ABSTRACT

Title of Dissertation:	RELATIONSHIPS OF SOCIAL AND PHYSICAL ENVIRONMENTAL FACTORS WITH CARDIOMETABOLIC OUTCOMES
	Dina Huang, Doctor of Philosophy, 2019
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The social and physical environmental factors impact health in general and have been linked with increased risks of cardiometabolic outcomes including obesity, diabetes, hypertension and cardiometabolic biomarkers. The dissertation added to important knowledge on this topic in two ways: 1) by leveraging innovative Twitter-derived characteristics to study the potential influence of social environment on cardiometabolic outcomes, 2) investigating the effects of air pollution exposures on cardiometabolic outcomes in youth living with type I diabetes.

The first study investigated the associations between Twitter-derived area-level predictors (happiness, diet, physical activity) with cardiometabolic outcomes (obesity, diabetes, hypertension) using a nationally representative sample from National Health and Nutrition Examination Survey (NHANES). People living in neighborhoods with higher happiness, healthier diet and more physical activity had lower prevalence of obesity and hypertension but not diabetes. Twitter-derived social neighborhood characteristics can be used to identify communities with higher risk of cardiometabolic outcomes.

We obtained data from SEARCH for Diabetes in Youth (SEARCH) study for the second and the third study. The second study examined the associations between chronic exposure to air pollution and glucose hemostasis (HbA1c) in youth living with type I diabetes. Particulate matter with aerodynamic diameter <2.5 ($PM_{2.5}$), proximity to heavily trafficked roads and annual average daily traffic count were associated with higher HbA1c in study site South Carolina, Colorado and Washington, but not in study site Ohio and California. Differences in particulate matter compositions may explain the inconsistent results. The third study assessed the

effect of acute exposure to air pollution on subclinical CVD markers including pulse wave velocity (PWV), augmentation index (AIx) and brachial distensibility (BrachD) using a repeated measures design. Reduction in $PM_{2.5}$ on the day prior to assessment was associated with lower AIx, but not associated with either PWV or BrachD. In summary, exposure to air pollution may be associated with cardiometabolic outcomes and reducing air pollution may have implications in early prevention of cardiovascular complications for youth living with type I diabetes.

Overall, reducing social stressors and reducing hazardous physical environmental factors may decrease the risk of cardiometabolic outcomes, providing possible directions for CVD prevention for public health practitioners.

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by

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Chapter 1: Introduction

1.1 Background and rationale

1.1.1 Social and physical environment and cardiometabolic outcomes

The environment in which we live, either social or physical environment, impacts our health and wellbeing. Social environment in a neighborhood, considered as both sociodemographic and the social relationship, social processes existed among residents, is associated with chronic health outcomes including obesity, hypertension and mental health [1]. Physical environmental factors, for example, exposure to ambient air pollution is associated with a wide array of cardiovascular disease (CVD) including atherosclerosis, myocardial infarction, stroke, coronary heart disease independent of CVD risk factors [2].

The risks of cardiometabolic outcomes, such as obesity, diabetes, impaired glycemic control and hypertension, had a dramatic increase in the past few years [3,4] and these cardiometabolic outcomes, alone or in combination, put individuals at higher risk of mortality [5]. Social environment is associated with cardiometabolic outcomes through social learning of healthy or risky behaviors [6]. Social norms on healthy behaviors may influence eating or physical activity behaviors. In addition, negative emotion and chronic stress from social environment might induce elevated inflammation and oxidation and disrupt cardiac function [7]. Exposure to air pollution was associated with cardiometabolic outcomes through three major pathways: 1) lung inflammation mediated systemic oxidative stress and inflammation; 2) activation of lung autonomic nervous system (ANS) arcs; 3) interaction between tissue and

pollutants being transmitted directly to circulating system [2]. People living with diabetes are at higher risk of developing CVD complications when exposed to elevated levels of ambient air pollution [8-10].

In this dissertation, we studied the relationships between social and physical environment factors with cardiometabolic outcomes. For social factors, we investigated the association between Twitter-derived social neighborhood characteristics and the prevalence of obesity, diabetes and hypertension in a nationally representative sample (Manuscript 1). For physical environment factors, we focused on the association between long-term exposure to ambient air pollution and glucose homeostasis (Manuscript 2) and the association between acute exposure to ambient air pollution and subclinical CVD markers (Manuscript 3) in youth living with type I diabetes.

1.1.2 Social neighborhood characteristics and cardiometabolic outcomes

Neighborhood environment has been recognized as an important determinant of health. Previous studies have identified associations between neighborhood characteristics with health behaviors [11,12], chronic conditions [13-16], mental health outcomes [17-21] as well as mortality [17,22,23]. Access to healthy food, proximity to park, green space, recreational facilities, and higher neighborhood walkability were identified as protective factors of obesity, diabetes and hypertension [23-26]. While neighborhood disadvantage and neighborhood level stressors were associated with obesity as well as higher blood pressure and neighborhood safety was inversely associated with the likelihood of hypertension [14,27-29].

In addition to physical features of the environment, social environment could affect health by providing emotional support to buffer the negative effects of neighborhood level stressors [30-34]. Prior studies suggested that greater social cohesion was inversely associated with hypertension [24,27] and happiness was linked with decreased obesity, hypertension, suicide rates as well as increased life expectancy [35-39]. Meanwhile, social environment is associated with health behaviors through social learning and social norms and ultimately associated with chronic conditions. Social learning provides opportunities to learn or adopt healthy promoting behaviors such as healthy diet, exercise and cancer screening. Nevertheless, information regarding negative behaviors such as smoking, alcohol consumption, drug use, and sleep deprivation could also spread over the social network [34,40-42] and these behaviors may be adopted through social learning as well. Similarly, social learning or mimicry could explain the spread of emotional state or "emotional contagion". Emotional states can be transferred through person to person contact and it could also travel via large social networks. [43-45]. A study followed over 20 years suggested an individual's perception of happiness was affected by social network including families, friends as well as neighbors [43]. Also, the degree of depressed emotions was correlated among friends and neighbors [42]. Besides, social norms provide a sense of acceptability regarding certain behaviors or conditions and social norm might further promote the spread of such behaviors or conditions in the social network. Social norms on diet and physical activity, which serve to provide people with perceived appropriateness of eating and exercise behaviors, were predictive for health eating behavior and physical activity,

respectively [46]. Christakis and colleagues reported that obesity could spread over the social tie and they argued that the acceptability of obesity within the social network may be the possible mechanism [47]. Smoking behaviors and smoking cessation are also associated with the acceptability and attitude towards smoking in social networks [31]. Therefore, a combination of neighborhood characteristics and social environment could explain the social neighborhood effects on the likelihood of developing cardiometabolic outcomes.

Social media, such as Twitter can be used to characterize the social neighborhood environment. For the food environment, healthy food tweets were positively associated with the number of grocery stores within a buffered geolocation of the Twitter users [48]. Nevertheless unhealthy food tweets were not restricted by the availability of fast food restaurants [48], suggesting that Twitter food predictors are complex measures of perceived food environment and personal preference in addition to providing information about the physical food environment. Widener and Li found that economically disadvantaged census tract areas had fewer positive tweets for healthy food but more unhealthy food tweets [49], indicating the role of Twitter food predictor in tracking disparities and differences across communities.

Additionally previous research has found physical activity tweets were significantly associated with numbers of exercise facilities such as fitness/recreational centers, nature parks, golf/country clubs, skiing facilities and bowling centers at zip code level [50]. Twitter has been used as a platform to encourage physical activity through hashtags such as #PlankADay [51].

1.1.3 Air pollution, cardiometabolic conditions and people living with diabetes

1.1.3.1 Air pollution and diabetes

Prior studies have investigated how acute and chronic exposure to ambient air pollution affects diabetes, cardiovascular complications and mortality among adults living with diabetes. Individuals with type II diabetes were more susceptible to vascular dysfunction, ventricular repolarization, arrhythmia, mortality in response to acute exposure to elevated levels of air pollutants including fine particles, black carbon, sulfates [52-54]. And significant increases of hospital admissions and emergency visits that attributed to heart disease were reported for individuals with type II diabetes following acute exposure to air pollutants such as particulate matter, nitrogen dioxide, and carbon monoxide [9,55]. In addition, studies investigating the effect of chronic exposure to air pollution suggested increased risks of mortality and diabetes-related mortality [56,57]. Large cohort studies also found that air pollution was associated with increased risks of developing type II diabetes [58-62].

Few studies researched on the effect of air pollution on type I diabetes among children and adolescents. Evidence suggested that chronic exposure to air pollution was associated with the incidence of type I diabetes. Hathout and colleagues found that increased levels of ozone and sulfate might contribute to the development of type I diabetes among children [63] and particulate matter with aerodynamic diameter <10 (PM_{10}) may be a critical factor that contribute to the development of type I diabetes for children before age 5 [64]. A study from Germany indicated that exposure to the traffic-related air pollutants such as PM_{10} and NO_2 may accelerate the manifestation

of Type I diabetes in very young children [65]. A study from Italy also reported that PM_{10} significantly affects the incidence of type I diabetes in children [66]. We are not aware of any studies researching on acute exposure to air pollution and health effects in children living in type I diabetes.

Biological studies suggested that air pollution was involved in the pathogenesis of type II diabetes through alterations in immune system, adipose, liver as well as central nervous system (CNS) [67]. While the mechanism linking air pollution to type I diabetes is not well understood. Butalia et al proposed that environmental factors including air pollution may trigger the autoimmune responses and the production of free radicals, subsequently leading to beta cells destruction and insulin deficiency [68].

1.1.3.2 The effect of air pollution in animal studies

Most animal studies focused on the effects of air pollution on inflammation and insulin resistance. Those studies suggested that exposure to ambient air pollution was associated with increased insulin resistance and elevated inflammation and the associations were more evident in animal model with high fructose or high fat diet. Sun and colleagues indicated that 9-day exposure to concentrated ambient fine particles (CAP) and ozone exaggerates inflammation and oxidative stress in epicardial adipose tissue and perirenal adipose tissue in male Sprague-Dawley rats and the rats fed with high fructose diet exhibited larger effect size compared to rats fed with normal diet [69]. Yan et al used the same rat model but fed with either high-fat diet or a normal diet and the rats received instillation of PM_{10}, particulate matter

with aerodynamic diameter <2.5 ($PM_{2.5}$) or normal saline for 3 weeks. They observed elevated homeostasis model assessment of insulin resistance (HOMA-IR) in mice fed high fat diet and increased fibrinogen in both mice fed high fat diet and normal diet [70]. In male C57BL/6 mice model fed high-fat diet, 24-week exposure to $PM_{2.5}$ was associated with marked whole-body insulin resistance, systemic inflammation and increases in visceral adipose [71]. Liu and colleagues investigated on the impact of $PM_{2.5}$ on time-response association in C57BL/6 mice model [72]. They reported significant increases in fasting glucose, HOMA-IR, and abnormal glucose tolerance at 17 weeks.

Few animal studies utilized animal model with type I diabetes in assessing the biological responses attributed to exposure to air pollution. In streptozotocin (STZ)-induced type I diabetic rats, markers of oxidative stress and endothelial dysfunction were increased compared to healthy mice following exposure to particulate matter [73]. And 16-week exposure to diesel exhaust particles (DEP), a major component of particulate matter, exacerbated the systemic inflammation, oxidative stress and coagulation events in STZ-induced rat model [74].

A few animal studies assessed the role of ambient air pollution in atherogenesis. Rabbits instilled with PM_{10} for 4 weeks were associated with progression of atherosclerotic lesions, increased plaque cell turnover and extracellular lipid pools in coronary and aortic lesions [75]. Mice with high-fat diet exhibited marked increases in macrophage infiltration, reactive oxygen species and exaggerated vasoconstrictor responses following 6-month exposure to $PM_{2.5}$ [76]. Another study

using mice models observed larger early atherosclerotic lesions for mice exposed to ultrafine particles for 40 days [77].

1.1.3.3 Air pollution and glucose homeostasis

Hemoglobin A1c (HbA1c) is a reliable marker for measuring glucose homeostasis. Poor glycemic control is associated with several CVD risk factors [78,79] and hyperglycemia is associated with adverse cardiovascular responses in individuals living with diabetes [80-86]. In addition, it was reported that elevated but non-diabetic level of glucose were also associated with increased risks of CVD [87].

Few studies have examined the relationship of ambient air pollution exposure and glucose homeostasis. The vast majority of these studies have focused on adults in the general population, and with fewer studies assessing this association among adults with diabetes, which is predominantly type II diabetes. Though the current study investigated the relationship of ambient air pollution exposures and glucose homeostasis in youth with type I diabetes, which differs mechanistically and etiologically from type II diabetes; we briefly describe the literature on adults, given the extremely limited information available on type I diabetes and ambient air pollution exposures. To date, findings are mixed. In general, studies from Asian countries reported positive associations, possibly due to higher levels of air pollutant exposures. A population-based study from Taiwan study suggested 3-day average PM_{10} per interquartile range (IQR: 34 ug/m^3) was associated with 0.06% (95% CI: 0.01-0.11) increase in HbA1c [88]. Liu and colleagues found that long-term exposure to $PM_{2.5}$ was associated with elevated HbA1c in a national-wide representative

sample of Chinese population aged 45 or older. They observed 0.08% increase in HbA1c with interquartile range increase in $PM_{2.5}$ (IQR: 41.1 ug/m^3) in a Chinese population [89]. While Sade et al from Israel reported three-month average PM_{10}, but not acute exposure (1- to 7- day) was associated with increases in HbA1c in adult living with diabetes in Southern Israel. Sade and colleagues observed 3.58% (95% CI: 1.03-6.20) and 2.93% (95% CI: 0.35-5.59) increase in HbA1c with interquartile range increase in PM_{10} (20 ug/m^3) and $PM_{2.5}$ (7 ug/m^3), respectively [90].

Unlike studies from Asian countries, studies from Europe and US exhibited inconsistent results. Wolf et al suggested no association between long-term exposure to PM_{10} (change between 95 percentile and 5 percentile: 7.9 ug/m^3) and $PM_{2.5}$ (change between 95 percentile and 5 percentile: 2.8 ug/m^3) with HbA1c were found in either all participants or participants living with diabetes in southern Germany [91]. Another study conducted by Tamayo and colleagues indicated exposure to PM_{10} may be associated with elevated HbA1c in newly diagnosed diabetes patients throughout Germany [92]. Tamayo et al observed significant lower HbA1c for participants exposed to lower quartiles of PM_{10} compared to higher quartiles, where the cut-offs for PM_{10} quartiles were 16.4 ug/m^3, 18.05 ug/m^3, 21.10 ug/m^3, respectively. For US studies, Li et al observed null associations between annual $PM_{2.5}$ and residential distance to road with HbA1c in the Framingham Offspring Cohort without diabetes [93]. Honda and colleagues reported a significant association between long term exposure to $PM_{2.5}$ and NO_2 with HbA1c in adults living with diabetes, while $PM_{2.5}$ was not associated with HbA1c among participants free of diabetes. A 1-year average interquartile increase in $PM_{2.5}$ (IQR: 3.9 ug/m^3) and NO_2 (IQR: 8.6 ppb) were

associated with 1.4% (SD: 0.6%) and 2.0% (SD: 0.7%) increase in HbA1c, respectively [94].

Until now, we are only aware of two studies, both conducted in Germany, that have focused on the impact of air pollution on glycemic control specially in youth living with type I diabetes. Tamayo et al and Lanzinger et al found no effects of chronic exposure to air pollutants such as PM_{10} and NO_2 on HbA1c among youth with type I diabetes [95,96]. However, an animal study using STZ-induced type I diabetic rats suggested sub-chronic exposure to $PM_{2.5}$ could alter glucose homeostasis even at low concentrations that is similar to current WHO air quality standards (10 ug/m^3) [97].

Type I and type II diabetes are different in pathology, where people living with type I do not have insulin-producing beta cells due to autoimmune destruction in contrast to people with type II diabetes who produce insulin but could not use them properly. However, both type I and type II diabetes patients are more likely to live with cardiovascular risk factors and they are more vulnerable to cardiovascular diseases [98-100]. Based on the existing evidence, we hypothesized that exposure to air pollution may exacerbate glycemic control and expediate adverse cardiovascular responses in people living with type I diabetes.

1.1.3.4 Air pollution and arterial stiffness

Arterial stiffness is an early sign of vascular alterations and is characterized by degenerative changes in extracellular matrix. It is related to oxidative stress, elevated inflammation as well as endothelial dysfunction [101]. Prior study suggested that

arterial stiffness may share pathophysiologic mechanisms including endothelial dysfunction and insulin resistance [101-103]. Although age and blood pressure could explain 70% of the variance in arterial stiffness [104], arterial stiffness was consistently found in people living with diabetes and people with metabolic syndrome [105,106]. In addition, arterial stiffness was associated with chronic inflammation [107,108], thus providing possible explanations linking exposure to air pollution with arterial stiffening.

