure at the time of the baseline interview and acquisition of blood data. Geo-coordinates for residential addresses were derived using a three-tiered system consisting of parcel matching, street network matching, and manual refinement using Google Earth (Rioux et al., 2010). 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 traveled per square mile (VMT/mi²) in each of 130 Traffic

Analysis Zones (TAZs) within the study area. ArcGIS software version 10.1 was used to construct 100 m and 200 m buffers along roadways of concern and to identify participants who resided within these buffers (Rioux et al., 2010a, 2010). TAZ data were developed by 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 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: (Chen et al., 2013) a three-tiered distance gradient (< 100 m; >100 and < 200; and >200 m); (Andersen et al., 2012) number of major roadways (0, 1, or 2+) within 200 m of a residence; and (Coogan et al., 2012) traffic density based on vehicle miles traveled per square mile. Four density-based exposure levels were defined, with level 4 representing the highest traffic density. Study participants were assigned the value for their residence (See 25 for additional details).

2.4. Statistical analysis

All statistical analyses were performed using IBM SPSS software, version 20 (2011). For univariate and bivariate analyses, mean $\pm$ SD and t-test or ANOVA were used for variables with normal distribution, and median and WRST or Kruskal–Wallis tests were used for variables with skewed distribution. For categorical variables, the frequency and the proportion of participants with events, or in that category, (%) were estimated. The chi-squared 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 longitudinal association between residential traffic exposure and change in lnCRP was evaluated using multivariable linear regression, with 2-year change in lnCRP as the outcome variable, controlling for baseline concentration of lnCRP. Results for lnCRP were exponentiated and reported as percent change in CRP concentration over the follow-up for each unit increase in exposure. We conducted a model building process using the same set of explanatory variables used in the prior cross-sectional analysis of the influence of type 2 diabetes medications on lnCRP and traffic (Rioux et al., 2011) including baseline values for: age, sex, BMI, plasma high-density lipoprotein (HDL) and albumin, smoking status, waist circumference, statin use, white blood cell count (WBC) and differential lymphocyte count, plasma glucose and glycosylated hemoglobin, duration of follow-up in months, plasma insulin concentration, attainment of 8th grade education or more, and whether or not total household income was above the Health and Human Service poverty threshold for the year the participant was interviewed (US Health and Human Services, 2007). Self-reported history of heart attack was also considered, based on observed differences for individuals with different medication types.

Four models were evaluated: (Chen et al., 2013) unadjusted models for change in lnCRP and each of the traffic indices; (Andersen et al., 2012) a baseline predictor model with the covariates sex, age, BMI, statin use, WBC, education, poverty threshold, months to follow-up, lnCRP, and self-reported heart attack; (Coogan et al., 2012) a change predictors model

using values for the changes in the same set of covariates in model 2 over the 2-year follow-up (ex. BMI value at 2-year minus the BMI value at baseline); and (Puett et al., 2011) a combination model, or main model that includes either the baseline or change value as the best predictor for change in lnCRP. Model 3 was primarily for exploratory purposes. The two-sided significance level was 0.05. For both the baseline and main models, our elimination criteria to address multicollinearity included tolerance values of <0.5 and variance inflation factors of >2.0 . We also eliminated predictors with p-values >0.2 and de minimus absolute standardized coefficients to avoid over-adjustment. With renewed screening conducted after each exclusion, the following variables were eliminated from further evaluation and assumed to contribute little to the overall equation and/or to be sufficiently represented by other variables: waist circumference, glucose, lymphocytes, insulin, albumin, and smoking.

Type 2 diabetes medications included insulin and oral hypoglycemic agents (metformin, sulfonylureas, and glitazones). Consistent with our cross-sectional study, we stratified this population into three groups: (Chen et al., 2013) those using insulin ($n = 91$); (Andersen et al., 2012) those using OHAs only ($n = 197$); and (Coogan et al., 2012) those not using any type 2 diabetes medications ($n = 68$), performing separate linear regression analyses on each group. Our evaluation was based on medication status at baseline.

