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The Relationship between Traffic-Related Air Pollution Exposures and Allostatic Load Score among Youth with Type 1 Diabetes in the SEARCH Cohort

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abstract

Objective: We investigated the effects of chronic exposures to particulate and traffic-related air pollution on allostatic load (AL) score, a marker of cumulative biological risk, among youth with type 1 diabetes.

Research Design and Methods: Participants were drawn from five clinical sites of the SEARCH for Diabetes in Youth (SEARCH) study (n=2,338). Baseline questionnaires, anthropometric measures, and a fasting blood test were taken at a clinic visit between 2001 and 2005. AL was operationalized using 10 biomarkers reflecting cardiovascular, metabolic, and inflammatory risk. Annual residential exposures to $PM_{2.5}$ and proximity to heavily-trafficked major roadways were estimated for each participant. Poisson regression models adjusted for sociodemographic and lifestyle factors were conducted for each exposure.

Results: No significant associations were observed between exposures to $PM_{2.5}$ or proximity to traffic and AL score, however analyses were suggestive of effect modification by race for residential distance to heavily-trafficked major roadways (p=0.02). In stratified analyses, residing <100, 100-<200 and 200-<400 m compared to 400 m or more from heavily-trafficked major roadways was associated with 11%, 26% and 14% increases in AL score, respectively (95% CIs: −4, 29; 9, 45.0; −1, 30) for non-white participants compared to 6%, −2%, and −2% changes (95% CIs: −2, 15; −10, 7; −8, 6) for white participants.

Conclusions: Among this population of youth with type 1 diabetes, we did not observe consistent relationships between chronic exposures to particulate and traffic-related air pollution and changes in AL score, however associations for traffic-related pollution exposures may differ by race/ethnicity and warrant further examination.

Keywords

air pollution; allostatic load; type 1 diabetes; chronic exposure

1. Introduction

Recent studies indicate that exposure to ambient air pollution may result in alterations to the physiologic parameters that quantify allostatic load (AL), a measure of cumulative biological risk that has been associated with cardiovascular disease (CVD) and all-cause morbidity and mortality (Logan and Barksdale, 2008; Karlamangla et al., 2006). For example, some studies have linked increased blood pressure (BP) and elevations in inflammatory biomarkers such as c-reactive protein (CRP), fibrinogen, and interleukin-6 (IL-6) with increased exposures to particulates <2.5 μm in diameter ($PM_{2.5}$) and other traffic-related air pollutants (Hajat et al., 2015; Hoffman et al., 2012).

The concept of AL is intertwined with allostasis, or the ability of the body to successfully adapt to changing environments and stressful challenges (Logan and Barksdale, 2008). Over time, frequent or chronic stimulation leads to wear and tear on the system as normal allostatic processes wear out or fail to engage. Chronic challenges to allostasis produce allostatic overload, associated with negative health consequences. In epidemiologic studies, AL is typically quantified using a multi-system framework that includes biomarkers of physiologic activity across a range of important regulatory systems (e.g., BP, BMI, total cholesterol [TC]).

It has been hypothesized that individuals with diabetes experience chronic AL, which is thought to play a role in the adverse health consequences associated with the condition, including CVD (Steptoe et al., 2014). There is a sizeable body of evidence indicating that exposure to particulate and traffic-related air pollution is a risk factor for cardiovascular morbidity and mortality, potentially through changes in systemic inflammatory responses, oxidative stress and/or vascular dysfunction (Brook et al., 2010; O'Neill et al., 2005). Furthermore, individuals with diabetes may be particularly vulnerable to the cardiovascular health effects associated with ambient air pollution. Increases in cardiovascular hospitalizations and mortality have been observed among individuals with diabetes during episodes of high ambient air pollution exposures (Zanobetti and Schwartz, 2002; Goldberg et al., 2001). Although the underlying pathophysiology is not fully understood, mechanistic evidence suggests that pro-inflammatory responses, chronic inflammation, and/or changes in vascular function may play a role (Brook et al., 2010; O'Neill et al., 2005; Jacobs et al., 2010).

Despite the existing biologic plausibility, there is a paucity of research examining the relationship between exposures to particulate and traffic-related air pollutants and a summary index of AL. One study conducted in Taiwan examined the relationship of AL score with short-term indoor $PM_{2.5}$ levels among office workers during a typical workday and reported no significant associations (Jung et al., 2014). The current study, to our knowledge, represents the first to examine whether long-term exposures to residential concentrations of $PM_{2.5}$ and traffic-related air pollution are associated with AL score. We

focus on youth with type 1 diabetes, a population with an elevated long-term risk of CVD-related morbidity and mortality (Allemann et al., 2009). Although CVD events are generally not expected to occur during childhood, our findings may help uncover how early life factors could translate into increased risk for major health outcomes including CVD later in life.

Using data from the SEARCH for Diabetes in Youth (SEARCH) study, a national multi-center study aimed at understanding diabetes among children and young adults in the US, we examined whether annual exposures to $PM_{2.5}$ and residential proximity to heavily-trafficked major roads were associated with AL score. We also examined differences in effect by sociodemographic factors.