Findings on exposure to air pollution and arterial stiffness are mixed. The majority of studies focused on acute exposure to air pollution and arterial stiffness. Pulse Wave Velocity (PWV) and Augmentation Index (AIx) are measures related to arterial stiffness that are frequently used. Wu et al reported 2.1% (95% CI: 0.7%, 3.6%) increase of brachial-ankle PWV for 10 ug/m^3 increase in exposure to $PM_{2.5}$ for 24 hours prior to vascular assessment in healthy adults [109]. Fang et al, Adamopoulos et al, and Mehta et al found positive associations between acute exposure to particulate matter and arterial stiffness in welders [110], in patients with hypertension [111] and in elderly men living in urban areas [112]. Lenters et al found long-term exposure to NO_2 and SO_2 was associated with increased arterial stiffness in young adults [113]. They found 4.1% (95% CI: 0.1%, 8.0%) increase in carotid-femoral PWV and 37.6% (95% CI: 2.2%, 72.9%) increase in AIx for a 25 ug/m^3 increase in NO_2; and detected 5.3% (95% CI: 0.1%, 10.4%) increase in carotid-femoral PWV for a 5 ug/m^3 increase in NO_2. However, long-term exposure to $PM_{2.5}$ was not associated with either carotid-femoral PWV or AIx in a group of young adults living in urban areas [113]. Small variations in $PM_{2.5}$ might explain the null

results. In addition, Weng et al reported 12-month average PM_{10} was positively associated with brachial-ankle PWV in patients undergoing hemodialysis [114]. Jiang et al found positive association between long-term exposure to traffic-related $PM_{2.5}$ and AIx in general urban population [115]. In another study of 23 people living in rural areas, AIx was not significantly increased for people exposed to high level of $PM_{2.5}$ (above median in the study) in 24 hours, possibly due to the small sample size and residual confounding of categorizing air pollution exposure [116]. We are not aware of any studies assessing the impact of acute exposure to air pollution on arterial stiffness in youth living with type I diabetes.

1.2 Objectives/research questions

1.2.1 Manuscript 1

Twitter-derived social neighborhood characteristics and individual level cardiometabolic outcomes in a nationally representative sample

The proposed study investigated the association between Twitter-derived neighborhood characteristics and cardiometabolic outcomes across the contiguous US. Taking advantage of the free Twitter streaming API service, we collected random 1% of the geotagged Twitter data from 2015 to 2016 to construct neighborhood characteristics including happiness, diet and physical activity. Cardiometabolic outcomes such as body mass index (BMI), obesity, diabetes and hypertension from National Health and Nutrition Examination Survey (NHANES) 2007-2016 were accessed through Restricted Data Center (RDC) at Maryland Federal Statistical

Research Data Center.

Research question: Do people living in neighborhoods with higher levels of happiness and more social modeling of healthy food behaviors and physical activity exhibit lower prevalence of cardiometabolic outcomes?

1.2.2 Manuscript 2

The association between long-term exposure to air pollution and glucose homeostasis in youth living with type I diabetes

The objective of the proposed study is to examine the impact of chronic exposure to air pollution on glucose homeostasis in youth living with type I diabetes in SEARCH for Diabetes in Youth Study. Specially, we examined the effect of long-term exposure to air pollution including estimated $PM_{2.5}$ average exposure for 12-month, annual average daily traffic count and residential distance to the nearest road on HbA1c, a reliable marker of glucose homeostasis. We also assessed the association between sub-chronic exposure to air pollution, measured as estimated $PM_{2.5}$ average exposure for 1-month prior to the blood draw, and glucose homeostasis.

Research question: 1) Are exposures to estimated average $PM_{2.5}$ for 1-month and for 12-month prior to the blood draw, annual average daily traffic count and residential distance to the nearest road associated with elevated levels of HbA1c in youth living with type I diabetes?

2) Are the associations between exposure to air pollution and glucose homeostasis modified by age, sex, race/ethnicity, smoking and BMI Z score?

1.2.3 Manuscript 3

The association between air pollution and subclinical Cardiovascular Disease (CVD) markers in youth living with type I diabetes

The objective of the study is to assess the association between changes in acute exposure to air pollution and subclinical CVD markers in youth living with type I diabetes. Subclinical markers of arterial stiffness including augmentation index (AIx), pulse wave velocity (PWV) and brachial distensibility (BrachD) were used as the outcomes. Single day estimates on the day of assessment, on each of the 7 days prior to assessment, moving averages for 2- to 5- day prior to assessment, as well as a weekly average were constructed for $PM_{2.5}$. A weekly average $PM_{2.5}$ EC was also constructed as acute exposure to ambient air pollution.

Research question: Are greater reductions in exposure to $PM_{2.5}$ and exposure to $PM_{2.5}$ EC associated with delayed arterial stiffening in youth living with type I diabetes?

1.3 Theoretical/conceptual framework and hypotheses

1.3.1 Neighborhood environment, social environment and health outcomes

A growing body of evidence has reported neighborhood characteristics were linked to chronic health outcomes such as obesity, diabetes and hypertension [23-26,117]. The possible mechanisms include 1) neighborhood characteristics are influential in shaping health behaviors and are linked to health outcomes through changing behaviors; 2) neighborhood stressors serve as sources of chronic stress that contribute to the increased risks of adverse health events.

Individuals lifestyle such as physical activity and diet can be influenced by the physical features of the neighborhood environment. Residential proximity to parks, green space, health centers and recreational facilities as well as higher neighborhood walkability were conducive to physical activity [12,24,25,118,119]. Regular physical activity is associated with reduced risks of many chronic conditions such as obesity, diabetes, high blood pressure and heart disease [120] . According to Physical Activity Guidelines for Americans, it is recommended to do at least 150 minutes of moderate-intensity weekly aerobic activity or 75 minutes vigorous-intensity weekly aerobic activity for greater health benefits among adults [121]. Access to grocery stores, healthy food and fast food service may shape individual's food choice [122-126]. And unhealthy eating habits are important risk factors that associated with higher risks of obesity, diabetes and cardiovascular outcomes.

Neighborhood stressors such as neighborhood noise, safety, traffic problems, incivility, socioeconomic disadvantage and lack of access to neighborhood amenities may become chronic source of stress and subsequently leading to adverse health outcomes [14,27,28,127-129]. Previous research reported disadvantaged neighborhood were associated with worse self-reported health [129] and worse control of hypertension among African Americans [28]. Disadvantaged neighborhoods tend to be associated with fewer recreational facilities, poor environment for walking or biking, few supermarkets, grocery stores and more fast food outlets and these features would have negative impact on shaping individual's health behaviors.

In addition to physical features within a neighborhood, social environment are also crucial factors associated with chronic health outcomes. Individual's health behavior can be adopted, changed, maintained and suspended by observing other people's attitude and behaviors according to the social learning theory [130]. Based on social learning theory, learning occurs in a social context [6]. Social contextual factors will influence individual's health behaviors through reciprocal interactions between people, and between people and the environment; through observational learning based on the "modeling" of behaviors; through self-initiated reinforcement or external reinforcement from social environment that facilitates or hinders an individual's behavior; and through expectations towards the successful completion of a certain health behavior [6]. In addition to social learning, social norms on healthy behaviors are also related to changing health behaviors. In addition, collective efficacy, described as a combination of social reinforcement and social cohesion [131], could buffer the negative effects of neighborhood stressors by providing physical material and mental support [32].

Emotional state can spread through the social network and negative emotions could be stressors that are detrimental to health [43,44,132]. Negative emotion and chronic stress contribute to unhealthy eating behaviors (e.g. alcohol drinking and poor eating habits) as coping strategies and are also associated with less physical activity as a result of self-isolation [133,134]. In addition, negative emotion and chronic stress might induce elevated inflammation, promote atherosclerosis and disrupt cardiac function [135-138].

Hypothesis: People living in zip codes with high levels of neighborhood happiness, healthy diet and physical activity have lower prevalence of cardiometabolic outcomes.

1.3.2 exposure to ambient air pollution and glucose homeostasis

Exposure to air pollution is associated with adverse cardiovascular responses through systemic inflammatory responses, oxidative stress, endothelial dysfunction and metabolic syndrome [2]. And individuals living with diabetes have a higher likelihood of developing cardiovascular outcomes. Given the extremely limited information available on type I diabetes and ambient air pollution exposures, we discuss the existing evidence in both type I and type II diabetes.

Though the mechanism of how air pollution affects glucose homeostasis in people living with diabetes are not fully understand, animal studies suggested elevated systemic inflammation, oxidative stress and endothelial dysfunction might be possible mechanisms. Animal studies using high-fat fed mice suggested that exposure to $PM_{2.5}$ was associated with worse insulin resistance, increased visceral adiposity and elevated systemic inflammation [70-72]. In animal studies using STZ-induced type I diabetic rats, marked increase in systemic inflammation, oxidative stress, endothelial dysfunction and dysregulated glycemic control were observed [73,97].

In epidemiologic studies, some studies found exposure to air pollution was associated with worse glycemic control in both individuals with and without diabetes (mostly type II diabetes) [88,90,92,93,139]. However, the results were inconsistent. Studies from Asian countries general reported positive associations between exposure

to air pollution and glucose homeostasis [88-90]. In contrast, studies from Europe and the US exhibited inconsistent results [91-94]. The mixed results might be attributable to differences in the distribution and concentration of air pollutants and differences in individual susceptibility.

The underlying mechanisms for the relationships between glucose homeostasis and CVD outcomes are not clear, however, epidemiologic studies indicated that elevated HbA1c was associated with higher risks of developing CVD outcomes. It was reported that hyperglycemia was associated with increased risks of CVD and mortality attributed to CVD in people living with type I diabetes [80]. And intensive control of glucose homeostasis prevents the development or delays the progression of microvascular complications of diabetes in both adults and adolescents with type I diabetes [78,82].

We are only aware of 2 studies focused on the impact of air pollution on glucose homeostasis in type I diabetes population. Tamayo reported quinquennial exposure to ozone exhibit favorable effect on glucose homeostasis and as annual exposure to PM_{10} and NO_2 were not associated with glucose homeostasis [95]. Lanzinger and colleagues also reported the same findings using quinquennial ozone and annual exposure to PM_{10} and NO_2 [96]. However, the two studies did not assess the effect of long-term exposure to $PM_{2.5,}$ which is smaller in size and can deposit deeper in the body. Both studies assigned air pollution exposures to participants by residential postcodes. Tamayo's study relied on self-reported HbA1c as the outcome and Lanzinger's study did not control for lifestyle factors. Further investigation with more specific exposure estimates, examined glucose homeostasis and extensive

information on covariates is needed. We hypothesized that long-term exposure to air pollution is associated with elevated levels of HbA1c in youth with type I diabetes based on the existing literature.

We identified a directed acyclic graph (DAG) based on existing studies assessing the association between air pollution and glucose homeostasis in healthy people from the general population [88,91,93], in people living with type II diabetes [90-92,94] and in youth living with type I diabetes [95,96]. Longer duration of diabetes and insulin regimen were correlated with elevated levels of HbA1c [78]. We suspect demographics and lifestyle factors could be potential confounders because they are not in the causal pathway but are related to both exposure to air pollution and HbA1c. Factors related to diabetes are associated with glycemic control but are less likely to be associated with exposure to air pollution directly. Figure 4.1 shows a proposed DAG for this study.

Hypotheses: 1) Exposure to estimated average $PM_{2.5}$ for 1-month and for 12-month prior to the blood draw, annual average daily traffic count are associated with elevated levels of HbA1c among youth living with type I diabetes. Youth living close to heavy trafficked road have increased HbA1c compared to youth living further away.

2) The associations between exposure to air pollution and glucose homeostasis differ by age, sex, race/ethnicity, smoking and BMI Z score.

1.3.3 exposure to ambient air pollution and arterial stiffness

Arterial stiffness is an early sign of vascular changes that is associated with cardiovascular disease morbidity and mortality [140,141]. Air pollution is a

modifiable risk factor for CVD and people living with diabetes have disproportionally high risk of developing cardiovascular complications. Inflammation and endothelial dysfunctions are possible mechanisms linking air pollution to arterial stiffness. Researchers observed positive correlation between brachial-ankle PWV and C-reactive protein (CRP) in patients undergoing hemodialysis [114]. In a double-blinded randomized trial, healthy people were randomized to group injected with vaccine or to group injected with normal saline to assess the effect of acute inflammation on arterial stiffness [142]. The results suggested vaccination was associated with significant increase in PWV at 8 hours and inflammatory biomarkers including CRP and Interleukin-6 (IL-6) were also correlated with PWV. However, AIx corrected for changes in heart rate decreased significantly at 8 hours after vaccination. Findings from the randomized trial suggested acute systemic inflammation aggravates large artery stiffening and was associated with decreased wave reflection. The author explained that decreased AIx was caused by decreases in incident wave reflected at peripheral sites rather than delayed return of reflective wave because the vaccine used in this study may activate Interleukin-1 which induces a NO-mediated vasodilation in veins in vivo [143]. The study provided evidence that AIx is different from PWV, where AIx may account for changes at veins, peripheral arteries as well as central arteries.

Endothelial dysfunction, which associated with both air pollution [144-146] and arterial stiffness, could be another mechanism explaining the effect of air pollution on arterial stiffening [147,148]. Endothelial dysfunction, characterized by a reduction of nitric oxide (NO), may lead to vasoconstriction, activation of platelets

and increased inflammation. Global endothelial function measured by ratio of response to albuterol to nitroglycerin (NTG), was negatively associated with PWV and AIx in healthy adults [147]. The study also suggested that endothelial dysfunction in smaller arteries may contribute to enhanced AIx since global endothelial function was negatively associated with AIx.

People living with diabetes are more likely to live with cardiovascular risk factors concurrently and they are at greater risks of developing CVD complications than the general population [149-151]. Evidence suggested arterial stiffness was frequently found in people with diabetes and in people living with metabolic syndrome [105,106]. Hence, we hypothesized that changes in acute exposure to air pollution are associated with subclinical CVD markers in youth living with type I diabetes.

Hypothesis: Changes in acute exposure to air pollution are associated with subclinical CVD markers including carotid-femoral PWV, AIx and BrachD in youth living with type I diabetes. Specifically, greater reduction of exposure to $PM_{2.5}$ and exposure to $PM_{2.5}$ EC are associated with delayed arterial stiffening.

1.4 Innovation and significance

1.4.1 Manuscript 1

The proposed study is innovative because we utilized large scale social media data source that are free to public to characterize neighborhoods. Social media provide a huge data source and researchers have become increasingly interested in

utilizing Twitter in public health research. However, existing research mainly focused on descriptive and content analysis, leaving Twitter data features under-utilized. In our study, we obtained Twitter data features including coordinates, tweet contents, timestamp to construct social neighborhood characteristics. We further linked Twitter information to individual level health outcomes via zip codes in a nationally representative sample.

The proposed study is significant because we were able to construct social neighborhood characteristics in national scale, providing opportunities for comparison of neighborhood studies across geographies in the US. Existing neighborhood studies mainly utilize survey questionnaires to collect information regarding health behaviors, emotional states as well as neighborhood characteristics. However, neighborhood data collection was not well established in some areas [152]. And there is a lack of resource to construct measurements of neighborhood features in a national scale. As a result, it is difficult to either perform a nationally representative neighborhood study or compare the results of neighborhood studies across the contiguous US. In our study, we processed Twitter data consistently across geographies. The method used in characterizing neighborhood features from Twitter data would provide guidance for future researchers who are interested in utilizing publicly available social media data.

The study is significant because we accessed a nationally representative sample and provided some scientific evidence of the relationships between social neighborhood characteristics and cardiometabolic outcomes, which may potentially inform community level interventions for health practitioners. For example, Twitter-

derived social neighborhood characteristics can be used to identify communities with higher risk of cardiometabolic outcomes. Health practitioners may use Twitter as a platform for health education. In addition to obesity and diabetes, which were investigated in prior Twitter-related studies, we additionally investigated hypertension, a costly and prevalent cardiometabolic condition in the US. To the best of our knowledge, no studies have assessed Twitter-derived characteristics and individual level hypertension so far.

1.4.2 Manuscript 2

The proposed study is innovative because we investigated long-term exposure to air pollution and glucose homeostasis in youth living with type I diabetes in SEARCH. We found that youth living with type I diabetes, who relied on insulin regime, did not manage their glucose as we expected. We focused on the impact of long-term exposure to air pollution on glycemic control to understand the marked vulnerability of youth living with type I diabetes when exposed to elevated levels of air pollution.

Our study is significant because it added scientific evidence to understand the effect of air pollution on youth living with type I diabetes, the fast growing and highly vulnerable population. In addition, our study may identify the potential risk of exposure to elevated levels of air pollution for youth living with type I diabetes at an early stage, informing the early prevention of CVD complications and potentially reducing the lifetime health burdens for them.