Each of the traffic variables was analyzed in separate regression models against 2-year values of lnCRP, controlling for baseline lnCRP. Indicator variables were used to evaluate the distance gradient (reference level >200 m); number of roadways near residence (zero as reference level); and traffic density (the lowest density levels as reference level).

To understand the modifying effects of the two types of medication, we also developed an interaction model including all individuals with type 2 diabetes, with interaction terms created for medication type and each traffic variable, e.g. use of OHAs multiplied by residence >100 m to road, use of OHAs multiplied by numbers of roadways within 200 m. The same approach was used to create terms for the interaction of insulin and traffic exposure. Interaction models used the same covariates as the main model.

3. Results

3.1. Study population and demographics at baseline

The study population is a subset of individuals evaluated in our prior cross-sectional analysis, i.e. those who remained at the same address over the follow-up period. Demographics and other characteristics are similar to those previously reported. The mean age of study participants at baseline was 59 ± 6.9 years and 73 percent were women (Table 1). Fourteen percent reported being employed and 46 percent reported education at or above the 8th grade level. The median CRP concentration was 4.1 mg/L. At baseline, mean systolic and diastolic blood pressures were 138 ± 18.6 and 80 ± 10.4 , respectively. Mean pulse pressure was 59 ± 15 with 70% >50 mmHg, a cut-off point associated with adverse cardiovascular outcomes (Haider et al., 2003). Hypertension, defined as systolic blood pressure ≥ 140 or diastolic blood pressure ≥ 90 or taking hypertension medication, was seen

in 77 percent of participants. Obesity, defined as body mass index ≥ 30 (kg/m²), was seen in 69 percent of participants.

Eighty one percent of the study population was on some form of type 2 diabetes medication. Twenty-six percent of study participants used insulin (n =91), and 55 percent used OHAs only (n =197). Of these, 195 were taking metformin, 115 sulfonyureas, and 67 glitazones. Thirty-six percent of those taking metformin (n = 71) were also taking sulfonyureas and 21 percent (n = 42) were also taking glitazones. Twenty-four percent (n = 24) of those taking sulfonyureas were also taking glitazones. With the exception of hypertension, baseline characteristics were not significantly different, at the $p < 0.05$ level, on the basis of residential distance to roadway.

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

Significant baseline to 2 year differences were seen for blood markers and health conditions, with respect to medication use and type (Table 2). Interestingly, CRP, glucose, and glycosolated hemoglobin declined over the follow-up period, with significant declines in glycosolated hemoglobin for all three groups. There was a significant increase in the number self-reporting a history of heart attack among those not on medication ($p = 0.045$) or using insulin ($p = 0.011$), and this approached significance ($p = 0.096$) for those taking OHAs. The directionality of change in variables tended to be the same for all three groups, with the exception of insulin concentration; they increased in people using insulin, but decreased in the other two groups. HDL cholesterol increased among those using insulin or OHAs. While these trends suggest improvement in health indicators, blood pressure, self-reported heart attack and statin medication use increased, suggesting a more complex picture of health status.

3.3. Medication and traffic interactions

For individuals using insulin, effect estimates for greater traffic exposure for all models were in the direction of higher CRP (Table 3). In the baseline model, residing ≤ 100 m from a roadway of concern approached significance, with 58.2% greater increase in CRP concentration, 95% CI: $-0.7, 152$); and residing >100 m – ≤ 200 m from a roadway was significantly associated with 81.1% greater increase in CRP concentration, 95% CI: $6.2, 209$), relative to >200 m. Residing near 2 or more roadways was associated with 190% greater increase in CRP concentration, 95% CI: $61.0, 424$), compared to zero roadways.