2.0 Methods

2.1 Study Design and Subjects

Participants included in this analysis were enrolled from January 1, 2001 through December 31, 2005 in the SEARCH study, a multi-center observational study that maintains an active registry of US children and young adults diagnosed with diabetes at age <20 years. Detailed study methods have been published elsewhere (Hamman et al., 2014). Briefly, SEARCH was initiated in 2000 with funding from the Centers for Disease Control and Prevention (CDC) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) to address gaps in the understanding of diabetes in youth. SEARCH centers conduct active surveillance using networks of health care providers, hospitals, community health centers, clinical and administrative data systems, and electronic medical records. Case ascertainment is based on verification of physician diagnosed diabetes. Health care providers assign the clinical type for all registered cases. The present analysis included participants from five of the six SEARCH sites in the contiguous US: Ohio (eight counties surrounding Cincinnati: Butler, Clermont, Hamilton, and Warren in Ohio, as well as Boone, Campbell, and Kenton in Kentucky, and Dearborn in Indiana), Colorado (statewide), Washington (five counties surrounding Seattle: King, Kitsap, Pierce, Snohomish, and Thurston), South Carolina (statewide), and California (health plan membership in seven counties of southern California: Los Angeles, Orange, Riverside, San Bernardino, Ventura, Imperial, and Kern). Only participants with type 1 diabetes who completed a baseline in-person visit for anthropometric and laboratory measures were included. This cross-sectional analysis used data from the baseline questionnaire that collected information on quality of care, quality of life, sociodemographic factors and health behaviors including diet and physical activity. Study participants included prevalent cases from 2001 and incident cases from 2002-2005. Written informed consent was obtained from all participants age ≥18 years or from parents/legal guardians if <18 years. The SEARCH protocol was reviewed and approved by the Institutional Review Boards (IRBs) at each participating institution and is in compliance with the Health Insurance Portability and Accountability Act (HIPAA). This research was also carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

2.2 Exposure Assessment

Residential addresses at the time of each clinic visit were geocoded to a projected coordinate system using ArcGIS 9.3 software (ESRI Inc., Redlands, CA) and Topologically Integrated Geographic Encoding and Referencing (TIGER) Road Network Files for 2000 and 2006 using a 30 m offset. Daily average (24-hour) concentrations of $PM_{2.5}$ mass were estimated across the conterminous US from 1999-2011 using spatio-temporal generalized additive mixed models described in detail elsewhere (Yanosky et al., 2014; Yanosky et al., 2018); predictions from these models at participants' geocoded addresses were averaged over the 12-months prior to the clinic visit to calculate annual averages. In brief, these spatio-temporal models were based on air pollution measurements from the US Environmental Protection Agency's Air Quality System (AQS) database, the Interagency Monitoring of Protected Visual Environments (IMPROVE) network, and the Southern Aerosol Research and Characterization Study (SEARCH) network, and incorporated meteorological covariates known to influence pollutant dispersion including wind speed, wind direction, air temperature, surface roughness, total precipitation and sensible heat flux, which were obtained from the Modern-Era Retrospective Analysis for Research and Applications (MERRA) Project (Rienecker et al., 2011). Also included were daily traffic counts obtained from Geographic Data Technology, Inc. (Lebanon, NH) Dynamap Traffic Counts v4.2. These were spatially joined to the ESRI StreetMap Pro 2007 network of road segments to obtain the US Census Feature Class Codes road class (A1 [primary roads or highways with limited access], A2 [primary roads or highways without limited access], A3 [secondary and connecting roads including state and county highways], A4 [local, neighborhood, and rural roads], and A6 [roads with special characteristics, including access ramps and exits]) and spatially smoothed using generalized additive models. Also, the models included county-level population data from the 2000 US Census (US Census Bureau, 2013) and elevation data from the USGS National Elevation Dataset (US Geological Survey, 2013). During development, the model was subject to extensive validation techniques. Predictive accuracy was high for 24-hr averages (CV R^2=0.758).

Residential distance to the nearest road and annual average daily traffic (AADT) estimates were calculated for road classes A1-A4. Roads with AADT counts ≥10,000 vehicles/day were considered heavily-trafficked. Our primary analysis focused on examining associations between long-term air pollution exposures (annual average $PM_{2.5}$ mass and residential proximity to heavily-trafficked major roads [classes A1-A3]) and AL score. We categorized distance to the nearest major roadway as <100 meters (m), 100-<200 m, 200-<400 m, and ≥400 m because previous research suggests that exposures to traffic-related air pollutants are highest within 400 m of a major road and concentrations decrease with distance (Zhou and Levy, 2007; World Health Organization, 2013). Further, we excluded participants living >1000 m from major roads because residential distance to road may represent rural and semi-rural exposures rather than traffic beyond that distance (Rice et al., 2018).