1.4.3 Manuscript 3

The proposed study is innovative because we obtained innovative markers of arterial stiffness including carotid-femoral PWV, AIx and BrachD. Carotid-femoral PWV is the "golden standard" marker of arterial stiffness [153], however, it is less used in epidemiologic studies. AIx is the most frequently used biomarker that indirectly measures arterial stiffness. AIx is considered a negative effect of arterial stiffening compared to carotid-femoral PWV [154] and AIx may represent both central artery stiffness and vascular functions as peripheral sites [142]. BrachD is a useful marker to measure subclinical vascular changes. Prior study found decreased BrachD in individuals with high levels of CVD risk factors across the normal range of pulse wave, suggesting BrachD as a sensitive marker to detect vascular changes [155]. We were able to compare results using different markers of arterial stiffness and compare our results to those from prior studies. In addition, we were able to assess the effect of changes in acute exposure to air pollution exposure on subclinical CVD markers using repeated measures. We are not aware of any studies that focused on the acute effect of air pollution on progression of arterial stiffness in a repeated measures design in youth living with type I diabetes.

The proposed study is significant because we assessed the effect of changing acute exposure to air pollution on subclinical CVD markers. Air pollution is a modifiable risk factor for CVD. It is important to understand the progression of subclinical CVD markers following exposure to air pollution, especially in youth living with type I diabetes. The results of our study may provide evidence for early

prevention of cardiovascular complications via reducing exposures to air pollution for youth living with type I diabetes.

Chapter 2: Methods

2.1 Detailed information about study design

2.1.1 Manuscript 1

The proposed study is a cross-sectional study utilizing Twitter-derived neighborhood characteristics as exposures of interest to examine the associations between social neighborhood characteristics and cardiometabolic outcomes including continuous BMI, obesity, diabetes and hypertension in a nationally representative sample.

The individual level health data from National Health and the Nutritional Examination Survey (NHANES) 2007-2008, 2009-2010, 2011-2012, 2013-2014, 2015-2016 were assessed through National Center for Health Statistics (NCHS) Restricted Data Center (RDC). A NCHS analyst merged zip code level Twitter characteristics with individual data through a one-to-many merge, where individuals living in the same zip code were merged with the same value of the Twitter characteristics. Adults aged over 20 were included in our study.

We used NHANES data from 2007-2016 as the full cohort to perform regression analyses. To lessen the discordance in time frame, a sub-cohort analysis was conducted with NHANES 2011-2016.

2.1.2 Manuscript 2

The proposed study is a cross-sectional study examining the association between long-term exposure to air pollution and glucose homeostasis in youth living with type I diabetes in SEARCH for Diabetes in Youth Study. Specially, we are

interested in assessing the effect of estimated $PM_{2.5}$ average exposure for 1-month and for 12-month prior to the blood draw, annual average daily traffic count and residential distance to the nearest road on glucose homeostasis measured by HbA1c.

Participants were recruited from SEARCH for Diabetes in Youth Study. SEARCH for Diabetes in Youth is a multi-center observational study on youth diagnosed with diabetes [156]. SEARCH was initiated in 2000 and started to enroll youth with prevalent diabetes in 2001 and youth with incident diabetes from 2002. Only youth aged under 20 years with physician-diagnosed diabetes were eligible to be included in the study from 6 study sites including South Carolina (statewide); Ohio (eight counties surrounding Cincinnati, Ohio including Butler, Clermont, Hamilton, Warren counties in Ohio, Boone, Campbell, and Kenton counties in Kentucky, and Dearborn, Indiana); Colorado (statewide); Washington (5 counties surrounding Seattle, King, Kitsap, Pierce, Snohomish and Thurston) and Southern California (health-care membership in 8 counties including Los Angeles, Orange, Riverside, San Bernardino, Ventura, Imperial, Kern), and Hawaii (health-care membership in Hawaii). In wave 1 of SEARCH, youth were asked to participate in a baseline visit and follow-up visits at approximately 12, 24, and 60 months following the baseline visit. The baseline visit included an in-person interview with the youth including questionnaires, blood measurements, and anthropometric measures and an in-person interview with the caretaker/parent.

We included youth from five SEARCH study sites (SC, OH, CO, WA, CA). Youth from Hawaii site were excluded because exposure to air pollution in Hawaii yields small variations and the air pollution is largely affected by the volcano

emissions. Youth aged under 20 with physician's diagnosis of type I diabetes were included. Youth were excluded if there is no existing baseline measure of glucose homeostasis (HbA1c) or we were unable to geocode participant's residential address which results in missing exposure data. We also excluded youth on lipid-lowering medication and excluded youth on anti-hypertensive medication because these medications would differentially affect cardiometabolic responses to air pollution [157-160].

2.1.3 Manuscript 3

The proposed study is a repeated measures study assessing the association between acute exposure to air pollution and subclinical CVD markers in youth living with type I diabetes in SEARCH for Diabetes in Youth Study. Acute exposure to air pollution is measured as $PM_{2.5}$ single day estimates on the day of assessment, $PM_{2.5}$ on each of the 7 days prior to assessment, $PM_{2.5}$ moving averages for 2- to 5- day prior to assessment, as well as a weekly average for $PM_{2.5}$. A weekly average for $PM_{2.5}$ EC was also used. Daily $PM_{2.5}$ and $PM_{2.5}$ EC was estimated using a highly specific spatio-temporal generalized additive mixed model.

The study participants were recruited from SEARCH CVD, an ancillary study of SEARCH. SEARCH for Diabetes in Youth is a multi-center observational study that focused on physician-diagnosed diabetes in youth aged under 20 from 6 study sites (South Carolina, Ohio, Colorado, Washington, Southern California and Hawaii) [156]. In Phase 1, youth were asked to participate in an in-person baseline visit for demographics, health behaviors, medical history, anthropometric measures and blood samples. Parents/legal guardian were asked to complete family history questionnaires.

SEARCH CVD is an ancillary study to SEARCH that included youth aged over 10 and were diagnosed with type I diabetes in Colorado and Ohio study sites [161,162]. Participants were aged over 10 at SEARCH baseline visit in 2004-2005 and had data collected on cardiovascular structure and function measures. A follow-up SEARCH CVD visit was conducted in 2009-2011 on eligible participants, where demographics, anthropometric, laboratory data and cardiovascular structure and function measures were obtained. In our study, youth were eligible if they had 2 assessments of subclinical CVD markers from SEARCH CVD. Subclinical CVD markers were markers of arterial stiffness including carotid-femoral PWV, AIx and BrachD. We only included youth from Ohio because very limited youth from Colorado had 2 assessments of CVD markers. Youth were excluded if we were unable to geocode their residential address and thus resulting in missing air pollution exposure. We excluded youth on anti-hypertensive medication since anti-hypertensive medication may differentially affect cardiometabolic responses to air pollution exposures [158]. Youth with missing information in baseline hemoglobin A1c (HbA1c) and area level percent of poverty were excluded. One participant with extreme AIx value was excluded.

2.2 Assessment of potential biases

2.2.1 Manuscript 1

In Twitter-derived social neighborhood study, misclassification could occur in processing Twitter data. The machine learning algorism could not recognize sarcastic

expressions and popular expressions when assigning sentiment to each tweet. For physical activity and food tweets, the text processing could miss out typos, abbreviations and popular expressions. To reduce the biases in processing tweets, we manually labeled tweets (n=1200) and observed a high agreement between machine and manually labeled data. To capture the food items and physical activity mentioned in the tweets, we constructed large training datasets for food items (n=1430) and physical activity items (n=376). In addition, we included both individual level demographics and zip code level demographics to address the confounding. To lessen the discordance of time frame between exposures and outcomes, we performed regression using NHANES 2007-2016 as the full cohort analysis as well as NHANES 2011-2016 as the sub-cohort analysis. We accounted for the survey design and assign appropriate weights to obtain unbiased estimates and standard error.

2.2.2 Manuscript 2

Use of lipid-lowering medication and anti-hypertensive medication may differentially affect cardiometabolic responses to air pollution exposures. Lipid-lowering medication such as statin have protective effect on cardiometabolic conditions due to the anti-oxidative and anti-inflammatory effect. Anti-hypertensive medication by types would posit either beneficial or adverse effect on cardiometabolic outcomes. We excluded youth with statin and with anti-hypertensive medications since few people were on these two medications.

We performed sensitivity analyses excluding youth not fasting on the day of blood draw. Our outcome, HbA1c is a measure of glycemic control over 3-month period. We expected the outcome to be less affected by fasting status. We also

exclude youth aged less than or equal to 10 as one of the sensitivity analyses because questionnaires asking physical activity and smoking were only administered to youth aged >10.

2.2.3 Manuscript 3

Aging is a significant risk factor for cardiovascular function. Mean arterial pressure (MAP), glucose homeostasis, lipid profile, adiposity, heart rate were also associated with arterial stiffness. We included both time-invariant covariates and time-varying covariates including age at SEARCH CVD visit 1, time-varying age, sex, race/ethnicity, MAP at visit 1, time-varying MAP, body mass index (BMI) Z score at visit 1, HbA1c at baseline, smoking at visit 1, time-varying smoking and area level percent below poverty at visit 1 and time-varying area level percent below poverty to address the confounding. Due to the limited sample size and limited information on medical profile, we were not able to adjust for lipid profile and heart rate.

2.3 Statistical approaches to test hypotheses

2.3.1 Manuscript 1

Linear regression was used for continuous outcome such as BMI; Poisson regression was used for modeling binary outcomes such as obesity, diabetes and hypertension. All the regression models accounted for individual level demographics (e.g. age, race/ethnicity, sex, education) as well as zip code level demographics (e.g.

population density, median age, median household income and percent of non-Hispanic white).

We accounted for the survey design and assigned appropriate weights to obtain unbiased estimates and standard error. A 10-year Mobile Examination Center (MEC) weight was used for the full cohort analyses using NHANES 2007-2016 because we appended 10-year data from 5 survey circles from NHANES and the outcomes are from examination data, laboratory data and supplemented with questionnaire data. Similarly, a 6-year MEC weight was used for sub-cohort analyses using NHAENS 2011-2016 data.

2.3.2 Manuscript 2

Linear mixed model was used to assess the association between exposure to air pollution and HbA1c. We performed stratified analyses grouped by study sites (site SC, CO and WA vs. site OH and CA) since the distributions of air pollution were not comparable. Stratified analyses could avoid spurious associations by combining different exposures, outcomes and individual characteristics and can still preserve the richness of the data. We fit separate models for each air pollutant exposure. The basic model included study site as a random effect. We then adjusted for demographic covariates including age, sex, race/ethnicity. Next, multivariate models were fit to additionally adjust for diabetes management factors including BMI Z score, diabetes duration, and type of insulin regime. Models were further adjusted for lifestyle factors including physical activity and smoking. Finally, fully-adjusted models were fit including all previous covariates plus a measure of area-level socioeconomic status.

We assessed effect modification by including interaction terms. Age (continuous) , sex (female vs. male), ever smoke (yes, no and don't known) , race/ethnicity (white, black, Hispanic and other race) and BMI Z score (underweight, slightly underweight, normal, overweight and obese) were considered as possible effect-modifiers. Two sensitivity analyses were conducted excluding youth not fasting on the day of blood draw and excluding youth aged less or equal to 10. We limited to youth aged >10 in one of the sensitivity analyses because questionnaires asking physical activity and smoking were only administered to youth aged >10.

2.3.3 Manuscript 3

Linear mixed effect models with random intercepts for each subject was used for the regression analyses. Separate models were fit for each air pollutant. First, we fit a basic model with air pollutant at SEARCH CVD visit 1, time-varying air pollutant. We then additionally adjusted for age at visit 1, time-varying age, sex and race/ethnicity, MAP at visit 1, time-varying MAP, BMI Z score at visit 1, HbA1c at baseline, smoking at visit 1, time-varying smoking and area level percent below poverty at visit 1 and time-varying area level percent below poverty. We were able to assess both cross-sectional effect and longitudinal effect of air pollution using this model. Sensitivity analyses were performed for youth whose residential address can be geocoded at a street match.

2.4 Assessment of potential mediation effects or interaction effects

We assessed effect modification by including interaction terms. Wald test was used to test the significance of the interaction terms. Stratified analyses were performed for effect-modifiers. We did not assess mediation effects in the dissertation.

2.5 Model specification

For Manuscript 1, we included both individual level demographics and zip code level demographics to address the confounding. For Manuscript 2, we identified directed acyclic graph (DAG; Figure 4.1) from existing studies assessing the association between air pollution and glucose homeostasis. For Manuscript 3, we identified covariates from existing literature, however, we were not able to control all the covariates due to small sample size and limited information on individual medical profile. We included age at visit 1, time-varying age, sex and race/ethnicity, MAP at visit 1, time-varying MAP, BMI Z score at visit 1, HbA1c at baseline, smoking at visit 1, time-varying smoking and area level percent below poverty at visit 1 and time-varying area level percent below poverty in the model.

2.6 Assessment of model assumptions

For all three manuscripts, we assessed distributions of outcomes and distributions of exposures. For manuscript 1 and 2, residual plots were used to assess

linear assumption. For manuscript 3, we assessed distributions of changes in outcomes and changes in air pollution exposures.

2.7 Limitations of the study

2.7.1 Manuscript 1

First of all, the proposed study did not establish a temporality between Twitter predictors and the outcomes. The Twitter data were collected from 2015 to 2016. To lessen the discordance in time frame, we performed full cohort analyses using NHANES data from 2007 to 2016 and also performed sub-cohort analyses using NHANES data from 2011 to 2016, respectively. We continue collecting Twitter data and will conduct studies with Twitter-derived social neighborhood characteristics preceding health outcomes in the near future.

The Twitter users are not a representative sample of the general US population and we only collected geotagged tweets to construct characteristics. Although Twitter has becoming increasingly popular, it is estimated that 27.7% of the online users are in possession of a Twitter profile [163]. And the Twitter users are generally young, and the prevalence of usage is inversely associated with age [164]. We are unable to obtain the information for people who are not familiar with the social media or don't use the Internet frequently. The limited representativeness may affect the construct validity of Twitter-derived characteristics as social neighborhood characteristics.

Twitter-derived characteristics are subject to misclassification in processing the tweets. The machine learning algorism could be inaccurate when assigning the

sentiment score to a tweet because the algorism could not recognize and differentiate sarcastic expressions. Though we formed comprehensive lists for food items and physical activities, the text processing could miss out typos, some of the abbreviations, and popular expressions. To reduce the potential misclassification, we performed validation for sentiment analysis comparing machine labelled and manually labeled tweets and we observed a high agreement between machine and manually labeled data. We also validated the Twitter predictors using Census variables. For example, greater numbers of fast food restaurants were associated with percentage of fast food tweets. To capture the food items and physical activity mentioned in the tweets, we constructed large training datasets for physical activity items (n=376) as well as food items (n=1430).

2.7.2 Manuscript 2

We were not able to conduct stratified analyses by statin use, anti-hypertensive medication use or fasting status due to limited youth on statin, on anti-hypertensive medication and limited youth not fasting on the day of blood draw. We excluded youth on statin and youth on anti-hypertensive medication in the main analyses. We also performed sensitivity analysis with individuals who were fasting prior to the blood draw.

Exposure to air pollution were assigned to each participant by the residential locations. Though people spend a lot of time around residential places, air pollution could occur at school, recreational facilities and travel.

2.7.3 Manuscript 3

We were not able to control all the covariates identified from existing literature due to the small sample size and limited information on medical profile. And we were not able to assess modification effects and perform stratified analyses. The analyses were performed for youth recruited from only one study site, thus the generalizability is compromised.

Chapter 3:Twitter-derived social neighborhood characteristics and individual level cardiometabolic outcomes in a nationally representative sample

Abstract

Social media, such as Twitter, can serve as a potential data source for public health research to characterize the social neighborhood environment. Few studies have linked Twitter-derived characteristics to individual level health outcomes.

This study aims to assess the association between Twitter-derived social neighborhood characteristics including happiness, food and physical activity mentions with individual cardiometabolic outcomes of obesity, diabetes and hypertension using a nationally representative sample. We collected a random 1% of the geotagged tweets from April 2015 to March 2016 utilizing Twitter's Streaming Application Interface (API). Twitter-derived zip code characteristics on happiness, food and physical activity were merged to individual outcomes from restricted-use National Health and Nutrition Examination Survey (NHANES) 2007-2016 data with residential zip codes. Separate regression analyses were performed for each of the neighborhood characteristics using NHANES 2011-2016 (sub-cohort, N range: 15,291-15,897, varies across outcomes) and NHANES 2007-2016 (full cohort, N range: 25,752-27,222, varies across outcomes).