For individuals using only OHAs, the highest traffic density was associated with lower CRP (49.3% relative decline in CRP concentration, 95% CI: $-73.6, -2.5$), compared to the lowest traffic density. For individuals not on type 2 diabetes medication, no consistent pattern was observed in the direction of the effect estimates and none of the traffic indices were significant in the baseline and main models. The main model, including baseline covariates for sex, age, BMI, lnCRP, education, months to follow-up, and poverty levels; and change covariates for HDL, glycosolated hemoglobin, statin use and self-reported history of heart attack, reflected the same patterns for all three groups, with stronger associations generally observed (lower p-values and higher absolute effect estimates) (Fig. 1).

The associations observed in the stratified models between OHAs and traffic exposure, and insulin and traffic exposure, were confirmed by interaction models. The interaction model included all persons with type 2 diabetes ($n = 356$), all covariates in the main model, as well as interaction terms for a subset of the traffic indices: residing ≤ 100 m, residing near 2 or more roadways compared to no roadways, and residing in the highest as compared to the lowest traffic density area each multiplied by the respective coding values for OHAs or insulin use. For individuals using only OHAs, interaction terms were all negative, though only significant for residing in the highest traffic density area as compared to the lowest ($P = 0.024$) (Table 4). For individuals using insulin, interaction terms were all positive and significant for residing near two or more roadways ($p < 0.002$).

4. Discussion

This study examined the influence of type of type 2 diabetes medication used on the response to residential traffic exposure with respect to changes in concentrations of CRP over a 2-year follow-up period for people with type 2 diabetes. This longitudinal analysis uses the same exposure characterization approach as our prior cross-sectional analysis (Rioux et al., 2010a, 2011) where we observed statistically significant associations with CRP and traffic proximity and density particularly for those using insulin and a possible protective effect for those on OHAs. Our aim here was to investigate whether changes in CRP would reflect the same pattern with respect to medication type.

The mean increase in CRP concentration was significant among those using insulin and living within 200 m of major roadways, but not among those using OHAs or those not using type 2 diabetes medication. Similar patterns were observed regarding the number of roadways as well. Participants using OHAs and in level 4 traffic density showed significant reduction in CRP concentration, but those on insulin or those not on type 2 diabetes medication had no significant change. These observations persisted after adjusting for age, HbA1c, history of heart attack, baseline CRP, HDL, and statin use, among other indicators of cardiovascular disease risk, and co-morbidities. Our findings suggest that progression in CRP concentration in relation to roadway proximity, number of roadways or traffic density varies by type of diabetes treatment. The adverse response we observe here may be associated with disease severity, disease duration, or the interactive effects of insulin with traffic exposure. Insulin use is typically associated with longer disease duration, and for these individuals, other indicators of diabetes progression such as vascular dysfunction, may be modifying the response to traffic exposure (Barzilay et al., 2001; Teichert et al., 2013; O'Neill et al., 2005; O'Neill et al., 2007; Stewart et al., 2010).

Our evaluation was based on medication status at baseline and we are limited by the absence of data on the length of medication use. In some cases, the type of medication used (insulin or OHAs only) changed during the follow-up period with 32 new participants reporting use of insulin at the 2-year point who were not using insulin at baseline. Adding these additional 32 participants to the original subgroup ($n = 91$) of those using insulin attenuated results with slightly lower beta coefficients in some cases and the p-value for one roadway category, >100 m and ≤ 200 m, moving from statistically significant to $p = 0.059$. We also evaluated the effect of removing these participants now using insulin from the subgroup of those

categorized as using only OHAs and observed no changes in statistical significance and declines in CRP changing from 52 to 57 percent for those at the highest traffic density level when compared to the lowest traffic density level. Interaction model results were unchanged in both cases. The effect of changing medication use, not uncommon in the treatment of type 2 diabetes overtime, requires further evaluation.

The most relevant predictors for the change in CRP over the follow-up period were found to be a combination of baseline characteristics and changes in other variables shown to be associated with CRP. BMI and CRP are often correlated, and in our prior cross-sectional analysis associations between CRP and traffic exposure were greatest among those with BMI ≥ 30 (Rioux et al., 2010a). For this cohort, over the follow-up period, BMI declined significantly for those using OHAs, remain unchanged for those using insulin, and declined slightly but not significantly in those not on diabetes medications. While initially eliminated as part of the model-building process using criteria to control for multi-collinearity and over-adjustment, we further evaluated changes in BMI, glucose and insulin for all subgroups again in the final model. None of these variables were found to be significantly associated with change in CRP nor were the associations between the traffic variables and change in CRP altered by the inclusion of these variables.