2.3 Assessment of Allostatic Load

The AL model was operationalized to include cardiovascular, metabolic, and inflammatory biomarkers guided by prior research (Jung et al., 2014; Rainisch et al., 2013; Robertson et al., 2015; Bird et al., 2010) and available SEARCH measures. Ten physiological parameters

were used to create a summary score representing AL. Cardiovascular biomarkers included diastolic blood pressure (DBP) and systolic blood pressure (SBP). Inflammatory biomarkers included CRP and fibrinogen. Biomarkers of metabolic risk included BMI, glycated hemoglobin (HbA1c), HDL, total cholesterol (TC), triglycerides and waist circumference (WC). For each of the selected biomarkers, cut-points identifying high risk were determined using a flexible spline function of age with the 75th percentile prediction bounds (with the exception of HDL, where the 25th percentile was used); youth exhibiting a high risk biomarker level received a score of 1 for that parameter (Table S1). A composite AL score was then created by summing the total number of parameters identified as high risk (range 0-10, with higher values signifying greater systemic dysregulation) (Figure S1).

BP was measured three times; the second and third determinations were used to calculate mean SBP and DBP. Height, weight, and WC were measured in duplicate according to the NHANES protocol in light clothing without shoes. Height and weight were measured to the nearest 0.5 cm and 0.1 kg using a stadiometer and digital scale, respectively. BMI was then calculated as weight in kilograms divided by the square of height in meters. WC was measured at the nearest 0.1 cm at the uppermost lateral border of the right ilium. The following measures were analyzed using a single aliquot of stored plasma from blood drawn at the baseline study visit after an 8-hour fast. HbA1c was measured using a dedicated ion-exchange high-performance liquid chromatography instrument (Tosoh Bioscience, San Francisco, CA). Measurements of TC, HDL-C and triglycerides were performed enzymatically on a Hitachi 917 autoanalyzer. CRP and fibrinogen were measured immunochemically using Siemens reagents on a nephelometer autoanalyzer (BNII).

2.4 Covariates

We constructed a directed acyclic graph (DAG) to assess potential sources of bias and confounding in our analyses (Figure S2). Based on the DAG and a review of the relevant literature, we considered the following variables as covariates: age, sex, race/ethnicity, physical activity, smoking status, and socioeconomic status (SES) (Dowd et al., 2009; Brody et al., 2014; Yang and Kozloski, 2011; Mair et al., 2011; Gay et al., 2015; Tomfohr et al., 2016).

Key demographic data were obtained at case ascertainment and verified at initial contact with the patient using a structured questionnaire that queried date of birth, date of diagnosis, sex, and race/ethnicity. Parental education level and family income were ascertained during the in-clinic visit in a parent/guardian interview. Neighborhood affluence was assessed by using residential addresses to obtain the percentage of the population below poverty in the census tract of residence from the 2000 US Census (US Census Bureau, 2013). Physical activity level and smoking status were assessed for patients age ≥10 years by interviewer-administered questionnaire with questions based on the CDC-sponsored Youth Risk Behavior Surveillance System. Questions regarding physical activity level ascertained usual participation in both sedentary and non-sedentary activities, including the average amount of time per week spent watching television and playing video/computer games, and the average number of days per week spent engaging in physical activity that made them sweat or breathe hard for at least 20 minutes. Cigarette smoking was assessed by querying whether

participants had ever smoked tobacco, and among those that had, how many days they smoked tobacco in the past 30 days. Parents/legal guardians were asked to waive their right to review their children's responses to the smoking questions.

2.5 Statistical Analysis

Baseline sociodemographic characteristics were calculated as either mean/standard deviation or median/interquartile range (IQR) for continuous variables and frequency (N) and percent for categorical variables.

Poisson regression models were used to estimate associations between annual average $PM_{2.5}$ concentrations or residential distance to heavily-trafficked major roadways and AL score. Results are presented as percent change in AL score with 95% Confidence Intervals (95% CI) calculated using robust standard errors to control for mild violations of the underlying assumption that the variance equals the mean (Cameron and Trivedi, 2009). Basic models were unadjusted. Demographic models included age (continuous), race/ethnicity (non-Hispanic white, non-white), sex, and percent below poverty in the census tract of residence (continuous). Fully adjusted models additionally included physical activity level (continuous), sedentary behaviors (continuous), history of smoking tobacco (never/ever tried smoking), and the number of days that the subject smoked tobacco in the past 30 days (continuous). For annual exposures to $PM_{2.5}$ (continuous), we calculated percent change in AL score corresponding to an IQR increase in pollutant exposure. For residential proximity to heavily-trafficked major roadways (categorical), we evaluated associations for distances of <100 m, 100-<200 m, and 200-<400 m compared to living ≥400 m away. Effect modification was assessed in separate fully adjusted models by including interaction terms between each pollutant exposure and the following variables: race/ethnicity, sex, smoking status, and age (<10 years old, ≥10 years old). We also conducted separate analyses stratifying by each of these variables, comparing point estimates along with 95% CIs among groups. We conducted sensitivity analyses including participants residing >1000 m from major roads and those living in proximity to major roads where the traffic count did not exceed 10,000 vehicles/day, as well as evaluating the relationship of AL score with distance to each of the major road classes individually. Seasonality was also considered as a covariate in sensitivity analyses.

All analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina). Statistical significance was determined by p-values <0.05 corresponding to two-sided tests.

3.0 Results

Our study population initially consisted of 3,530 individuals with type 1 diabetes. We excluded participants with missing information on biomarkers included in the AL score (n=436), exposure estimates (n=279), percent below poverty in the census tract of residence (n=29), clinic site (n=4), and sex (n=1). We additionally excluded individuals residing >1000 m from major roads (n=289) as well as those living within 1000 m of a major road if the AADT estimate was <10,000 vehicles/day (n=96). The final study population for our analysis included 2,338 participants.

Characteristics of the study population are presented in Table 1. Approximately 78% of participants were non-Hispanic white and 49% were female. The mean AL score was 3.2 (SD 2.2). Average age was 12.5 years (SD 4.3) with a range of 3-22. The estimated annual average concentration of $PM_{2.5}$ was 13.4 μg/m^3 (SD 5.2). Approximately 20% of participants resided within 100 m of a major road, 18% lived within 100-<200 m, 35% lived within 200-<400 m, and 28% resided ≥400 m away.

In our main analyses (Table 2), exposure to annual $PM_{2.5}$ and proximity to traffic were not associated with AL score in fully adjusted models. In univariate analysis, an IQR increase in annual average $PM_{2.5}$ exposure was associated with a 7.2% increase in AL score (95% CI 2.3, 12.1). However, after adjustment for covariates, the association attenuated to a null relationship (0.0% change; 95% CI −3.9, 8.9). In the unadjusted distance to road analyses, participants residing <100 m from heavily-trafficked major roads had a 12.9% increase in AL score (95% CI 3.9, 22.5) compared to those who lived ≥400 m away, while we did not observe statistically significant increases among participants residing at other distances. Although these associations remained positive in fully adjusted models, all were below the level of statistical significance.

We observed some evidence of effect modification of the association between AL score and residential distance from heavily-trafficked major roads by race/ethnicity (interaction term in fully-adjusted models p=0.02) (Table 3). For example, in stratified analyses the AL score increased 25.7% (95% CI 8.8, 45.2) among non-white participants residing 100-<200 m from heavily-trafficked major roadways while white participants living at the same distance had lower AL scores (−2.0% change; 95% CI −9.9, 6.7) when compared respectively to their counterparts living ≥400 m away. However, the relationship between AL score and residential distance from heavily-trafficked roads did not monotonically increase with decreasing categorical distance for either race/ethnic group. No other interactions were significant and no consistent differences were observed in stratified analyses by race/ethnicity, age, smoking status or sex (Tables S2-S4).

In sensitivity analyses, the addition of participants residing >1000 m from major roadways and participants who lived near major roads that were not heavily-trafficked did not substantially affect the results (Table S5). The addition of seasonality as a covariate in our fully adjusted models did not appreciably alter the observed associations (Table S5). We also evaluated associations between proximity to major roadways with AL score by individual road class (e.g., A1, A2, and A3) in separate models, and no significant associations were observed (data not shown).

4.0 Discussion

In this study of youth with type 1 diabetes, we did not observe significant associations between long-term exposure to particulates or proximity to traffic and AL score in our main fully-adjusted analyses. However, we observed a statistically significant interaction by race/ethnicity for the association of AL score with residential distance from a heavily-trafficked major road by race/ethnicity. In stratified analyses, among those residing less than 400 m away from major roadways with heavy traffic, associations between AL score and each

category of residential distance from heavily-trafficked roads were positive among non-white participants and lower among white participants, although most of these results were not statistically significant. We observed no other evidence for effect modification by race/ethnicity, sex, age or smoking status. To our knowledge, these relationships have not been examined in the existing literature.

We identified one prior study that investigated the relationship of indoor $PM_{2.5}$ exposure with AL among 115 office workers in Taiwan (Jung et al., 2014). $PM_{2.5}$ concentrations were measured during an 8-hour workday using aerosol monitors. Biomarkers included in the AL score were BMI, body fat percentage, SBP, DBP, heart rate, IL-6, tumor necrosis factor alpha, cortisol, epinephrine, norepinephrine, and creatinine. In that analysis, indoor $PM_{2.5}$ exposure was not significantly associated with total AL (β=−0.014, SE= 0.006). Direct comparisons with our findings are difficult due to differences in methodology, including data analysis, exposure assessment and operationalization of AL.

Many prior studies have indicated that racial/ethnic minorities have higher overall AL scores compared to their non-Hispanic white counterparts, and that racial/ethnic differences in AL exist among younger age groups including youth and adolescents (Rainisch et al., 2013; Duru et al., 2012; Santos-Lozada and Daw, 2018). We report mean AL scores of 3.6 and 3.1 for non-white and non-Hispanic white participants, respectively. Despite wide reports of racial/ethnic differences in AL, the influence of particulate and traffic-related air pollution exposures remain largely unexplored.