In sub-cohort analyses, individuals living zip codes with the two highest tertiles of happy tweets had body mass index (BMIs) that were 0.65-0.85 kg/m^2 lower than those living in zip codes with the lowest frequency of happy tweets. Happy

tweets were also associated with 6-8% lower hypertension prevalence. Higher prevalence of food tweets was linked with an 11% lower obesity prevalence. Those living in the two highest tertiles of physical activity tweets also had lower hypertension by 8-10%. Twitter-derived neighborhood characteristics were not associated with diabetes. Results were similar using the full cohort. Twitter-derived social neighborhood characteristics were associated with individual level obesity and hypertension, in a nationally representative sample of U.S. adults. Twitter data may have utility in capturing neighborhood sociocultural influences on chronic conditions.

Introduction

General background

The neighborhood environment has been recognized as an important determinant of health. Previous studies have identified associations between neighborhood characteristics and health behaviors [11,12], chronic conditions [14,15], and mental health outcomes [165,166], as well as mortality [167,168]. Access to healthy food, proximity to parks, green space, recreational facilities, and neighborhood walkability have been found to be protective factors of obesity, diabetes and hypertension [23-26]. Conversely, neighborhood disadvantage and neighborhood level stressors, such as feeling unsafe, have been found to be associated with higher obesity and blood pressure [14,27,29,169].

In addition to physical features of the environment, social contextual factors have also been found to be associated with a variety of health outcomes. Greater community happiness is associated with decreased obesity, hypertension, suicide

rates as well as increased life expectancy [35-37]. Greater social cohesion has been linked with lower hypertension [24,27] and social capital has been linked with lower obesity, hypertension and mental health conditions [170,171].

Social media, such as Twitter, can serve as a potential data source to characterize the social neighborhood environment. Unlike traditional indicators of neighborhood environment, Twitter indicators reflect an individual's perception and attitude towards the neighborhood environment, as well as an individual's use of neighborhood resources [49]. Twitter data may also collect reactions to certain topics that are not captured in traditional survey studies due to the pressure to provide socially desired responses. Traditional neighborhood studies mainly rely on time-consuming neighborhood audits and expensive survey data collection within limited geographical areas. In comparison, use of Twitter-derived indicators as proxy measures for neighborhood factors provides opportunities to conduct neighborhood studies at the national level economically and to study the association between geographic factors and health outcomes.

Mechanisms

Based on social learning theory, learning occurs in a social context [6]. Social contextual factors influences individual's health behaviors through reciprocal interactions between people and between people and the environment, through observational learning based on the "modeling" of behaviors, through self-initiated reinforcement or external reinforcement from social environment that facilitates or hinders an individual's behavior, and through expectations towards the successful completion of a certain health behavior [6].

Twitter is a public online platform where users can observe social behavior models, learn about new behaviors and new trends, and then adopt those actions through social learning. Individuals might reproduce health behaviors, such as healthy diet, physical activity and smoking cessation observed from Twitter [31,172], and they may maintain such behaviors via social support, self-initiated reinforcement and external reinforcement. In addition, social norms, in combination with social learning theory, could potentially explain how social influence from Twitter affect individual's health behaviors. Prior studies demonstrated that social norms on diet and physical activity, which can inform social perceptions of appropriate eating and exercise behavior, were associated with healthy eating behavior and physical activity, respectively [46,173]. Observational learning of modeled behaviors, expectations towards better health, and social norms around healthy behaviors may explain the spread of such health behaviors.

In addition to health behaviors, emotional states, both positive and negative, can spread via person to person contact and network-level interaction [43-45]. Individual perceptions of happiness are affected by social networks including family, friends and neighbors [43]. Conversely, negative emotion and depression have been found to correlate within social networks [42]. Negative emotions over time can damage biological systems and lead to obesity, heart disease, diabetes, stroke, and declines in cognitive function [174,175]. Chronic anxiety and stress can disrupt cardiac function by altering the heart's electrical stability, promoting atherosclerosis, and increasing inflammation [135-138]. Negative emotions like depression can discourage physical activity and exercise through the processes of demoralization and

self-isolation [133,176]. People may drink alcohol and consume energy dense food as coping strategies to deal with negative emotions [133,134]. Positive emotions, on the other hand, are regularly associated with better health status [177-179].

Study aims and hypothesis

In this study, we utilized Twitter-derived characteristics including happiness, food and physical activity as social neighborhood predictors and assessed the associations between the Twitter-derived characteristics and cardiometabolic outcomes including obesity, diabetes and hypertension using a nationally representative sample from the National Health and Nutrition Examination Survey (NHANES). We hypothesize that people living in zip codes with high levels of Twitter-derived neighborhood happiness, healthy diet and physical activity have lower mean body mass index (BMI) and lower prevalences of obesity, diabetes and hypertension, respectively.

Materials and Methods

Twitter-derived social neighborhood characteristics

A random 1% of the geotagged tweets that are publicly available was collected through Twitter's streaming application programming interface (API) from February 2015 to March 2016. Geotagged tweets are tweets that have the latitude and longitude coordinates of where they were sent. In total, 79,848,992 million geotagged tweets were collected across the contiguous United States (including Washington D.C.) and we identified 603,363 unique Twitter users. Duplicated tweet and tweets that identified as job postings through hashtags were removed.

Geotagged tweets were spatially joined to 2010 Census zip code areas file using Python based on the latitude and longitude coordinates. Each tweet was assigned to the corresponding zip code of where it was sent. We implemented sentiment analysis with the Machine Learning for Language Toolkit (MALLET) to compute happiness score (range from 0 to 1) for each of the tweets. A higher happiness score indicated more positive sentiment. We included diverse sources of training data such as Sentiment140 [180], Sanders Analytics [181], and Kaggle [182]. A binary variable of happiness was created for each tweet based on the MALLET score where a score greater than 0.8 was defined as happy. The cut-point of 0.8 reached the highest accuracy of classifying happy tweets and maintained the same prevalence of happy tweets as was found in the human labeled dataset of tweets [50]. After assigning each tweet with "happy" versus "unhappy", percent of happy tweets was calculated within each zip code [183].

For food analysis, we created a list of over 1430 popular food words from the US Department of Agriculture's National Nutrient Database [184]. We considered fruits, vegetables, nuts, and lean proteins such as fish, chicken and turkey as healthy food. A total of 340 food items were considered as healthy food in the list. Fast food restaurants, for example, McDonald, Kentucky Fried Chicken were also included in the list (n=154). Among the collected tweets, 4,041,521 tweets were geotagged and were related to food. To construct food variables, each tweet was searched for the expressions that are matched to the items on our list. Subsequently, we labeled each tweet as mentioning healthy food or fast food. Percentage of general food tweets,

percentage of healthy food tweets and percentage of fast food tweets were calculated at zip code level.

Similar to our food analysis, we created a list of physical activities using the published list of physical activity terms collected from physical activity questionnaires, compendium of physical activities and popular available fitness programs [185-187]. A total of 376 items were gathered and the list included activities from gym exercise, sports, recreational activities and household chores. Expressions such as "running late" and "walk away" were excluded. We collected 1,473,976 geotagged tweets associated with physical activity. Percent of physical activity tweets were aggregated at zip code level. In summary, Twitter-derived zip code level neighborhood characteristics constructed for this study included: 1) happiness; 2) general food tweets, healthy food tweets, fast food tweets; and 3) physical activity. Each zip code Twitter-derived characteristic was also categorized into tertiles (high, medium, low) [183].

NHANES data

Individual level health data were obtained from the National Health and the Nutritional Examination Survey (NHANES) 2007-2008, 2009-2010, 2011-2012, 2013-2014, 2015-2016. We obtained approval to access the restricted geocoded data (zip code) from the National Center for Health Statistics (NCHS) Restricted Data Center (RDC). NHANES data and Twitter-derived predictors were merged via zip code linkages by a NCHS analyst. The merged data were then delivered to the Maryland Federal Statistical Research Data Center. All the statistical analyses were performed at Maryland Federal Statistical Research Data Center and all the output

were reviewed by an RDC staff to avoid information disclosure. We followed the RDC confidentiality and disclosure review policies to protect the confidentiality of the NCHS study participants.

NHANES data consist of interview data (demographic, socioeconomic, and health-related questions) and examination data (physiological checks as well as laboratory tests). Data collection for NHANES was approved by the NCHS Research Ethics Review Board (ERB). Analysis of de-identified data from the survey is exempt from the federal regulations for the protection of human research participants. Analysis of restricted data through the NCHS Research Data Center is also approved by the NCHS ERB. The study was approved by University of Maryland Institutional Review Board (IRB).

We examined the following cardiometabolic outcomes: BMI, obesity, diabetes and hypertension. NHANES measured weight and height data were used to calculate the BMI. *Obesity* was defined as BMI greater or equal to 30. *Hypertension* was defined as having elevated blood pressure or self-report of taking medications for hypertension. Each participant had three measures of systolic blood pressure (SBP) and diastolic blood pressure (DBP). The second and the third measures were used to calculate mean systolic and diastolic blood pressure. A mean SBP over 130 or a mean DBP over 80 millimeters of mercury (mmHg) was defined as hypertension based on the guidelines by the American Heart Association [188]. *Diabetes* was defined as having a glycohemoglobin (%) value greater than or equal to 6.5% or self-reported diagnoses of diabetes [189] .

In our examination of the possible association between Twitter-derived social neighborhood characteristics and individual health outcomes, we controlled for both individual-level and zip code level covariates to help account for confounding. Individual level covariates included the following: age, sex, race/ethnicity and annual household income obtained from NHANES. Zip code level characteristics included the following: percent of non-Hispanic white, median household income, population density and median age obtained from the 2011-2015 American Community Survey (ACS) 5-year estimates [190] .

Analytic Approach

We implemented regression analyses for each of the outcomes separately. Linear regression was used for continuous outcomes such as BMI; Poisson regression was used for modeling binary outcomes including obesity, diabetes and hypertension, to estimate prevalence ratios [191]. All models controlled for individual level demographics and zip code level characteristics. We analyzed health outcomes for the sub-cohort (NHANES 2011-2016) which is closer in time to the Twitter data (2015). In supplemental analyses, to obtain a sample with a higher diversity of zip codes (2,116 zip codes in the "full cohort" analyses and 1,384 zip codes for the "sub cohort" analyses), we analyzed NHANES data from the most recent five survey cycles from 2007 to 2016 (described below as the "full cohort"). We excluded participants who were less than 20 years old and obtained a total of 29,201 participants from the full cohort. The analytic sample was 27,764 for analyses involving obesity, 27,019 for analyses involving diabetes, and 26,924 for analyses involving hypertension as the health outcome in the full cohort. For the sub-cohort, 17,048 participants were aged

over 20 and the analytic sample was 16,163 for analyses involving obesity, 15,774 for analyses involving diabetes and 15,830 for analyses involving hypertension. Survey design and weights were accounted for in all statistical analyses to obtain unbiased estimates and standard errors. A 10-year Mobile Examination Center (MEC) weight was used for NHANES data from 2007 to 2016 and a 6-year MEC weight was used for NHANES data from 2011 to 2016 [192,193]. Analyses were implemented in Stata MP15 (StataCorp LP, College Station, TX).

Results

Descriptive Statistics

Descriptive statistics are shown in Table 3.1. We were not able to report the Twitter characteristics specifically for the study population living in 2,116 zip codes given the NCHS RDC disclosure manual [194]. The zip code level Twitter characteristics presented in the table were calculated for all the zip codes in the United States. About 19% of tweets were happy. About 2% of tweets mentioned physical activity and 5% mentioned food. There were fewer tweets about healthy foods (1%) and fast food (0.3%).

For the full cohort, the mean age was 47 years, and 52% of the participants were female. A majority of participants were non-Hispanic whites (67%); 14% were Hispanics; 11% were non-Hispanic blacks and 8% were of other races. In terms of education, 17% had less than a high school education; 22% had a high school degree; 31% had some college education and 29% had college education or higher. For socioeconomic status, 15% had annual household incomes less than $20,000. The

mean body mass index (BMI) was 29 kg/m^2 and the prevalence of obesity was 37%. The mean glycohemoglobin (%) was 5.6% and the prevalence of diabetes was 12% in the full cohort. The prevalence of hypertension was 48%. The individual demographic characteristics in the sub-cohort were similar to those in the full cohort.

Regression Results

Zip code level happiness was associated with lower individual mean BMI, as well as lower prevalence of hypertension (Table 3.2). Comparing individuals living in the medium (2nd tertile) and the highest (3rd tertile) levels of happy tweets to lowest level (1st tertile), mean BMI decreased by 0.65 kg/m^2 (95% Confidence Interval (CI): -1.10, -0.20) and 0.85 kg/m^2 (95% CI: -1.48, -0.21), respectively. The prevalence of hypertension was 8% (Prevalence Ratio (PR): 0.92; 95% CI: 0.86, 0.98) and 6% (PR: 0.94; 95% CI: 0.88, 1.00) lower, comparing those in the 2^{nd} and 3^{rd} tertile with the lowest tertile (Table 3.2). Happy tweets were not associated with obesity or diabetes.

High levels of Twitter-derived physical activity was associated with lower prevalence of hypertension. Comparing individuals living in zip codes with medium and the highest levels of physical activity tweets to those with lowest level, hypertension decreased by 8% (PR: 0.92; 95% CI: 0.87, 0.98) and 10% (PR: 0.90; 95% CI: 0.85, 0.96), respectively. Physical activity tweets were not associated with BMI, obesity and diabetes.

Food tweets and healthy food tweets were linked to BMI, obesity and hypertension. Food tweets were associated with 4-7% lower hypertension prevalence, comparing individuals living in zip codes with medium (PR: 0.93; 95% CI: 0.87,

0.99) and highest (PR: 0.96; 95% CI: 0.90, 1.03) levels of food tweets to those with the lowest level. Individuals living in zip codes with the most food tweets had BMI values that were 0.77 kg/m^2 lower (95% CI: -1.34, -0.19) and obesity prevalence that were 11% lower (PR: 0.89; 95% CI: 0.82, 0.98). Healthy food tweets were inversely associated with BMI and obesity.

In supplemental analyses using NHANES 2007-2016 (Table 3.3), we observed associations that exhibited similar patterns as the regression results using the sub-cohort data, with some stronger associations. Happiness was significantly associated with lower mean BMI and lower prevalence of obesity and hypertension. The prevalence of diabetes was lower comparing the highest level of happiness to the lowest, but the association was not significant comparing the medium level of happiness to the lowest level. Comparing the highest level of physical activity tweets to the lowest, mean BMI, prevalence of obesity, and prevalence of hypertension were lower. Lower mean BMI and lower prevalence of obesity and hypertension were observed comparing the highest level of food tweets to the lowest. Healthy food tweets were associated with lower mean BMI and prevalence of obesity.

Discussion

This study is one of the first to investigate the relationship between Twitter-derived social neighborhood characteristics and individual cardiometabolic outcomes utilizing a nationally representative population. We found Twitter-derived happiness and healthy food were associated with lower BMI and lower risk of hypertension and Twitter-derived physical activity was associated with lower prevalence of hypertension. The associations between Twitter-derived predictors and obesity were

more evident in the full cohort (NHANES 2007-2016) than in the sub-cohort (NHANES 2011-2016), possibly due to the larger sample size and stronger statistical power.

Twitter-derived happiness was associated with lower prevalence of obesity, suggesting the protective effect of positive emotion on obesity and the link between healthy eating habits and obesity. Ties found between Twitter-derived physical activity mentions and lower hypertension suggest social modeling of physical activity (social learning of modeled behavior) through tweets may be effective at promoting the prevention of this condition. Health behaviors, including physical activity, occur in clusters rather than independently [195,196].

Study findings in context

In our study, we focused on neighborhood level happiness derived by Twitter, which is different from individual level happiness. However, social networks spread happiness and an individual's happiness is correlated to the happiness of their neighbors, friends and families [43]. The influence of affective state on outcomes via health behaviors could be a possible explanation linking happiness to lower prevalence of health outcomes. Prior studies found negative emotion, including anger, depression and anxiety, as well as stress, were associated with overeating, sedentary lifestyle and physical inactivity [134,197,198]. People may overeat to cope with negative emotions and stress [133,134,199]. In addition, negative emotion and chronic stress may induce hemodynamic responses that lead to sustained elevation of blood pressure [200]. In contrast, greater happiness is associated with lower cortisol and reduced plasma fibrinogen stress responses, indicating lower risk for CVD [201].