We are not aware of any studies that have examined the effect of different types of diabetes medication on the relationship of CRP with proximity to highways, major roadways or traffic density. As previously reported (Rioux et al., 2011), most earlier studies asked participants to abstain from taking their type 2 diabetes medications prior to biological sampling, did not report on, specifically evaluate, or have access to information on medication use (Teichert et al., 2013; O'Neill et al., 2005; O'Neill et al., 2007; Ostro et al., 2006; Schneider et al., 2008); or were conducted prior to the introduction of two of the oral medications evaluated here (Zanobetti and Schwartz, 2002; Bateson and Schwartz, 2004). Individuals with type 2 diabetes appear to be particularly vulnerable to air pollution (Gold, 2008) though particulate matter-induced CRP responses have not been consistent, perhaps due to the use of anti-inflammatory medications in this population (Li et al., 2012).

The lowering effect (or in our case slowing of progression) of CRP concentration by OHAs, but not by insulin, has been reported previously. What is new here is the observation that the lowering effect of OHAs appears to be higher in those living closest to major roadways, living near more major roadways or living in the highest traffic density. While results were not significant, one study suggested that type 2 diabetes medication may influence the response to traffic pollution exposure. In a randomized controlled study with 19 subjects with type 2 diabetes, 14 of whom were on oral type 2 diabetes medication, CRP concentration measured at 0.5 h, 3.5 h, 21 h, and 45 h decreased from baseline in those exposed to elemental carbon ultrafine particulates (count median diameter, 32 nm). In those exposed to filtered air, CRP increased initially, then decreased to a lesser extent (Stewart et al., 2010).

According to our findings, OHAs users may be protected over time compared to insulin users. CRP concentration progressed in those on insulin but remained steady in those on OHAs, in relation to proximity or number of major roadways. These findings support the

hypothesis generated by our previous cross-sectional study, i.e., that participants on insulin respond more adversely to traffic pollution exposure, while OHAs may have a protective effect. Our findings here suggest that those patterns persist longitudinally.

Based on our observational findings, several issues remain unclear. First, it is difficult to distinguish whether the associations observed are specifically with the type of type 2 diabetes disease (insulin dependent vs. non-insulin dependent) or with the type of diabetes medication used (insulin vs. OHAs). Evidence that OHAs, and not insulin, may reduce CRP concentration supports the likelihood that the observed pattern of associations is due to the medication and not the disease. In addition, the associations persisted after adjustment for important disease and co-morbidity parameters.

Testing prospectively whether OHAs are protective in populations closest to major roadways poses some ethical challenges making it difficult to determine this by using a trial design. This highlights the importance of findings from observational studies such as ours in providing insight on this issue. The likely mechanism related to this observation may be mediated through synergistic inflammatory processes associated with insulin dependent type 2 diabetes. In contrast, the anti-inflammatory qualities of OHAs may lessen the impact of high exposure to pollutants. It is also unclear whether the lowering effect of CRP concentration translates to reduction in cardiovascular risk. Thus, an important question that arises from this study is whether anti-inflammatory qualities of OHAs can be exploited to lessen cardiovascular risk of those most exposed to near highway pollution.

Limitations include potential introduction of selection bias, based on those re-assessed during follow-up, small sample sizes which limit power, and multiple tests of association that could yield significant results by chance. In general the extent of covariate information on health-related variables, biomarkers and socioeconomic factors allowed for control of a number of important diabetes-related variables, though the lack of clinical assessment of type 2 diabetes and information on duration of illness and medication use are limitations. Strengths of this study include its longitudinal design, ability to evaluate interactions with type of type 2 diabetes medications, proximity to major roadways, traffic density, and CRP concentration, and that the study addresses an a priori hypothesis generated from a cross-sectional study.