We observed a statistically significant interaction by race for the relationship of AL score with living less than 400 m from major roadways with heavy traffic. As an exposure metric, residential distance to the nearest roadway is a surrogate measure that represents the effects of multiple traffic-related air pollutants, such as particulates, nitrogen oxides and carbon monoxide, as well as other potentially important components such as traffic noise (Stansfeld, 2015; Batterman et al., 2014). Though caution is warranted for over-interpretation of our findings, they support further investigation. Larger studies with more diverse participants could help confirm whether differences exist and are indeed pollutant effects or are instead due to other unmeasured factors that differ by race/ethnicity.

Both short and long-term exposures to $PM_{2.5}$ have been shown previously to increase BP, particularly among high cardiovascular risk individuals and persons with diabetes (Hoffman et al., 2012; Giorgini et al., 2016). Similarly, increases in inflammatory biomarkers such as CRP have also been associated with exposure to $PM_{2.5}$ (Hajat et al., 2015; Li et al., 2017). However, existing studies of air pollution and health have not considered AL as an outcome. Although AL score was not significantly associated with our exposure metrics after adjustment for demographic and lifestyle covariates in the main analysis, alterations in the physiologic parameters included in the AL score might become more apparent after a longer duration of time (e.g., 2-5 years) or with the inclusion of adult populations who typically have higher AL scores than youth (Crimmins et al., 2003).

Study limitations included estimation of exposures at participants' residential addresses in the absence of data on the duration of time spent away from the home. We were also unable

to include information on exposure to second-hand smoke in the household. The biomarker measurements included in the AL score represent biological activity at a single point in time and may not characterize typical physiologic activity for an individual or reflect variability in the measures. Data unavailability precluded incorporation of immune or neuroendocrine function biomarkers (e.g., cortisol or epinephrine) in the AL score. In addition, AL biomarkers were selected for inclusion based on the existing body of literature; however, while these measures are frequently used among adult populations, less work has been conducted in children. Although we used flexible spline functions at the 75th or 25th (HDL) percentile prediction bounds for age to define high risk cut-offs for the AL biomarkers, the AL score was highly dependent on the study sample. While alternate methods for calculating AL score have been employed in existing research (e.g., use of age and sex specific cut-offs based on national guidelines), clinical cut-points have not been established for some of the AL biomarkers in children. There is also an overall lack of information regarding operationalization of AL in individuals with type 1 diabetes, including youth and children. Our study is focused on youth with type 1 diabetes and may not be generalizable to other populations. We also cannot exclude the possibility that our results were affected by residual confounding or random error.

5.0 Conclusions

Concerns about ambient air pollution effects on cardiovascular, metabolic, and inflammatory markers of AL in populations with underlying health risks motivated the investigation of these associations in a geographically-diverse sample of youth with type 1 diabetes. Ours is the first study to investigate the effects of long-term exposures to particulate and traffic-related air pollution on AL score. In this study population, we did not find associations between annual average $PM_{2.5}$ exposures or proximity to heavily-trafficked major roadways and AL score in the main analysis. We observed some suggestion for potential racial/ethnic differences in the relationship of traffic-related exposures with AL score which supports further examination, especially among those with type 1 diabetes or cardiometabolic conditions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

Allemann S, Saner C, Zwahlen M, Christ ER, Diem P, Stettler C, 2009. Long-term cardiovascular and non-cardiovascular mortality in women and men with type 1 and type 2 diabetes mellitus: a 30-year follow-up in Switzerland. Swiss Med Wkly 139, 576–583. https://doi.org/smw-12785 [PubMed: 19838876]

Batterman S, Burke J, Isakov V, Lewis T, Mukherjee B, Robins T, 2014. A comparison of exposure metrics for traffic-related air pollutants: application to epidemiology studies in Detroit, Michigan. Int J Environ Res Public Health 11, 9553–9577. 10.3390/ijerph110909553 [PubMed: 25226412]

Bird CE, Seeman T, Escarce JJ, Basurto-Dávila R, Finch BK, Dubowitz T, Heron M, Hale L, Merkin SS, Weden M, Lurie N, 2010. Neighbourhood socioeconomic status and biological “wear and tear” in a nationally representative sample of US adults. J Epidemiol Community Health 64, 860–865. 10.1136/jech.2008.084814 [PubMed: 19759056]

Brody GH, Lei M-K, Chen E, Miller GE, 2014. Neighborhood poverty and allostatic load in African American youth. Pediatrics 134, e1362–1368. 10.1542/peds.2014-1395 [PubMed: 25311604]

Brook RD, Rajagopalan S, Pope CA, Brook JR, Bhatnagar A, Diez-Roux AV, Holguin F, Hong Y, Luepker RV, Mittleman MA, Peters A, Siscovick D, Smith SC, Whitsel L, Kaufman JD, American Heart Association Council on Epidemiology and Prevention, Council on the Kidney in Cardiovascular Disease, and Council on Nutrition, Physical Activity and Metabolism, 2010. Particulate matter air pollution and cardiovascular disease: An update to the scientific statement from the American Heart Association. Circulation 121, 2331–2378. 10.1161/CIR.0b013e3181dbece1 [PubMed: 20458016]

Cameron AC, Trivedi P, 2008. Microeconometrics Using Stata. STATA Press, College Station, TX.