Our study results were consistent with previous research involving Twitter, although the majority of these studies were ecological. A county-level study found that Twitter-derived indicators of happiness, food, and physical activity were associated with lower county level prevalence of obesity [202]. Unlike our results, an ecological study found higher caloric density of food tweets was significantly related to higher prevalence of diabetes at the state level [203]. Abbar and colleagues found food calories identified from tweets were significantly correlated with state-level obesity and diabetes [204]. Chunara and colleagues found that higher proportion of activity-related interests on Facebook was associated with a significant lower prevalence of obesity and overweight both across US metros and across neighborhoods within New York City [205]. The one other study examining individual health outcomes merged individual level administrative and clinical records in Utah with Twitter data and found that people living in zip codes with the greatest percentage of happy and physical activity tweets had lower individual level prevalence of obesity. Additionally, more happy tweets and lower caloric density of food tweets within a zip code was associated with lower individual level prevalence of diabetes in Utah [206]. The inconsistencies in findings for diabetes may be caused by differences in study designs (ecological vs. individual) as well as differences in the geography (local vs. national).

Study strengths and limitations

We utilize an innovation study design to investigate sociocultural influences on health. Our study has several advantages. First, utilizing a publicly available big data source allowed us to create neighborhood characteristics for small areas across

the entire contiguous United States. This differs significantly from the majority of neighborhood studies that are restricted to a local geography given the time-consuming and expensive nature of gathering neighborhood data. Moreover, our study advances the use of social media in health research by constructing social neighborhood characteristics. Although researchers have been increasingly aware of the value of using social media data in health research, the majority of existing health studies were content analyses. Leveraging individual data from NHANES allowed us to incorporate objective health assessments and extensive individual level demographic information. This is a significant advantage given that many neighborhood studies are at the ecological level.

Nonetheless, it is important to note that this study is subject to some limitations. First, we were not able to establish the temporality between Twitter-derived social neighborhood characteristics and cardiometabolic outcomes and causality cannot be inferred from our results due to the cross-sectional design. Ideally, Twitter data should precede the cardiometabolic outcomes since information spread on Twitter would have an impact on health via social learning and social norms. However, Twitter data were collected from 2015-2016 and health data from NHANES were gathered over multiple years (2007-2016) to ensure adequate inclusion of geographically diverse participants from across the U.S. and to ensure sufficient statistical power. The discordance may be acceptable because social neighborhood environment may not change dramatically. To lessen the discordance in time frame and reduce the potential bias introduced from changing social environments, we implemented separate regression analyses for NHANES data from

2011 to 2016 and from 2007 to 2016. Results generally followed the same pattern for the two time periods, and we observed associations between Twitter-derived characteristics with obesity and hypertension.

Second, the study is observational and cross-sectional, which inhibits causal inference. We report on observed associations. Unlike other types of exposures, randomized trials for neighborhood characteristics are rare, with the exception of randomized mobility studies investigating the effects of housing vouchers. Future studies investigating changes in neighborhood characteristics and change in health outcomes may additionally help advance understanding of contextual effects.

Third, Twitter-derived predictors are subject to potential misclassification in processing. The machine learning algorithm could be inaccurate when assigning the sentiment score to a tweet due to the difficulty in recognizing and differentiating sarcastic expressions and humor. The text processing may not be able to process typos, some abbreviations and popular expressions and falsely label tweets in generating food and physical activity predictors. To reduce potential misclassification, we performed validation for sentiment analysis comparing machine labeled and manually labeled tweets and we observed a high agreement between machine and manually labeled data [50]. We also constructed comprehensive lists for food items and physical activity keywords from compendia to capture the food items and physical activity items mentioned in the tweets.

Moreover, we only collected geotagged tweets that had the latitude and longitude coordinates of where they were sent, which was necessary for constructing neighborhood indicators. Nevertheless, geotagged tweets represent a small fraction of

all tweets and may differ in characteristics. Additionally, Twitter users are not a representative sample of the general US population. Although Twitter is becoming increasingly popular, only about 27.7% of the online users have a Twitter profile in 2018 [163]. Twitter users are also generally younger [164]. Thus, Twitter does not capture information for people who do not use social media. However, tweets may offer important information on the shared social environment, which can be used to examine health disparities across geographies.

Conclusions and Study Implications

Social media platforms provide large volumes of data every day and offer extensive opportunities for understanding geographic distribution of health behaviors and health conditions. Although researchers have conducted both qualitative and quantitative studies using Twitter, links to individual level health outcomes have been less frequently studied [207]. Our study investigated the relationships between Twitter-derived social neighborhood features and individual cardiometabolic outcomes in a nationally representative population. Our research findings show Twitter as an emerging and cost-effective data source for public health that could be used to understand the potential influence of social context on important chronic health conditions. Researchers and public health practitioners may use Twitter as a public health surveillance tool to identify communities with greater risk of cardiometabolic outcomes. Practitioners could also utilize Twitter as a platform for health education and the social promotion of healthy behaviors aimed at reducing the burden for cardiometabolic outcomes.

Table 3. 1 Descriptive characteristics for Twitter social neighborhood characteristics and individual characteristics from NHANES

Zip code level Twitter characteristics	**N**	**Mean (SE)**
% of tweets that are happy	29,606	18.97% (0.0006)
% of tweets about physical activity	29,604	2.23% (0.0002)
% of tweets about food	24,177	4.95% (0.0003)
% of tweets about healthy food	24,173	1.01% (0.0002)
% of tweets about fast food	24,174	0.31% (0.0001)

Individual-level characteristics	*(NHANES 2007-2016)*		*(NHANES 2011-2016)*	
	N	***Mean (SE)***	***N***	***Mean (SE)***
Age (years)	29,201	47.33 (0.25)	17,048	47.60 (0.36)
% Female	15,040	51.90% (0.01)	8,803	51.97% (0.01)
% Married	14,836	55.04% (0.01)	8,534	54.24% (0.01)
% non-Hispanic black	6,179	11.39% (0.01)	3,830	11.43% (0.01)
% non-Hispanic white	12,113	66.63% (0.02)	6,376	65.35% (0.02)
% Hispanic ethnicity	7,627	14.25% (0.01)	4,156	14.76% (0.01)
Education				
% Less than high school	7,579	17.17% (0.01)	3,942	15.52% (0.01)
% High school	6,596	22.14% (0.01)	3,708	20.88% (0.01)
% Some college	8,366	31.35% (0.01)	5,119	32.45% (0.01)
% College or greater	6,621	29.34% (0.01)	4,262	31.15% (0.01)
Total annual household income				
% Less than $20,000	6,247	14.98% (0.01)	3,593	14.91% (0.01)
% $20,000 to $55,000	11,518	37.13% (0.01)	6,453	36.14% (0.01)
% $55,000 to $75,000	2,965	12.57% (0.01)	1,709	12.26% (0.01)
% $75,000 to $100,000	2,503	11.44% (0.01)	1,437	10.80% (0.01)
% $100,000 and Over	4,399	23.88% (0.01)	2,861	25.89% (0.02)
Body mass index (kg/m^2)	28,818	28.92 (0.09)	16,830	29.10 (0.12)
Obesity	10,478	36.52% (0.01)	6,144	37.63% (0.01)
Hemoglobin A1c (%)	27,775	5.63% (0.01)	16,280	5.65% (0.01)
Diabetes	4,603	12.08% (0.01)	2,741	12.56% (0.01)
Hypertension	14,336	48.13% (0.01)	8,411	48.81% (0.01)

Table 3. 2 Twitter-derived neighborhood characteristics and adult health outcomes in sub cohort

Zip code level Twitter predictors	Body Mass Index (kg/m^2) Beta (95% CI)[b]	Obese Prevalence Ratio (95% CI)[b]	Hypertension Prevalence Ratio (95% CI)[b]	Diabetes Prevalence Ratio (95% CI)[b]
Happy tweets				
3rd tertile	**-0.85 (-1.48, -0.21)***	0.92 (0.82, 1.04)	**0.94 (0.88, 1.00)***	0.90 (0.76, 1.05)
2nd tertile	**-0.65 (-1.10, -0.20)***	0.95 (0.86, 1.04)	**0.92 (0.86, 0.98)***	1.02 (0.90, 1.15)
Physical activity tweets				
3rd tertile	-0.57 (-1.27, 0.12)	0.94 (0.85, 1.04)	**0.90 (0.85, 0.96)***	1.09 (0.87, 1.37)
2nd tertile	-0.18 (-0.83, 0.47)	1.00 (0.91, 1.09)	**0.92 (0.87, 0.98)***	1.09 (0.91, 1.32)
Food tweets				
3rd tertile	**-0.77 (-1.34, -0.19)***	**0.89 (0.82, 0.98)***	0.96 (0.90, 1.03)	0.99 (0.82, 1.20)
2nd tertile	-0.33 (-0.84, 0.18)	0.94 (0.87, 1.03)	**0.93 (0.87, 0.99)***	0.97 (0.84, 1.12)
Fast Food tweets				
3rd tertile	-0.37 (-0.84, 0.11)	0.98 (0.90, 1.07)	0.96 (0.88, 1.04)	1.00 (0.84, 1.19)
2nd tertile	-0.47 (-1.04, 0.10)	0.99 (0.89, 1.10)	0.95 (0.89, 1.02)	1.00 (0.83, 1.21)
Healthy Food tweets				
3rd tertile	**-1.02 (-1.75,-0.28)***	**0.88 (0.79,0.98)***	0.99 (0.91, 1.06)	1.00 (0.83, 1.21)
2nd tertile	**-0.73 (-1.39, -0.07)***	0.95 (0.86, 1.04)	**0.94 (0.88, 1.00)***	1.00 (0.85, 1.16)
Caloric density				
3rd tertile	-0.20 (-0.79, 0.40)	0.94 (0.87, 1.02)	1.03 (0.96, 1.11)	0.93 (0.82, 1.05)
2nd tertile	**-0.74 (-1.38, -0.11)***	**0.87 (0.78, 0.96)***	0.99 (0.92, 1.06)	**0.84 (0.73, 0.97)***
N(Happy, Exercise)	15,897	15,897	15,412	15,473
N(Food, Healthy Food, Fast Food)	15,774	15,774	15,291	15,353

[a]Data source for health outcome: NHANES 2011-2016 among adults 20 years and older

[b]Adjusted regression models were run for each outcome separately. For dichotomous outcomes such as obesity and diabetes (0=no; 1=yes), Poisson models were utilized. For continuous variables like body mass index, linear regression was used. Models controlled for individual level demographics including age, gender, race/ethnicity, annual household income as well as zip code level characteristics including population density, percent of White, median age and median household income. Built environment characteristics were categorized into tertiles, with the lowest tertile serving as the referent group. Analyses accounted for survey weights and complex survey design to produce nationally representative estimates.

*$p<0.05$

Table 3. 3 Twitter-derived neighborhood characteristics and adult health outcomes in full cohort

Zip code level Twitter predictors	Body Mass Index (kg/m^2)	Obese	Hypertension	Diabetes
	Beta (95% CI)[b]	Prevalence Ratio (95% CI)[b]	Prevalence Ratio (95% CI)[b]	Prevalence Ratio (95% CI)[b]
Happy tweets				
3rd tertile	**-0.79 (-1.25, -0.33)***	**0.90 (0.82, 0.98)***	**0.94 (0.89, 0.99)***	**0.87 (0.77, 0.99)***
2nd tertile	**-0.53 (-0.81, -0.24)***	**0.93 (0.88, 0.99)***	**0.94 (0.89, 0.98)***	0.99 (0.90, 1.09)
Physical activity tweets				
3rd tertile	**-0.69 (-1.19, -0.19)***	**0.89 (0.82, 0.97)***	**0.91 (0.87, 0.96)***	1.04 (0.87, 1.24)
2nd tertile	-0.34 (-0.80, 0.12)	0.95 (0.89, 1.02)	**0.93 (0.89, 0.97)***	1.03 (0.90, 1.18)
Food tweets				
3rd tertile	**-0.74 (-1.16, -0.33)***	**0.88 (0.81, 0.94)***	**0.94 (0.89, 0.99)***	0.95 (0.83, 1.09)
2nd tertile	-0.26 (-0.61, 0.09)	0.95 (0.90, 1.01)	**0.94 (0.80, 0.99)***	0.95 (0.86, 1.06)
Fast Food tweets				
3rd tertile	-0.19 (-0.60, 0.22)	1.00 (0.93, 1.08)	0.95 (0.89, 1.01)	1.05 (0.91, 1.23)
2nd tertile	-0.26 (-0.71, 0.18)	1.01 (0.94, 1.10)	0.96 (0.91, 1.02)	1.05 (0.90, 1.23)
Healthy Food tweets				
3rd tertile	**-1.02 (-1.54, -0.51)***	**0.87 (0.80, 0.94)***	0.96 (0.91, 1.01)	0.93 (0.80, 1.09)
2nd tertile	**-0.80 (-1.26, -0.33)***	**0.92 (0.86, 0.98)***	**0.93 (0.89, 0.97)***	0.94 (0.83, 1.07)
Caloric density				
3rd tertile	-0.03 (-0.49,0.43)	0.97 (0.90, 1.03)	1.02 (0.96, 1.08)	0.97 (0.87, 1.08)
2nd tertile	**-0.58 (-1.04,-0.12)***	**0.88 (0.81,0.95)***	0.98 (0.93,1.04)	0.91 (0.82, 1.03)
N(Happy, Exercise)	27,222	27,222	26,151	26,429
N(Food, Healthy Food, Fast Food)	26,814	26,814	25,752	26,029

[a]Data source for health outcome: NHANES 2007-2016 among adults 20 years and older

[b]Adjusted regression models were run for each outcome separately. For dichotomous outcomes such as obesity and diabetes (0=no; 1=yes), Poisson models were utilized. For continuous variables like body mass index, linear regression was used. Models controlled for individual level demographics including age, gender, race/ethnicity, annual household income as well as zip code level characteristics including population density, percent of White, median age and median household income. Built environment characteristics were categorized into tertiles, with the lowest tertile serving as the referent group. Analyses accounted for survey weights and complex survey design to produce nationally representative estimates.

*$p<0.05$

Chapter 4: The association between exposure to air pollution and glucose homeostasis among youth with type I diabetes

Abstract

Evidence suggests that individuals living with diabetes are at greater risk than healthy populations for cardiovascular disease (CVD) when exposed to ambient air pollution. Air pollution exposure is a modifiable risk factor for CVD, and long-term exposure to air pollution may worsen glucose metabolic control. In this study, we assessed the association between long-term exposure to air pollution and glucose homeostasis in youth living with type I diabetes from SEARCH for Diabetes in Youth Study.

From five of the SEARCH Study sites, we included youth aged under 20 years with physician's diagnosis of type I diabetes . The outcome, glucose homeostasis was measured by glycated hemoglobin (HbA1c) at the baseline visit. $PM_{2.5}$ average exposure for 1-month and for 12-month periods prior to blood draw, annual average daily traffic counts (AADT) and residential distance to roads were used to estimate air pollution exposure. Linear regression was used to assess the association between exposure to air pollution and glucose homeostasis. Due to differences in air pollution distributions and study populations identified via initial exploratory analyses, we performed stratified analyses by study sites. In the modeling process, we adjusted for demographics (e.g. age, sex, race/ethnicity), diabetes management factors (e.g. type of insulin regime, diabetes duration, body mass index (BMI) Z score), lifestyle factors

(e.g. physical activity, smoking) and area level socioeconomic status. These factors were selected a priori based on a directed acyclic graph (DAG) which drew from existing scientific literature. In addition, we assessed effect-modification by sex, ever smoke, race/ethnicity and BMI Z score.

A total of 2,864 youth living with type I diabetes were included from SEARCH. The average age was 12.2 years and about half of participants were female. In fully-adjusted models 1 $\mu g/m^3$ increase in estimated $PM_{2.5}$ average exposure for 12-month prior to blood draw was associated with a 0.06 increase (95% CI: 0.01, 0.10) in HbA1c for study site SC, CO and WA and a 0.02 decrease (95% CI: -0.04, 0.00) for sites OH and CA, respectively. We observed weak positive or null associations in fully-adjusted models with residential distance to heavily trafficked roads. For example, for study site SC, CO and WA and site OH and CA, respectively, compared to living >200m from major road, youth living within 50 m of a major road was associated with 0.21 increase in HbA1c (95% CI: 0.00, 0.42) and 0.20 increase in HbA1c (95% CI: -0.08, 0.48). Comparing the highest level of AADT to the lowest level in fully adjusted models, AADT in road classes A4 was associated with 0.29 increase in HbA1c (95% CI: 0.12, 0.46) for site SC, CO, WA, and was associated with 0.06 lower HbA1c (95% CI: -0.29, 0.18) for site OH, CA, respectively. For the association between residential distance to heavily trafficked roads, youth with Hispanic ethnicity exhibited stronger positive associations compared to other race/ethnicity groups for site SC, CO, WA. No effect-modification was observed for sex, ever smoke and BMI Z score.

Long-term exposure to air pollution may be associated with glucose homeostasis in youth living with type I diabetes in certain areas. Reducing exposure to ambient air pollution may be preventive of future CVD outcomes for some youth living with type I diabetes. Differences in sociodemographic may explain the differential responses to air pollution across study sites. Future research is needed to identify factors influencing the association between exposure to air pollution and glucose homeostasis in youth living with type I diabetes.