The use of surrogate measures of traffic exposure, i.e. proximity to roadways and overall traffic density, is a practical approach to examining previously unexplored associations given implementation costs and other technical challenges in characterizing spatial and temporal variations in traffic-related air pollution. The limitations of using surrogate measures are most notably exposure misclassification resulting from geocoding addresses, or for individuals living near an exposure category boundary, e.g. highest vs next highest traffic density or within or outside of the 200 m roadway buffer. Additional factors not included in our analysis are time and activity relationships, including the relative time spent indoors versus outdoors, the location and orientation of apartments within a building, infiltration rates, and ventilation systems. A low employment rate (20%) among this older population suggests time spent at home was relatively high.

In a review of 25 studies using land use regression to characterize several parameters including NO₂, NO_x, PM_{2.5}, and VOCs, traffic density was the most significant predictor or one of the two strongest predictors for pollution levels in a majority of studies (Hoek et al., 2008). We believe traffic density may be a reasonable surrogate for overall pollution levels though we only observed statistically significant associations, and notably inverse associations, between change in percent CRP and the highest traffic density level for those on OHAs. Proximity to roadway was a more consistent predictor of adverse outcomes (increases in CRP) but only for the subgroup on insulin. We recognize the limitations of these surrogates both in terms of fully capturing non-traffic sources of air pollution and for capturing the dispersion and degradation profiles of traffic related pollution.

Important neighborhood factors such as safe and walkable streets, age-appropriate and culturally appealing recreational opportunities, transportation resources, and access to healthy and affordable food may also influence type 2 diabetes development and progression and were not addressed in our study.

Generalizability may be constrained in that the population is entirely Puerto Rican and mostly very low-income with multiple serious chronic conditions.

5. Conclusions

In this population, the inflammatory response to traffic exposure, as measured by increasing concentrations of CRP over a 2-year follow-up, was most detrimental for those using insulin. OHAs use was associated with lower CRP concentration among those exposed to the highest traffic levels. Further study in a larger cohort is needed to help identify the specific mechanism of action of OHAs in accordance to our observation and to better understand the role of OHAs and public health.

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Fig. 1. Percent Change in C-reactive protein over 2-yr follow-up and 95% CI associated with traffic indices (main model) compared to reference levels among individuals using only OHAs and using insulin. legend: ≤ 100 = location of residence less than or equal to 100 m 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; DenseLevel3 and DenseLevel4 = Traffic density level.

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 = 356	100 m (n = 73)	>100– 200 m (n = 77)	>200 m (n = 206)	p-Value
<i>Basic descriptive (self-reported)</i>					
Age (years)	59 ± 6.9	58	60	59	0.53
Female sex	282 (73)	53	66	163	0.06
Employed	44 (14)	13	4	27	0.09
Length of residence	7.7 ± 7.3	6.4	7.9	8	0.44
Education 8th grade or more	176 (46)	41	30	105	0.08
Below poverty threshold	230 (72)	45	50	135	0.98
Smoking					0.76
never	176 (49)	37	35	104	
past	113 (32)	23	26	64	
current	67 (18)	13	16	38	0.62
Alcohol					
not current	239 (68)	54	48	137	
current moderate	99 (28)	14	26	59	
current heavy	13 (0.3)	3	2	8	
<i>Health status (measured except noted)</i>					
High density lipoprotein (mg/dl)	43 ± 11	45	42	43	0.20
Low density lipoprotein (mg/dl)	95 ± 34	97	90	96	0.20
Triglycerides (mg/dl)	172 ± 115	156	194	170	0.20
Albumin (g/dl)	7.1 ± 10	5.7	7.2	7.5	0.96
BMI (kg/m ²)	34 ± 6.9	33	33	34	0.62
Systolic BP (mm Hg)	138 ± 19	138	139	138	0.90
Diastolic BP (mm Hg)	80 ± 10.6	79	80	80	0.91
Pulse pressure (mm Hg)	58 ± 16	59	60	58	0.74
Hypertension	329 (85)	59	75	195	0.02
Heart attack (% self-reported)	48 (14)	6	10	32	0.49
Heart disease (% self-reported)	62 (17)	12	13	37	0.20