Crimmins EM, Johnston M, Hayward M, Seeman T, 2003. Age differences in allostatic load: an index of physiological dysregulation. Exp. Gerontol 38, 731–734. [PubMed: 12855278]

Dowd JB, Simanek AM, Aiello AE, 2009. Socio-economic status, cortisol and allostatic load: a review of the literature. Int J Epidemiol 38, 1297–1309. 10.1093/ije/dyp277 [PubMed: 19720725]

Duru OK, Harawa NT, Kermah D, Norris KC, 2012. Allostatic load burden and racial disparities in mortality. J Natl Med Assoc 104, 89–95. [PubMed: 22708252]

Gay JL, Salinas JJ, Buchner DM, Mirza S, Kohl HW, Fisher-Hoch SP, McCormick JB, 2015. Meeting physical activity guidelines is associated with lower allostatic load and inflammation in Mexican Americans. J Immigr Minor Health 17, 574–581. 10.1007/s10903-013-9950-1 [PubMed: 24242155]

Gehring U, Heinrich J, Krämer U, Grote V, Hochadel M, Sugiri D, Kraft M, Rauchfuss K, Eberwein HG, Wichmann H-E, 2006. Long-term exposure to ambient air pollution and cardiopulmonary mortality in women. Epidemiology 17, 545–551. 10.1097/01.ede.0000224541.38258.87 [PubMed: 16755270]

Giorgini P, Di Giosia P, Grassi D, Rubenfire M, Brook RD, Ferri C, 2016. Air Pollution Exposure and Blood Pressure: An Updated Review of the Literature. Curr. Pharm. Des 22, 28–51. [PubMed: 26548310]

Goldberg MS, Burnett RT, Bailar JC, Brook J, Bonvalot Y, Tamblyn R, Singh R, Valois MF, Vincent R, 2001. The association between daily mortality and ambient air particle pollution in Montreal, Quebec. 2. Cause-specific mortality. Environ. Res 86, 26–36. 10.1006/enrs.2001.4243 [PubMed: 11386738]

Hajat A, Allison M, Diez-Roux AV, Jenny NS, Jorgensen NW, Szpiro AA, Vedal S, Kaufman JD, 2015. Long-term exposure to air pollution and markers of inflammation, coagulation, and endothelial activation: a repeat-measures analysis in the Multi-Ethnic Study of Atherosclerosis (MESA). Epidemiology 26, 310–320. 10.1097/EDE.0000000000000267 [PubMed: 25710246]

Hamman RF, Bell RA, Dabelea D, D'Agostino RB, Dolan L, Imperatore G, Lawrence JM, Linder B, Marcovina SM, Mayer-Davis EJ, Pihoker C, Rodriguez BL, Saydah S, SEARCH for Diabetes in Youth Study Group, 2014. The SEARCH for Diabetes in Youth study: rationale, findings, and future directions. Diabetes Care 37, 3336–3344. 10.2337/dc14-0574 [PubMed: 25414389]

Hoffmann B, Luttmann-Gibson H, Cohen A, Zanobetti A, de Souza C, Foley C, Suh HH, Coull BA, Schwartz J, Mittleman M, Stone P, Horton E, Gold DR, 2012. Opposing effects of particle pollution, ozone, and ambient temperature on arterial blood pressure. Environ. Health Perspect 120, 241–246. 10.1289/ehp.1103647 [PubMed: 22020729]

Jacobs L, Emmerechts J, Mathieu C, Hoylaerts MF, Fierens F, Hoet PH, Nemery B, Nawrot TS, 2010. Air pollution related prothrombotic changes in persons with diabetes. Environ. Health Perspect 118, 191–196. 10.1289/ehp.0900942 [PubMed: 20123602]

Jung C-C, Liang H-H, Lee H-L, Hsu N-Y, Su H-J, 2014. Allostatic load model associated with indoor environmental quality and sick building syndrome among office workers. PLoS ONE 9, e95791. 10.1371/journal.pone.0095791 [PubMed: 24759685]

Karlamangla AS, Singer BH, Seeman TE, 2006. Reduction in allostatic load in older adults is associated with lower all-cause mortality risk: MacArthur studies of successful aging. Psychosom Med 68, 500–507. 10.1097/01.psy.0000221270.93985.82 [PubMed: 16738085]