Introduction

A substantial body of evidence has suggested that exposure to ambient air pollution is associated with increased risk of developing adverse chronic health outcomes, particularly cardiovascular disease (CVD) and mortality due to CVD [2,208-210]. Possible pathways linking air pollution to CVD morbidity and mortality include oxidative stress, inflammation, endothelial dysfunction and metabolic syndrome [2]. Some studies have suggested that people living with diabetes mellitus (DM) are at greater risk than healthy individuals for developing CVD when exposed to air pollution [8,9,211,212]. These studies mainly focused on the effects of air pollution among adults, most of whom are living with type II diabetes [213]. Little is known about the impact of air pollution on CVD risk for youth living with type I diabetes.

According to the American Diabetes Association, about 1.25 million Americans are living with type I diabetes, including 200,000 youth under age 20, and it is estimated that about 600,000 youth will be living with type I diabetes by 2050 [214,215]. Compared to the general pediatric population, youth living with type I

diabetes are more likely to be living with CVD risk factors concurrently [216,217]. In SEARCH for Diabetes in Youth Study, it was estimated that 14% of the youth with type I diabetes are living with more than two CVD risk factors [149]. A study using 26 Norway pediatric clinic data suggested that 45% youth with type I diabetes are living with more than two CVD risk factors [150]. Another population-based study in Germany reported the prevalence of having two or more CVD risk factors ranges from 6.2% to 21.7% , with the highest prevalence found in the oldest age group (age:17-26) [151]. Hence, youth with type I diabetes may be more susceptible to the cardiovascular risks triggered by air pollution.

Exposure to air pollution may also expedite the development of complications or lead to CVD events in adulthood. Maintaining euglycemic blood glucose is an important task for people living with diabetes and failure to maintain a normal range of blood glucose could lead to higher risks of developing diabetes-related cardiovascular complications [80-84,218,219]. Poor glycemic control is associated with several CVD risk factors [78,79]. It was reported that elevated but non-diabetic levels of glucose were associated with increased risks of CVD [87].

A few studies have examined the relationship of ambient air pollution exposure and glucose homeostasis. The majority of these studies have focused on adults in the general population [88,89,91,93], with few studies assessing this association among adults with diabetes [90-92,94], which is predominantly type II diabetes. These studies generally suggest a link between exposure to air pollution and glycemic control [88-90,92,93,220]. Extremely few studies have focused on the impact of air pollution on glycemic control among youth living with type I diabetes.

We are only aware of two studies, both conducted by German research groups, that have assessed this association [95,96].

Similar to human studies, there are very few animal studies assessing the impact of air pollution on animal models induced with type I diabetes. Using streptozotocin (STZ) induced type I diabetic animal models, studies found that both acute and sub-chronic exposure to particulate matter were associated with exaggerated responses in oxidative stress, systemic inflammation, endothelial function and glucose homeostasis [73,74,97]. Yan and colleagues indicated that sub-chronic exposure to particulate matter with an aerodynamic diameter less than 2.5 micrometer ($PM_{2.5}$) could alter glucose homeostasis and they concluded that exposure to particulate matter may induce vascular complications in DM through chronic hyperglycemia and systemic inflammation, thus providing support for the biologic plausibility of a potential relationship between air pollution exposures and glycemic control.

In this study, we aim to investigate the association between long-term exposure to ambient air pollution and glucose homeostasis among youth with type I diabetes. Our study will add information to the growing scientific body of work investigating the relationship between metabolism and air pollution in an under-investigated population. In addition, this study will potentially inform future air quality policies and treatment or prevention guidelines.

Materials and Methods

Study Population

SEARCH for Diabetes in Youth is a multi-center observational study of youth diagnosed with diabetes [156]. SEARCH was initiated in 2000 and started to enroll youth with prevalent diabetes in 2001 and youth with incident diabetes from 2002. Only youth aged under 20 years with physician-diagnosed diabetes were eligible to be included in the study from 6 study sites including South Carolina (statewide); Ohio (eight counties surrounding Cincinnati, Ohio including Butler, Clermont, Hamilton, Warren counties in Ohio, Boone, Campbell, and Kenton counties in Kentucky, and Dearborn, Indiana); Colorado (statewide); Washington (5 counties surrounding Seattle, King, Kitsap, Pierce, Snohomish and Thurston) and Southern California (health-care membership in 8 counties including Los Angeles, Orange, Riverside, San Bernardino, Ventura, Imperial, Kern), and Hawaii (health-care membership in Hawaii). In wave 1 of SEARCH, youth were asked to participate in a baseline visit and follow-up visits at approximately 12, 24, and 60 months following the baseline visit. The baseline visit included an in-person interview with the youth including questionnaires, blood measurements, and anthropometric measures and an in-person interview with the caretaker/parent. Questionnaires asking physical activity and smoking were only administered to youth aged >10. For youth aged <18, their caretakers/parents were asked to waive their right to review participant's responses before completing these questionnaires.

This cross-sectional study is an ancillary study of SEARCH for Diabetes in Youth Study. We included the baseline visit of participants from five of the study

sites (OH, CO, WA, SC, CA). Youth were eligible if they were living with prevalent type I diabetes in 2001 or with incident type I diabetes diagnosed from 2002. In addition, we limited participants to those with residential addresses geocoded at a street level match for greater accuracy of geocoding and assigned air pollution exposure estimates. A total of 3,434 participants were obtained from SEARCH. We excluded participants without an existing baseline measure of glucose homeostasis (glycated hemoglobin (HbA1c), n=41) and without air pollution exposure estimates (n=348). We further eliminated participants with missing diabetes management factors including diabetes duration (n=1), type of insulin regimen (n=42) and body mass index (BMI) z score (n=51). We also excluded youth on lipid-lowering medication (n=21) and excluded youth on anti-hypertensive medication (n=66). These youth were excluded because lipid-lowering medication and antihypertensive medication may differentially affect cardiometabolic responses to air pollution exposures [157-160]. After exclusions, 2,864 participants were included in the study.

Health Outcome

The health outcome was glucose homeostasis measured by glycated hemoglobin (HbA1c). Youth were asked to fast for 8 hours prior to blood draw. Blood samples were collected to examine HbA1c. The blood samples were shipped to the Northwest Lipid Metabolism and Diabetes Research Laboratories in Seattle, WA within 24 hours of blood collection. An Ion-exchange high performance liquid chromatography system (TOSOH, Bioscience, Inc., San Francisco, CA) was used to measure the blood HbA1c.

Exposure Assessment

Long-term air pollution exposures were assessed by estimated daily $PM_{2.5}$ mass measures averaged for the 12 months prior to blood draw , annual average daily traffic (AADT) count on the closest road to the residence and residential distance to road [221,222]. Sub-chronic exposure to air pollution was assessed by $PM_{2.5}$ mass daily exposure estimates averaged over the month prior to blood draw.

We geocoded the residential address of each participant at the baseline visit and assigned the modeled air pollution exposure to each participant by residential location. ArcGIS 9.3 software (ESRI 2008) and the TIGER 2000 and 2006 Road Network Files were used for geocoding.

Residential distance to US Census Feature Class Code (CFCC) [223] road class A1-A4 was also estimated as a proxy for long term traffic-related air pollution exposure. The CFCC road classes were: A1 (primary roads, typically interstates, with limited Access), A2 (primary major, non-interstate roads, without limited access), A3 (smaller, secondary roads, state or county highways), A4 (local, neighborhood and rural road). For analysis, we selected road class categorization scheme that would allow for the majority suburban/rural distribution of the study population. Following previously published categorizations, distance to the most proximal A1 road and A2 were divided into less than or equal to 150 m and greater than 150 m [224,225]; less than or equal to 200 m, 200 to 400 m and greater than 400 m [226] for statistical analysis. Distance to nearest road in class A3 and distance to the nearest major road (A1-A3) were divided into three categories (<50 m, 50-200 m and >=200 m) [227]. Distance to road A4 was divided into two categories (<=50 m vs. >50 m) [224,225].

Prior studies have suggested that levels of traffic air pollutants including $PM_{2.5}$ and nitrogen oxides decrease rapidly with increasing distance from road [228,229]. Zhu et al suggested the level of traffic air pollutants approach the background concentration at 150 meters from major roadway [230,231].

Traffic intensity data were obtained from Geographic Data Technology, Inc. (Lebanon, NH) Dynamap Traffic Counts v4.2. The traffic intensity data were spatially joined to ESRI StreetMap Pro 2007 to obtain CFCC road classes. Spatial smoothing generalized additive models (GAMs) were used to generate annual average daily traffic count (AADT) by road classes. The generic form of GAM is:

$$y_{i,t} = \alpha_t + g(s_i) + e_{i,t};$$
$$e_{i,t} \sim N(0, \sigma^2{}_t) \qquad (1)$$

where $y_{i,t}$ represents meteorological factors at location i=1…I on day t=1…T, α_t is an intercept of the adjusted mean on a given day, $g(s_i)$ is a two-dimensional penalized thin-plate smoothing spline, with $k=I*0.9$ as the basis dimension chosen to allow some flexibility in the function. The estimation of AADT was performed separately for each road classes(hereafter AADT-A1 to AADT-A4). Prior studies have utilized quantiled AADT including tertile, quartile and quintile [232-235]. In our study, AADT was categorized into tertiles for each road class separately.

Estimated $PM_{2.5}$ average exposure for 1-month and for 12-month were constructed based on $PM_{2.5}$ daily predictions from spatio-temporal generalized additive mixed models (GAMMs) [221,222]. The spatio-temporal model was developed using $PM_{2.5}$ monitoring data, time-varying meteorological data, GIS-based

time-invariant spatial covariates and smooth function of GIS-based time-invariant spatial covariates. $PM_{2.5}$ monitor data were obtained from the U.S. Environmental Protection Agency's Air Quality System (AQS) network, from the Interagency Monitoring of Protected Visual Environments (IMPROVE), and from the Southern Aerosol Research and Characterization Study (SEARCH) network [236]. Traffic-related PM were obtained from Atmospheric Dispersion Modeling System (ADMS) – Roads v2.3 software (CERC, Cambridge, UK). The meteorological factors that are influential to air pollution dispersion including wind speed, temperature and total precipitation were obtained from the National Climatic Data Center [237]. Elevation data were obtained from U.S. Geological Survey (USGS) National Elevation Dataset [238] and land use data were obtained from the USGS 1992 National Land Cover Dataset [239].

The generic form of the GAMM model is:

$$y_{i,t} = \alpha + \alpha_{t,r} + \sum_q d_q(X_{i,q}) + \sum_p f_{p,r}(Z_{i,t,p}) + g_{t,r}(s_i) + g(s_i) + b_i + e_{i,t};$$
$$b_i \sim N(0, \sigma^2{}_b); \quad e_{i,t} \sim N(0, \sigma^2{}_{e\,\mathrm{r},t}) \qquad (2)$$

where $y_{i,t}$ is the natural-log transformed daily average $PM_{2.5}$ at monitor site i (i=1 to I_r sites) in region r and at time t (t=1 to T monthly time periods), s_i is the pair of projected coordinates for site i. $X_{i,q}$ are GIS-based time-invariant spatial characteristics for q=1…Q, $Z_{i,t,p}$ are spatio-temporal characteristics for p=1…P, and $\alpha_{t,r}$ is a daily intercept representing the adjusted mean across all sites within the region. d_q and $f_{p,r}$ are penalized spline smooth functions of Q GIS-based time-invariant spatial characteristics and P time-varying meteorological factors, both with

a basis dimension of 10. $g_{t,r}(s_i)$ accounts for residual daily spatial variability within the region, and $g(s_i)$ accounts for time-invariant spatial variability across the contiguous US. b_i is the random effect representing unexplained site-specific variability.

Covariates

We selected covariates a priori through the use of directed acyclic graph (DAG) (Figure 4.1). The DAG was identified based on existing studies assessing the association between air pollution and glucose homeostasis in healthy people from the general population [88,91,93], in people living with type II diabetes [90-92,94] and in youth living with type I diabetes [95,96].

We included age, sex and race/ethnicity, type of insulin regimen, diabetes duration (in years) and continuous body mass index Z score (BMI Z score), physical activity, smoking and area level socioeconomic status. Race/ethnicity was categorized as black, white, other race and Hispanic. Type of insulin regimen was categorized as 1) insulin pump; 2) long and short/rapid insulin, 3 or more times a day; 3) long and any other combination, 2 or more times a day; 4) Any combination of insulins excluding long, 3 or more times/day; 5) Any insulin(s) taken 1 time/day, or any insulin combination excluding long 2 times/day. Physical activity was measured as number of days exercised at least 20 minutes that caused the participant to sweat and time spent on computer or watching TV. Smoking was assessed as ever smoke and days smoked in the past 30 days. Area level socioeconomic status (SES) was assessed by percent below poverty at Census Block of residence from the US Census 2000 [240].

Statistical Methods

In exploratory analyses, we examined the distribution of exposure to ambient air pollution by study sites and examined basic characteristics of the participants grouped by study sites. The distributions of estimated $PM_{2.5}$ measures were non-overlapping with mean values around 9-10 $\mu g/m^3$ for study site SC, CO and WA, and mean values over 17 $\mu g/m^3$ for study site OH and CA. The differences in the distribution of $PM_{2.5}$ suggested the overall air pollution levels may differ in SC, CO and WA versus OH and CA. In addition, chemical compositions of air pollutants may differ across study sites, thus inducing differential physiological effects [241]. The chemical composition of $PM_{2.5}$ varies spatially and temporally across the US [241,242]. Organic carbon constitutes a large proportion of $PM_{2.5}$ in the western US compared to $PM_{2.5}$ mass in the eastern US while sulfate is more prevalent in $PM_{2.5}$ mass in the eastern US. In addition, the demographics and glycemic control were different. Youth in OH, CA were more diverse in race/ethnicity with 28.2% non-White. Only 18.2% of the youth in SC, CO, WA were non-White. About 36% of the youth in OH and CA were in long and short/rapid insulin, 3 or more times a day while only 23.4% of the youth in SC, CO and WA took the same insulin regime. Additionally, more youth in OH and CA reported good HbA1c level (49.7%) compared to youth in SC, CO and WA (41.8%). Based on the exploratory analyses, we decided to perform stratified analyses grouped by study sites (SC, CO and WA vs. OH and CA) to avoid spurious associations by combining different exposures, outcomes and individual characteristics and still preserve the richness of the data.

Linear regression was used to assess the association between exposure to air pollution and HbA1c. Separate models were fit for each air pollutant exposure. The basic model included study site as a random effect. We then adjusted for demographic covariates including age, sex, race/ethnicity. Next, multivariate models were fit to additionally adjust for diabetes management factors including BMI Z score, diabetes duration, and type of insulin regime. Models were further adjusted for lifestyle factors including physical activity and smoking. Finally, fully-adjusted models were fit including all previous covariates plus a measure of area-level socioeconomic status.

We assessed effect modification by including interaction terms in the models. Sex (female vs. male), lifetime smoking status (yes, no and don't known), race/ethnicity (white, black, Hispanic and other race) and BMI Z score (underweight, slightly underweight, normal, overweight and obese) were considered as possible effect-modifiers. Two sensitivity analyses were conducted excluding youth not fasting on the day of blood draw and excluding youth aged less or equal to 10. SAS 9.4 (SAS Institute Inc., Cary, NC, USA) was used for all the statistical analyses.

Results

Basic characteristics of all the study participants and characteristics grouped by study sites are presented in Table 4.1. For all the youth included in the study, the mean age was 12.2 years (SD: 4.3) and 48.9% were female. Among the participants, 78.4% were White; 8.5% were Black; 10.4% were Hispanic and 2.6% were Other race. Few participants were not fasting on the day of blood draw (9.9%). Mean estimated 1-month $PM_{2.5}$ average exposure and mean estimated 12-month $PM_{2.5}$ average exposure were 12.7 $\mu g/m^3$ (SD:5.7) and 13.0 $\mu g/m^3$ (SD: 5.2), respectively

(Table 4.1). Estimated $PM_{2.5}$ exposures by study sites are presented in Table 4.2. Mean estimated $PM_{2.5}$ average exposure for 1 month and for 12-month were around 9 to 10 $\mu g/m^3$ (SD range: 1.2-1.6) for study site SC, CO, WA, and were over 17 $\mu g/m^3$ (SDs over 3.9) for study site OH and CA. Distributions of annual average daily traffic count by road classes (AADT-A1 to AADT-A4) are presented in Table 4.3. Study site OH and CA had higher mean AADT by road classes. Distributions of study participants by residential distance to road categories are presented in Table 4.4.