Characteristics	Total sample n = 356	100 m (n = 73)	>100– 200 m (n = 77)	>200 m (n = 206)	p-Value
<i>Medications (confirmed via observation)</i>					
Statins	220 (62)	50	52	118	0.83
Anti-hypertensives	275 (77)	51	62	162	0.10
Diabetes medications (any)	288 (81)	53	68	167	0.09
Insulin	91 (26)	18	23	50	0.40
Oral hypoglycemic agents only	197 (55)	35	45	117	0.48
Metformin (1)	195 (55)	38	43	114	0.96
Sulfonylureas (1)	115 (32)	17	26	72	0.21
Glitazones (1)	67 (18)	11	17	39	0.69
Non-steroidal anti-inflammatory drugs	122 (34)	25	29	68	0.90
<i>Confirmed conditions</i>					
Obesity (BMI ≥ 30)	239 (69)	50	45	144	0.26
<i>Inflammatory biomarkers</i>					
C-reactive protein (mg/l)	4.1 (0.0–127)	3.8	4.5	4.0	0.57
Log-transformed C-reactive protein (mg/l)	1.36 ± 1.2	1.29	1.35	1.4	0.91

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

p-values are derived from Pearson chi-square for binary variables and t-test for independent samples for continuous variables. (1) Includes people also on insulin.

Table 2

Comparison of baseline and 2-year values for health status, blood markers and medications by diabetes medication status.

Characteristics	Insulin users (n = 91)			OHAs/No insulin (n = 197)			No diabetes medication (n = 68)		
	Baseline	2-Year	p-value	Baseline	2-Year	p-value	Baseline	2-Year	p-value
Body mass index (kg/m ²)	34.1 ↓	34.1 ↓	0.96	33.2 ↓	32.7 ↓	0.009	33.8 ↓	33.4 ↓	0.12
C-reactive protein (ln) (mg/l)	1.5 ↓	1.5 ↓	0.50	1.2 ↓	1.0 ↓	0.04	1.7 ↓	1.4 ↓	0.06
Glucose (mg/dl)	174 ↓	162 ↓	0.20	140 ↓	137 ↓	0.40	168 ↓	136 ↓	0.001
Glycosolated hemoglobin (%)	9.1 ↓	8.5 ↓	0.01	8.1 ↓	7.7 ↓	0.01	7.8 ↓	7.3 ↓	0.016
High density lipoprotein (mg/dl)	43 ↑	44 ↑	0.47	43 ↑	45 ↑	0.02	44 -	44 -	0.90
Insulin levels (uiu/ml)	33 ↑	39 ↑	0.54	16 ↓	16 ↓	0.93	32 ↓	20 ↓	0.001
Albumin (g/dl)	4.2 -	4.2 -	0.73	4.3 -	4.3 -	0.40	4.2 -	4.2 -	0.17
Heart attack (self-report)	20% ↑	29% ↑	0.01	10% ↑	13% ↑	0.10	6% ↑	12% ↑	0.05
Heart disease (self-report)	24% ↓	22% ↓	0.71	16% ↑	18% ↑	0.21	15% ↑	19% ↑	0.18
Hypertension	90% ↑	91% ↑	0.71	85% ↑	88% ↑	0.07	79% ↑	82% ↑	0.48
Taking statins	70% ↑	73% ↑	0.69	67% ↑	72% ↑	0.15	35% ↑	50% ↑	0.01
Taking anti-hypertensive medication	81% ↑	87% ↑	0.17	79% ↑	85% ↑	0.01	66% ↑	71% ↑	0.26

Table 3
Percent change in C-reactive protein associated with traffic indices stratified by medication use.