Li W, Dorans KS, Wilker EH, Rice MB, Ljungman PL, Schwartz JD, Coull BA, Koutrakis P, Gold DR, Keaney JF, Vasan RS, Benjamin EJ, Mittleman MA, 2017. Short-Term Exposure to Ambient Air Pollution and Biomarkers of Systemic Inflammation: The Framingham Heart Study. Arterioscler. Thromb. Vasc. Biol 37, 1793–1800. 10.1161/ATVBAHA.117.309799 [PubMed: 28751572]

Logan JG, Barksdale DJ, 2008. Allostasis and allostatic load: expanding the discourse on stress and cardiovascular disease. J Clin Nurs 17, 201–208. 10.1111/j.1365-2702.2008.02347.x [PubMed: 18578796]

Mair CA, Cutchin MP, Kristen Peek M, 2011. Allostatic load in an environmental riskscape: the role of stressors and gender. Health Place 17, 978–987. 10.1016/j.healthplace.2011.03.009 [PubMed: 21543249]

Miller KA, Siscovick DS, Sheppard L, Shepherd K, Sullivan JH, Anderson GL, Kaufman JD, 2007. Long-term exposure to air pollution and incidence of cardiovascular events in women. N. Engl. J. Med 356, 447–458. 10.1056/NEJMoa054409 [PubMed: 17267905]

O'Neill MS, Veves A, Zanobetti A, Sarnat JA, Gold DR, Economides PA, Horton ES, Schwartz J, 2005. Diabetes enhances vulnerability to particulate air pollution-associated impairment in vascular reactivity and endothelial function. Circulation 111, 2913–2920. 10.1161/CIRCULATIONAHA.104.517110 [PubMed: 15927967]

Pope CA, Dockery DW, 2006. Health effects of fine particulate air pollution: lines that connect. J Air Waste Manag Assoc 56, 709–742. [PubMed: 16805397]

Rainisch BKW, Upchurch DM, 2013. Sociodemographic correlates of allostatic load among a national sample of adolescents: findings from the National Health and Nutrition Examination Survey, 1999-2008. J Adolesc Health 53, 506–511. 10.1016/j.jadohealth.2013.04.020 [PubMed: 23763967]

Rice MB, Li W, Dorans KS, Wilker EH, Ljungman P, Gold DR, Schwartz J, Koutrakis P, Kloog I, Araki T, Hatabu H, San Jose Estepar R, O'Connor GT, Mittleman MA, Washko GR, 2018. Exposure to Traffic Emissions and Fine Particulate Matter and Computed Tomography Measures of the Lung and Airways. Epidemiology 29, 333–341. 10.1097/EDE.0000000000000809 [PubMed: 29384790]

Rienecker MM, Suarez MJ, Gelaro R, Todling R, Bacmeister J, Liu E, Bosilovich MG, Schubert SD, Takacs L, Kim G-K, Bloom S, Chen J, Collins D, Conaty A, da Silva A, Gu W, Joiner J, Koster RD, Lucchesi R, Molod A, Owens T, Pawson S, Pegion P, Redder CR, Reichle R, Robertson FR, Ruddick AG, Sienkiewicz M, Woollen J, 2011. MERRA: NASA's Modern-Era Retrospective Analysis for Research and Applications. Journal of Climate 24, 3624–3648. 10.1175/JCLI-D-11-00015.1

Robertson T, Benzeval M, Whitley E, Popham F, 2015. The role of material, psychosocial and behavioral factors in mediating the association between socioeconomic position and allostatic load (measured by cardiovascular, metabolic and inflammatory markers). Brain Behav. Immun 45, 41–49. 10.1016/j.bbi.2014.10.005 [PubMed: 25459100]

Santos-Lozada AR, Daw J, 2018. The contribution of three dimensions of allostatic load to racial/ethnic disparities in poor/fair self-rated health. SSM Popul Health 4, 55–65. 10.1016/j.ssmph.2017.11.007 [PubMed: 29349273]

Stansfeld SA, 2015. Noise Effects on Health in the Context of Air Pollution Exposure. Int J Environ Res Public Health 12, 12735–12760. 10.3390/ijerph121012735 [PubMed: 26473905]

Steptoe A, Hackett RA, Lazzarino AI, Bostock S, La Marca R, Carvalho LA, Hamer M, 2014. Disruption of multisystem responses to stress in type 2 diabetes: investigating the dynamics of allostatic load. Proc. Natl. Acad. Sci. U.S.A 111, 15693–15698. 10.1073/pnas.1410401111 [PubMed: 25331894]

Tomfohr LM, Pung MA, Dimsdale JE, 2016. Mediators of the relationship between race and allostatic load in African and White Americans. Health Psychol 35, 322–332. 10.1037/hea0000251 [PubMed: 27018723]

US Census Bureau, n.d. 2000 Census Data Sets [WWW Document]. URL https://www2.census.gov/census_2000/datasets/ (accessed 2.9.13).

US Geological Survey, n.d. National Elevation Dataset [WWW Document]. URL https://www.usgs.gov/core-science-systems/national-geospatial-program/national-map (accessed 5.19.13).