We ran stratified analyses grouped by study sites since the distributions of estimated $PM_{2.5}$ exposures were not comparable for SC, CO and WA and for OH and CA (Table 4.2) and demographics of participants were different in SC, CO and WA versus OH and CA (Table 4.1). Regression results for SC, CO and WA are presented in Table 4.5a and results for OH and CA are presented in Table 4.5b. For SC, CO and WA, 1 $\mu g/m^3$ increase in $PM_{2.5}$ average exposure for 1 month and for 12-month were associated with 0.01 (95% Confidence interval (CI): -0.02, 0.04) and 0.11 (95% CI: 0.06, 0.16) increase in HbA1c in basic models, respectively. The effects of exposure to $PM_{2.5}$ for 12-month attenuated after sequentially controlled for demographics, diabetes management factors, lifestyle factors and area level SES. In fully adjusted model, 1 $\mu g/m^3$ increase in $PM_{2.5}$ average exposure for 12-month was associated with 0.06 (95% CI: 0.01, 0.10) increase in HbA1c. For OH and CA, 1 $\mu g/m^3$ increase in $PM_{2.5}$ average exposure for 1 month and for 12-month were not associated with HbA1c (β: 0.00, 95% CI: -0.01, 0.02 and β: -0.01, 95% CI: -0.03, 0.01, respectively) in basic models. The effects of exposure to $PM_{2.5}$ for 12-month did not change after sequentially adjusted for demographics, diabetes management factors, lifestyle factors

and area level SES. In fully adjusted model, 1 $\mu g/m^3$ increase in $PM_{2.5}$ average exposure for 12-month was not associated with HbA1c (β: -0.02, 95% CI: -0.04, 0.00).

For SC, CO and WA, distance to the road A1 (<=150 m, >150 m and <=200 m, 200-400 m, >400 m), distance to the road A2 (<=150 m, >150 m and <=200 m, 200-400 m, >400 m) and distance to the road A4 (<=50 m, >50 m) was not associated with HbA1c in basic models but distance to the road A3 (<=50 m, 50-200 m, >200 m) and distance to road major road (<=50 m, 50-200 m, >200 m and <=50 m, 50-100 m, 100-200 m, 200-400m, >400 m) were positively associated. HbA1c increased by 0.51 (95% CI: -0.10, 1.12) and 0.41 (95% CI: -0.02, 0.84), comparing youth living within 150 m to youth living further away from a road A1 and comparing youth living within 150 m to youth living further away from a road A2, respectively (Table 4.5 a). Similarly, HbA1c increased by 0.36 (95% CI: -0.09, 0.81) and 0.41 (95% CI: -0.02, 0.84), comparing youth living within 200 m to youth living at >400 m from a road A1 and comparing youth living within 200 m to youth living at >400 m from a road A2, respectively. Comparing youth living within 50 m with youth living at >200 m to road A3, HbA1c increased by 0.39 (95% CI: 0.15, 0.63). For residential distance to the nearest major road, HbA1c increased by 0.35 (95% CI: 0.12, 0.58), comparing youth living within 50 m with youth living at >200 m. Youth living within 50 m to a road A4 have 0.26 lower HbA1c (95% CI: -0.58, 0.07) compared to youth living further away. The associations between residential distance to road and HbA1c attenuated after sequentially adjusted for demographics, diabetes management, lifestyle factors and area level social economic status. In fully adjusted model, HbA1c

increased by 0.30 (95% CI: -0.27, 0.86) and 0.26 (95% CI: -0.14, 0.67), comparing youth living within 150 m to youth living further away from a road A1 and comparing youth living within 150 m to youth living further away from a road A2, respectively. HbA1c increased by 0.28 (95% CI: -0.14, 0.69) and 0.11 (95% CI: -0.23, 0.46), comparing youth living within 200 m to youth living at >400 m from a road A1 and comparing youth living within 200 m to youth living at >400 m from a road A2, respectively. Youth living within 50 m to road A3 had 0.25 (95% CI: 0.03, 0.47) HbA1c than youth living further away. Youth living within 50 m to a major road had 0.21 (95% CI: 0.00, 0.42) higher HbA1c than youth living further away. Youth living within 50 m to a road A4 have 0.23 lower HbA1c (95% CI: -0.52, 0.07) compared to youth living further away.

For OH and CA, distance to road A3 and distance to major road were associated with HbA1c in basic models but not in fully adjusted models (Table 4.5 b). In basic models, youth living within 50 m to a road A3 had 0.34 (95% CI: 0.03, 0.65) higher HbA1c than youth living further away. Youth living within 50 m to a major road had 0.35 (95% CI: 0.05, 0.65) higher HbA1c than youth living further away. The associations were attenuated after adjusting for demographics, diabetes management factors, lifestyle factors as well as the socioeconomic status sequentially. In fully adjusted models, HbA1c increased by 0.18 (95% CI: -0.11, 0.47) , comparing youth living within 50 m to a road A3 with youth living at >200 m. HbA1c increased by 0.20 (95% CI: -0.08, 0.48), comparing youth living within 50 m to a major road with youth living at > 200 m. Distance to road A1, A2 and A4 were not associated with

HbA1c in basic models, in models adjusted for covariates sequentially and in fully adjusted models.

For SC, CO and WA, HbA1c increased by 0.31 (95% CI: 0.11, 0.51), 0.30 (95% CI: 0.10, 0.49), 0.22 (95% CI: 0.03, 0.42) and 0.35 (95% CI: 0.16, 0.53) comparing youth exposed to the highest levels of AADT for road classes A1 to A4 (AADT-A1 to AADT-A4) to youth exposed to the lowest levels in basic models, respectively (Table 4.5 a). The associations between air pollution exposures and HbA1c first attenuated after adjusting for demographics, diabetes management factors sequentially, but then had a slight stronger effect after adjusted for lifestyle and area level socioeconomic status generally. Comparing youth exposed to the highest levels of AADT for road classes A1 to A4 to youth exposed to the lowest levels in fully adjusted models, HbA1c increased by 0.20 (95% CI: 0.05, 0.34), 0.20 (95% CI: 0.03, 0.37), 0.15 (95% CI: -0.02, 0.32) and 0.29 (95% CI: 0.12, 0.46), respectively.

For OH and CA, HbA1c increased by 0.04 (95% CI: -0.20, 0.29), 0.25 (95% CI: 0.01, 0.49), 0.11 (95% CI: -0.13, 0.36) and decreased by 0.03 (95% CI: -0.27, 0.22), comparing youth exposed to the highest levels of AADT near road A1 to A4 (AADT-A1 to AADT-A4) to youth exposed to the lowest levels of AADT in basic models, respectively (Table 4.5 b). Comparing the highest tertiles of AADT for road classes A1, A3 and A4 to the lowest in fully adjusted models, HbA1c decreased by 0.10 (95% CI: -0.35, 0.16), 0.07 (95% CI: -0.31, 0.18) and 0.06 (95% CI: -0.35, 0.14), respectively. AADT-A2 was associated with higher HbA1c was higher (β: 0.05, 95% CI: -0.19, 0.29) for youth exposed to the highest level of traffic near A2 road compared to youth exposed to the lowest level of traffic near A2 road.

In sensitivity analyses excluding youth not fasting on the day of blood draw, results were similar to the main results for both SC, CO, WA and OH, CA (Table 4.6 a and Table 4.6 b). For the sensitivity analyses excluding youth ages 10 or younger, $PM_{2.5}$ average exposure for 12-month, distance to major road were not associated with HbA1c in fully adjusted model for SC, CO and WA. A 1 $\mu g/m^3$ increase in $PM_{2.5}$ average exposure for 12-month were associated with 0.06 (95% CI: 0.00, 0.12) increase in HbA1c. Youth living within 50 m of a major road and living between 50-200 m of a major road had 0.27 (95% CI:0.00, 0.54) and 0.14 (95% CI: -0.07, 0.34) higher HbA1c compared to youth living at >200 m (Table 4.6 a).

We did not observe any effect modification by smoking, BMI or sex. Race/ethnicity modified the association between distance to road A3 and glucose homeostasis for SC, CO and WA (Table 4.7). Hispanic and white youth living with 50 m to a road A3 had larger increases in HbA1c (Hispanic β: 1.16, 95% CI: 0.12, 2.19; White β: 1.16, 95% CI: 0.01, 0.46) compared to Hispanic and White youth living 200 m away or further. Black and Other race youth exhibited null associations in comparison.

Discussion

Our study suggests that long-term exposure to air pollution may be associated with glucose homeostasis. In SC, CO and WA, we found positive associations between $PM_{2.5}$ average exposure for 12-months prior to blood draw, residential distance to heavily trafficked roads, and AADT with glucose homeostasis measured by HbA1c. In OH and CA, null associations were observed except for distance to heavily trafficked roads. We performed stratified analyses grouped by sites because

the distributions of estimated $PM_{2.5}$ measures were non-overlapping and the chemical composition of $PM_{2.5}$ varies spatially and temporally across the US with greater proportion of organic carbon constitutes found in Western US compared to greater proportion of sulfate found in the Eastern US [241,242]. Though the mechanisms are not fully understood, air pollution constituents can be associated with varying physiological effects [241]. It is possible that pro-oxidative chemicals including metals and organic compounds may deposit in the vasculature and promote inflammation [243]. Short-term exposure to elemental carbon, calcium, zinc were associated with cardiovascular hospitalization and short-term exposure to aluminum, calcium, chlorine, elemental carbon, nickel, silicon, titanium and vanadium were associated with respiratory admissions [244]. Differences in demographics and glycemic control might also explain the inconsistencies in stratified results. Sociodemographic profile was strongly associated with risks factors in controlling type I diabetes [245]. And glycemic control and CVD risk factors were different by race/ethnicity based on National Health and Nutrition Examination Survey (NHANES) [246]. Until now, the effect of race/ethnicities in the association between exposure to air pollution and cardiovascular outcomes is less studied and existing studies yielded inconsistent results. Blacks exhibited stronger association between long-term exposure to $PM_{2.5}$ and left-ventricular mass index in comparison to Whites in the Multi-ethnic Study of Atherosclerosis [247]. Other studies suggested non-White showed similar [248] or attenuated [249] effects between long-term exposure to air pollution and cardiovascular outcomes compared to White. The dissimilarity in race/ethnicity between study site SC, CO and WA and study site OH and CA may

affect the associations between long-term exposure to air pollution and glucose homeostasis.

We observed associations for $PM_{2.5}$ average exposure for 12-month but not for 1-month. This is not surprising because HbA1c is a measure of average blood sugar for the past 2-3 months. Exposure to $PM_{2.5}$ 1-month prior to blood draw is less likely to affect glucose homeostasis measured by HbA1c. Prior study suggested the association between exposure to $PM_{2.5}$ and mortality manifested within 2 year's exposure [250]. We are not clear that exposure to $PM_{2.5}$ at which lag period has the maximum effect on glucose homeostasis. Future studies may explore the time-response relationships between exposure to $PM_{2.5}$ and HbA1c. The knowledge of concentration-response and time-response relationships may potentially inform prevention guidelines of CVD for youth living with type I diabetes.

Site OH and CA, have higher means and variations in $PM_{2.5}$ average exposure for 1-month and for 12-month prior to the blood draw. However, both $PM_{2.5}$ measures were not associated. And youth registered at OH and CA had better glycemic control than youth registered at SC, CO and WA. In addition to demographics differences stated above, access to care, insurance and other unknown factors may play an important role. Large variation in diabetes management across states can be explained by demographics, however, much variability remained unexplained [251]. Future research may focus on identify the influencing factors, informing diabetes management for youth living with type I diabetes.

We did not observe associations for distance to road A1, A2, A4 but found positive associations for road A3 and A1-A3 for study site SC, CO and WA. Different

population distributions in distance to roadways A1-A4 may explain the inconsistent associations. Road A1 and road A2 are interstate highways and nationally and regionally important highways. In our study, 53 participants live within 150 m of road A1, accounting for 1.9% of the participants and 81 live within 150 m of road A2, that is 2.8% of the participants. We used another categorization scheme (<=200 , 200-400 m and > 400 m) based on existing literature, however, more than 90% of youth living at >400 m for road A1 and A2, respectively. Conversely, over 90% of the youth live within 50 m of road A4, which represented local, neighborhood and rural roads. The small numbers of youth live near roadways A1 and A2 and small number for youth live further away from A4 yielded limited power to detect the association between distance to road and glucose homeostasis. We further stratified by study sites, leaving even fewer numbers for youth live near road A1, A2 and fewer youth living further away from A4 in the analyses. In comparison, more people live near road A3, which included state highway and county highway connecting small towns and neighborhoods. We have a sufficient number of youth included in each category for distance to road A3 and distance to major road. We additionally used distance to major road categorized into <50 m, 50-100 m, 100 – 200 m, 200 -400m and >=400 m to compare with prior study. We generally observed negative associations for youth living 200 – 400 m to a major road compared to youth living 400 m away. For people living far away from a major road, traffic emission from roadways is less likely to be a major source of ambient air pollution since traffic-related air pollutant may decay to background levels rapidly with increasing distance from road [228]. Therefore, those living far away from a major road may be less affected. For OH and CA, distance to

road A3 was associated with HbA1c in basic model and the association became non-significant after controlling for demographics. This may potentially support our explanation that demographics affect the association between exposure to air pollution and glucose homeostasis. Distance to road A3 was associated with HbA1c after sequentially adjusted for diabetes management and lifestyle factors. However, the association turned to non-significant after adjusting for area level socioeconomic status. Similarly, distance to road A1-A3 was positively associated with basic model, models sequentially adjusted for demographics, diabetes management and lifestyle factors, respectively. After adjusting for area level SES, distance to road A1-A3 was not associated. The results suggested that area level SES or factors related to SES may accounted for the variation in HbA1c. We don't have household SES for youth in this study. It is possible that sociodemographic related to SES affected the association between long-term exposure to air pollution and glucose homeostasis. Identifying the influencing factors may inform glycemic control for youth living with type I diabetes.

For SC, CO and WA, we observed higher HbA1c comparing youth exposed to the highest level of AADT near a road A1 to youth exposed to the lowest level near A1and comparing youth exposed to the highest level of AADT near a road A2 to youth exposed to the lowest level near A2, respectively. The results suggested that the null results identified in the association between distance to road A1 and distance to road A2 with glucose homeostasis might be attributable to the uneven distribution of youth being included in each category. Similarly, AADT-A4 was positively associated with HbA1c but residential distance to road A4 was not. Although A4 road

has less traffic volume, over 90% of youth in our study live near road A4. The results suggested that a combination of distance to roadways and traffic volume may affect glucose homeostasis. In comparison, AADT-A3, which had less traffic volume compared to roadways A1, A2 and was not close enough to youth as A4, was not associated with glucose homeostasis. For OH and CA, AADT-A1 to AADT-A4 were not associated with glucose homeostasis. We are not sure of the differed results by study sites for AADT. Future research is needed to investigate the differential associations across geographies.

We found race/ethnicity may be an effect-modifier. For SC, CO and WA, Hispanics living close to A3 road had exceptionally higher HbA1c, compared to other race/ethnicity groups. White youth also showed elevated HbA1c. However, our results should be interpreted with caution since we only have 149 Hispanic youth in the analysis for SC, CO and WA. Prior studies researching on the modification effect of race/ethnicity in the association between exposure to air pollution and CVD outcomes yielded inconsistent results and the mechanisms are not clear. Stronger association between long-term exposure to $PM_{2.5}$ and abdominal aortic calcification were found in Hispanics in the Multi-Ethnic Study of Atherosclerosis (MESA) [252]. Another study investigated the role of race/ethnicity found stronger associations between exposure to air pollution and CVD outcomes in Blacks using data from MESA [247]. Future research on the role of race/ethnicity in the association between exposure to air pollution and CVD is needed.

For the sensitivity analyses excluding youth aged under or equal to 10, $PM_{2.5}$ average exposure for 12-month, distance to major road were not associated with

HbA1c in fully adjusted model for SC, CO and WA. The differences in regression results may be caused by reduced power since only 1342 youth were included in analyses for youth >10 for SC, CO and WA in comparison to 1899 youth included in the main analyses for SC, CO and WA.