Medication type	(n)	Crude model			Baseline model			Main model					
		Coeff	95% CI	p-Value	Coeff	95% CI	p-Value	Coeff	95% CI	p-Value			
Individuals using insulin (n = 91)													
3-Tiered gradient													
100 m	18	78	17	169	0.007	58	-0.7	152	0.054	98	19	228	0.009
>100– 200 m	23	67	7	161	0.026	81	6.2	209	0.030	75	14	171	0.012
Number of roadways													
1 roadway	30	117	23	282	0.008	35	-11	105	0.15	48	-1	122	0.058
2+ roadways	10	356	101	935	<0.001	190	61	424	0.001	195	71	409	<0.001
Traffic Density													
Level 2	39	13	-38	108	0.69	34	-12	103	0.17	40	-7	112	0.11
Level 3	10	37	-48	262	0.52	-4	-55	103	0.91	11	-46	128	0.77
Level 4	6	62	-53	461	0.44	21	-46	171	0.63	35	-39	196	0.45
Individuals using only OHAs (n = 197)													
3-Tiered gradient													
100 m	45	5	-34	65	0.84	42	-3	108	0.07	36	-7	98	0.11
>100– 200 m	35	-4	-42	59	0.87	6	-29	58	0.76	5	-29	56	0.81
Number of roadways													
1 roadway	61	-6	-38	43	0.77	30	-7	83	0.13	28	-8	80	0.15
2+ roadways	19	25	-34	137	0.50	9	-34	79	0.74	0.4	-39	67	0.99
Traffic Density													
Level 2	81	-27	-51	11	0.14	-10	-36	26	0.53	-9	-35	28	0.58
Level 3	30	-20	-54	39	0.43	9	-30	70	0.69	11	-29	71	0.65
Level 4	11	-65	-85	-22	0.01	-49	-74	-2	0.04	-52	-75	-8	0.03
Individuals not using diabetes medications (n = 68)													
3-Tiered gradient													
100 m	9	149	0.6	519	0.05	48	-27	202	0.27	52	-24	205	0.23
>100– 200 m	20	-44	-74	18	0.12	2	-44	86	0.94	-18	-54	45	0.48
Number of roadways													

Medication type	(n)	Crude model			Baseline model			Main model					
		Coeff	95% CI	p-Value	Coeff	95% CI	p-Value	Coeff	95% CI	p-Value			
1 roadway	24	6	-49	121	0.87	30	-23	118	0.32	14	-33	92	0.63
2+ roadways	6	-28	-79	150	0.60	-27	-72	87	0.50	-24	-68	78	0.51
Traffic Density													
Level 2	28	2	-52	118	0.95	43	-19	154	0.21	31	-25	128	0.34
Level 3	12	-18	-69	112	0.67	24	-35	139	0.51	16	-40	127	0.65
Level 4	4	86	-63	829	0.44	8	-66	243	0.89	14	-62	244	0.81

Baseline model adjusted for baseline values for: age, sex, bmi*, hdl, statin use, lnCRP*†#, glycosolated hemoglobin#, heart attack, months to follow-up, poverty/income ratio and education.

Main model adjusted for baseline values for: age, sex, bmi*, lnCRP*†#, education, poverty/income, months to follow-up and change values for hdl, statin use, glycosolated hemoglobin#, heart attack.

* Significant ($p < 0.05$) for OHAs models; † Significant ($P < 0.05$) for insulin models; # for no med 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 = 299)	
	β	p-Value
OHAAs $\times$ traffic interaction terms		
OHAAs $\times$ 100 m	-0.099	0.704
OHAAs $\times$ 2 or more roadways	-0.558	0.097
OHAAs $\times$ Traffic density level 4	-1.012	0.024
Insulin $\times$ traffic interaction terms		
Insulin $\times$ 100 m	0.537	0.071
Insulin $\times$ 2 or more roadways	1.158	0.002
Insulin $\times$ Traffic density level 4	0.798	0.107

Models adjusted for same covariates as main model.

Reference levels were: >200 m for 50 m.

0 (roadways) for number of roadways 200 m of a residence.

Traffic density level 1 for Traffic density (see text).