World Health Organization, n.d. Review of evidence on health aspects of air pollution – REVIHAAP Project Technical Report. Technical Report 309.

Yang Y, Kozloski M, 2011. Sex differences in age trajectories of physiological dysregulation: inflammation, metabolic syndrome, and allostatic load. J. Gerontol. A Biol. Sci. Med. Sci 66, 493–500. 10.1093/gerona/glr003 [PubMed: 21350248]

Yanosky JD, Fisher J, Liao D, Rim D, Wal RV, Groves W, Puett RC, 2018. Application and validation of a line-source dispersion model to estimate small scale traffic-related particulate matter concentrations across the conterminous US. Air Qual Atmos Health 11, 741–754. 10.1007/s11869-018-0580-6

Yanosky JD, Paciorek CJ, Laden F, Hart JE, Puett RC, Liao D, Suh HH, 2014. Spatio-temporal modeling of particulate air pollution in the conterminous United States using geographic and meteorological predictors. Environ Health 13, 63. 10.1186/1476-069X-13-63 [PubMed: 25097007]

Zanobetti A, Schwartz J, 2002. Cardiovascular damage by airborne particles: are diabetics more susceptible? Epidemiology 13, 588–592. 10.1097/01.EDE.0000020321.67963.7B [PubMed: 12192230]

Zhou Y, Levy JI, 2007. Factors influencing the spatial extent of mobile source air pollution impacts: a meta-analysis. BMC Public Health 7, 89. 10.1186/1471-2458-7-89 [PubMed: 17519039]

Highlights

- In main analyses, AL score was not associated with $PM_{2.5}$ or traffic-related exposures
- However, race/ethnicity may modify traffic-related pollution changes in AL score
- Non-white participants living near heavily traveled roads had higher AL scores

Table 1.

Summary statistics among SEARCH for Diabetes in Youth participants

Variable	N (%) or Mean (SD)
Age (years)	12.5 (4.3)
Female	1146 (49.0)
Race/Ethnicity	
Non-white	525 (22.5)
White	1813 (77.5)
Smoking	
Ever tried cigarettes, even one or two puffs	403 (17.2)
Never tried cigarettes	1302 (55.7)
Missing	633 (27.1)
Days of vigorous exercise in past week	
0	241 (10.3)
1-4	932 (39.9)
5-7	531 (22.7)
Missing	634 (27.1)
Clinic	
South Carolina	199 (8.5)
Ohio	503 (21.5)
Colorado	713 (30.5)
California	302 (12.9)
Washington	621 (26.6)
Percent below poverty in census tract of residence	8.2 (0.08)
Allostatic Load Score	3.2 (2.2)
Annual average $PM_{2.5}$ ($\mu g/m^3$)	13.4 (5.2)
Median (IQR)	11.1 (8.0)
Distance to nearest major road (m)	
<100	465 (19.9)
100-<200	413 (17.7)
200-<400	806 (34.5)
≥400	654 (28.0)

Table 2.

Associations of annual average $PM_{2.5}$ concentrations and residential distance to major roadways with allostatic load score among youth with T1D

	N	Percent Change in AL Score	95% CI
Unadjusted Results			
Annual Average $PM_{2.5}$, $\mu g/m^3$	2338	7.2	2.3, 12.1 *
Distance category, m			
<100	465	12.9	3.9, 22.5 *
100-<200	413	3.1	−5.4, 12.4
200-<400	806	6.8	−0.8, 15.0
400+	654	0.0	
Fully Adjusted Results			
Annual Average $PM_{2.5}$, $\mu g/m^3$	2338	0.0	−3.9, 8.9
Distance category, m			
<100	465	5.5	−1.7, 13.2
100-<200	413	3.6	−3.7, 11.3
200-<400	806	0.8	−5.3, 7.3
400+	654	0.0	

* = Statistical significance at $p<0.05$. Adjusted for age, sex, race/ethnicity, physical activity, smoking status, and socioeconomic status (SES).

Table 3.

Associations of annual average $PM_{2.5}$ concentrations and residential distance to major roadways with allostatic load score among youth with T1D, stratified by race/ethnicity

	N	Percent Change in AL Score	95% CI
Non-White Participants			
Annual Average $PM_{2.5}$, $\mu g/m^3$	525	−3.0	−9.3, 3.7
Distance category, m			
<100	128	11.2	−3.8, 28.6
100-<200	108	25.7	8.8, 45.2*
200-<400	189	13.7	−0.8, 30.4
400+	100	0.0	
White Participants			
Annual Average $PM_{2.5}$, $\mu g/m^3$	1813	2.0	−2.9, 7.2
Distance category, m			
<100	337	6.2	−2.1, 15.2
100-<200	305	−2.0	−9.9, 6.7
200-<400	617	−1.6	−8.4, 5.6
400+	554	0.0	

*= Statistical significance at $p<0.05$. Adjusted for age, sex, race/ethnicity, physical activity, smoking status, and socioeconomic status (SES).