Prior studies on exposure to air pollution and glucose homeostasis are very limited. We are only aware of two studies conducted by Tamayo et al and Lanzinger et al that have assessed the association between long-term exposure to air pollution and glucose hemostasis in youth living with type I diabetes. Both studies found no associations between annual exposure for particles with aerodynamic diameter less than 10 micrometers (PM_{10}) and annual NO_2 with HbA1c, but inverse association between quinquennial ozone and HbA1c [95,96]. Compared to our study, the two studies were focused on large particles (PM_{10}) and gaseous traffic air pollutants (NO_2 and ozone) while our study assessed the impact of smaller particles ($PM_{2.5}$) and $PM_{2.5}$-related traffic air pollution including residential distance to road and annual average daily traffic by road classes on glucose homeostasis. In the two studies, exposure to air pollution were smoothed utilizing chemical REM-CALGRID(RCG) model with an 8 km by 8 km cell size and the estimated air pollutants were linked to participants via five-digit postcode. Our study utilized a spatio-temporal model for estimated $PM_{2.5}$ average exposures and assigned the estimates to participant's residency at a street level match. We obtained estimated average $PM_{2.5}$ for 1 month and for 12- month prior to the blood draw, which are more accurate than the measure of annual exposure of air pollutants. Both Tamayo et al and Lanzinger et al found inverse association between quinquennial ozone and HbA1c in the two studies, which

had different time window in the measure of exposure. In terms of study population, Tamayo and colleagues conducted the study with a smaller group of youth (n=771) from German Diabetes Center (DDZ registry) with self-reported outcome [95]. Participants in this study were older in mean age and had longer diabetes duration compared to youth included in our study. Lanzinger and colleagues conducted the study in 37,372 youth living with type I diabetes sampled from 344 German centers of the prospective diabetes follow-up registry (Diabetes-Patienten-Verlaufsdokumentatior [DPV]) [96]. We assumed the majority of youth were Caucasians in both studies considering the demographics of German population. In comparison, our study population was diverse in race/ethnicity. We have a sufficient number of participants and were able to adjust multiple confounders and assess modification effects by age, sex, race/ethnicity, ever smoking and BMI Z score utilizing the rich exiting information from SEARCH. Lanzinger's study included a nationwide cohort of youth living with diabetes, however, they were not able to adjust for lifestyle factors due to lack of data.

As for prior research on residential distance to road, Li et al. assessed distance to major road (A1-A3) and HbA1c in 5958 participants without type II diabetes at examination visit from the Framingham Offspring cohort examination cycle 7 (1998–2001) and 8 (2005–2008) and Third Generation cohort examination cycle 1 (2002–2005) and cycle 2 (2008–2011) [93]. The study found no association for living closer to major road, that is, no association was observed comparing participants who live 64m (25^{th} percentile) from major roads to those who live 413m (75^{th} percentile) away. Li et al. also reported no association for categorized distance

to major road (<50m, 50-100m, 100-200m, 200-400m, 400-1000m). Our study utilized the same cutoff but not excluding youth living further than 1000m away from the road. We did not observe a positive association; however, the positive association existed if we collapsed the distance to major road categories to <50 m, 50-200 m and >200 m. The maximum effect of traffic-related air pollution measured by distance to road on health outcomes is unclear. However, people living further away from a major road may be less affected by traffic-related air pollution as air pollutant may decay gradually to background levels within 150-600 m [253].

The bulk of prior research on air pollution and glucose homeostasis has been conducted among adults, who predominantly have type II diabetes. Findings regarding air pollution and glucose homeostasis among healthy adults and among adults living with diabetes mellitus are mixed. In general, studies from Asian countries reported positive associations, possibly due to higher levels of air pollutant exposures [88-90]. Unlike studies from Asian countries, studies from Europe and the USA exhibited inconsistent results. In Germany, Wolf et al reported no association between annual average exposure to PM_{10} and $PM_{2.5}$ and HbA1c among adults living with diabetes mellitus in Southern Germany [91]. However, Tamayo and colleagues indicated long term exposure to PM_{10}, defined as annual average exposure to PM_{10}, may be associated with elevated HbA1c in newly diagnosed diabetes patients throughout Germany [92]. For US studies, Li et al observed null associations between annual $PM_{2.5}$ and residential distance to road with HbA1c in the Framingham Offspring Cohort without diabetes [93]. While Honda and colleagues reported a significant association between long-term exposure to $PM_{2.5}$ and NO_2 with HbA1c in

adults living with diabetes. An 1-year average IQR increase in $PM_{2.5}$ (IQR: 3.9 ug/m^3) and NO_2 (IQR: 8.6 ppb) were associated with 1.4% (SD: 0.6%) and 2.0% (SD: 0.7%) increases in HbA1c, respectively [94].

We are aware that the pathogenesis for type I and type II diabetes are different, where type I diabetes is an autoimmune disease and type II diabetes is more related to lifestyle. Although the mechanisms are not fully understood, animal studies suggested elevated inflammation, oxidative stress, endothelial dysfunction caused by exposure to air pollution may disrupt metabolic control in mice induced with type I and type II diabetes [69,70,74,97]. Findings from animal studies provided the potential mechanisms for the vulnerability of CVD for people living with diabetes. The pathways linking long-term exposure to air pollution to HbA1c in people living with type I and type II diabetes require further investigation.

There are a few limitations in this study. Potential residual confounding existed by categorizing residential distance to road and AADT. However, we tried different cutoffs for residential distance to road variables. The categorization scheme presented in this study were previously used in air pollution studies and we selected these cutoffs to ensure certain numbers of youth being included in each category. A potential measurement error could occur since exposure to estimated average $PM_{2.5}$ were assigned to each participant by the residential locations. Though youth spend a lot of time around residential places, air pollution could occur at school, recreational facilities and travel. We were not able to conduct stratified analyses by fasting status due to small sample size for youth not fasting on the day of blood draw. Instead of stratified analyses by fasting status, we performed sensitivity analysis for youth that

were fasting prior to the blood draw. We ran a lot of models, however, fewer numbers of models addressed the same type of pollutant thus we did not adjust for multiple testing.

Our study has some notable strengths. We utilized the SEARCH for Diabetes in Youth, a multi-center study that allows adequate inclusion of geographically and racial/ethnically diverse population. We have extensive information on individual level covariates including demographics, diabetes management, lifestyle factors as well as area level socioeconomic status. We performed stratified analyses by study sites to avoid spurious associations by combining different exposures, outcomes and individual characteristics and still preserve the richness of the data. Sensitivity analyses were also conducted restricting the study population to youth fasting on the day of blood draw and youth aged over 10, respectively. In addition, our particulate matter estimates derived from highly specific spatio-temporal GAMM were more precise and exposure to estimated average $PM_{2.5}$ were assigned to participants at a street level match in comparison to prior study, which have linked estimated air pollution measures to participants via five-digit postcodes residency. Furthermore, our study focused on $PM_{2.5}$, an air pollutant that could travel further into the body to impact several cardiovascular conditions, and differing traffic-related measures of exposure near residency for youth. To the best of our knowledge, this study is the first in the U.S. assessing the effect of chronic exposure to air pollution on glucose homeostasis in youth living with type I diabetes.

Conclusion

Our findings suggested long-term exposure to $PM_{2.5}$, residential distance to highly trafficked road and annual average daily traffic count may be associated with glucose homeostasis in youth living with type I diabetes in SC, CO and WA. Reducing exposure to ambient air pollution may have implications in prevention of CVD conditions for youth living with type I diabetes in certain areas. Differences in demographics and socioeconomic status may explain the differential responses to air pollution across study sites. Future research is needed to identify factors influencing the association between exposure to air pollution and glucose homeostasis in youth living with type I diabetes.

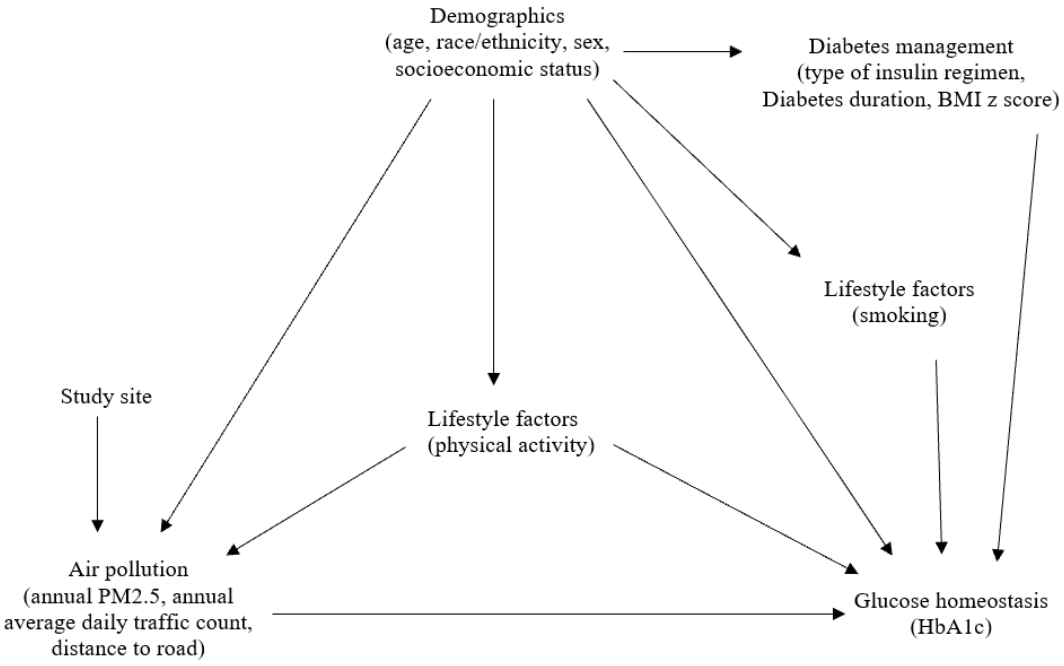


Figure 4. 1 Directed Acyclic Graph (DAG)

Table 4. 1 Characteristics of youth living with type I diabetes

Characteristics	Mean (SD)/ N(%)		
	all sites (N=2848)	SC, CO, WA (N=1899)	OH, CA (N=949)
Age, years	12.2 (4.3)	12.0 (4.3)	12.4 (4.4)
BMI z score	0.6 (0.9)	0.6 (0.9)	0.7 (0.9)
Diabetes duration, years	3.7 (3.9)	3.6 (3.9)	3.8 (3.9)
Total DASH adjusted for quality (n=1400)	42.5 (8.7)	42.8 (8.7)	41.8 (8.7)
HbA1c	8.2 (1.6)	8.2 (1.6)	8.0 (1.6)
Log HbA1c	2.1 (0.2)	2.1 (0.2)	2.1 (0.2)
Percent below poverty	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)
Days smoked in the past 30 days (n=463)	2.5 (2.3)	2.4 (2.3)	2.6 (2.3)
Days exercised at least 20 minutes that made you sweat (n=2022)	3.3 (2.2)	3.4 (2.2)	3.3 (2.2)
Time spent on computer (n=2018)	2.7 (1.5)	2.7 (1.5)	2.8 (1.6)
Time spent watching TV (n=2018)	4.0 (1.5)	3.9 (1.5)	4.1 (1.5)
Sex			
Female	1393 (48.9%)	927 (48.8%)	466 (49.1%)
Male	1455 (51.1%)	972 (51.2%)	483 (50.9%)
Race/Ethnicity			
Black	243 (8.5%)	147 (7.7%)	96 (10.1%)
Hispanic	297 (10.4%)	150 (7.9%)	147 (15.5%)
Other	74 (2.6%)	49 (2.6%)	25 (2.6%)
White	2234 (78.4%)	1553 (81.8%)	68 (71.8%)
Study site			
SC	317 (11.1%)	317 (16.7%)	
OH	599 (21.0%)		599 (63.1%)
CO	889 (31.2%)	889 (46.8%)	
CA	350 (12.3%)		350 (36.9%)
WA	693 (24.3%)	693 (36.5%)	
Ever Smoke (n=2134)			
Yes	452 (22.1%)	278 (20.7%)	516 (73.8%)
No	1569 (76.8%)	1053 (78.3%)	174 (24.9%)
Missing	23 (1.1%)	14 (1.0%)	9 (1.3%)
Fasting Status			
Yes	2566 (90.1%)	1767 (93.1%)	799 (84.2%)
No	282 (9.9%)	132 (7.0%)	150 (15.8%)
Type of insulin regime			
Pump	502 (17.6%)	328 (17.3%)	174 (18.3%)
Long + short/rapid insulin, 3 or more times a day	785 (27.6%)	445 (23.4%)	340 (35.8%)
Long + any other combination, 2 or more times a day	267 (9.4%)	253 (13.3%)	14 (1.5%)
Any combination of insulins excluding long, 3 or more times/day	396 (13.9%)	236 (12.4%)	160 (16.9%)

Any insulin(s) taken 1x/day, or any insulin combination excluding long 2x/day	898 (31.5%)	637 (33.5%)	261 (27.5%)
1-month $PM_{2.5}$	12.7 (5.7)	-	-
12-month $PM_{2.5}$	13.0 (5.2)	-	-

Table 4. 2 Distribution of estimated $PM_{2.5}$ exposures by study sites

Study site	1-month $PM_{2.5}$ Mean (SD)	12-month $PM_{2.5}$ Mean (SD)
SC	9.7 (2.5)	9.9 (1.2)
OH	17.4 (5.3)	17.5 (3.9)
CO	9.6 (2.2)	9.7 (1.6)
CA	20.5 (6.6)	21.6 (4.8)
WA	9.9 (2.7)	10.5 (1.3)
Total	12.7 (5.7)	13.0 (5.2)

Table 4. 3 Distribution of annual average daily traffic count by study sites

Study site	All sites Mean (SD)	SC, CO, WA Mean (SD)	OH, CA Mean (SD)
AADT-A1	37085 (18381)	32275 (11188)	44049 (22890)
AADT-A2	13568 (4782)	13315 (5020)	13833 (3963)
AADT-A3	7752 (3424)	7052 (2902)	8837 (3764)
AADT-A4	2463 (943)	2415 (967)	2536 (883)

Table 4. 4 Distribution of study participants by residential distance to road categories

	All sites, n=2848			
	cutoff	**N (%)**	**cutoff**	**N (%)**
Distance to road A1	**<=150 m**	53 (1.9%)	**<=200 m**	82 (2.9%)
	>150 m	2795 (98.1%)	**200-400 m**	111 (3.9%)
			>400 m	2655 (93.2%)
Distance to road A2	**<=150 m**	81 (2.8%)	**<=200 m**	116 (4.1%)
	>150 m	2767 (97.2%)	**200-400 m**	156 (5.5%)
			>400 m	2576 (90.5%)
Distance to road A3	**<50 m**	321 (11.3%)		
	50-200 m	596 (20.9%)		
	>=200 m	1931 (67.8%)		
Distance to road A4	**<=50 m**	2673 (93.9%)		
	>50 m	175 (6.1%)		
Distance to road A1-A3	**<50 m**	356 (12.5%)	**<50 m**	356 (12.5%)
	50-200 m	704 (24.7%)	**50-100 m**	230 (8.1%)
	>=200 m	1788 (62.8%)	**100-200 m**	474 (16.6%)
			200-400 m	733 (25.7%)
			>=400	1055 (37.0%)
	SC, CO and WA, n=1899			
	cutoff	**N (%)**	**cutoff**	**N (%)**
Distance to road A1	**<=150 m**	27 (1.4%)	**<=200 m**	50 (2.6%)
	>150 m	1872 (98.6%)	**200-400 m**	55 (2.9%)
			>400 m	1794 (94.5%)
Distance to road A2	**<=150 m**	54 (2.8%)	**<=200 m**	77 (4.1%)
	>150 m	1845 (97.2%)	**200-400 m**	113 (6.0%)
			>400 m	1709 (90.0%)
Distance to road A3	**<50 m**	205 (10.1%)		
	50-200 m	398 (21.0%)		
	>=200 m	1296 (68.3%)		
Distance to road A4	**<=50 m**	1799 (94.7%)		
	>50 m	100 (5.3%)		
Distance to road A1-A3	**<50 m**	230 (12.1%)	**<50 m**	230 (12.1%)
	50-200 m	471 (24.8%)	**50-100 m**	145 (7.6%)
	>=200 m	1198 (63.1%)	**100-200 m**	326 (17.2%)
			200-400 m	475 (25.0%)
			>=400	723 (38.1%)
	OH and CA, n=949			
	cutoff		**cutoff**	
Distance to road A1	**<=150 m**	26 (2.7%)	**<=200 m**	32 (3.4%)
	>150 m	923 (97.3%)	**200-400 m**	56 (5.9%)
			>400 m	861 (90.7%)
Distance to road A2	**<=150 m**	27 (2.9%)	**<=200 m**	39 (4.1%)
	>150 m	922 (97.2%)	**200-400 m**	43 (4.5%)
			>400 m	867 (91.2%)
Distance to road A3	**<50 m**	116 (12.2%)		
	50-200 m	198 (20.9%)		
	>=200 m	635 (66.9%)		
Distance to road A4	**<=50 m**	874 (92.1%)		

	>50 m	75 (7.9%)		
Distance to road A1-A3	**<50 m**	126 (13.3%)	**<50 m**	126 (13.3%)
	50-200 m	233 (24.6%)	**50-100 m**	85 (9.0%)
	>=200 m	590 (62.2%)	**100-200 m**	148 (15.6%)
			200-400 m	258 (27.2%)
			>=400	332 (35.0%)

Table 4. 5 Regression results

Table 4.5 a Regression results of the association between exposure to air pollution and glucose homeostasis (study site SC, CO and WA, n=1899)

air pollutant		β (95% CI)	P value
1-month PM2.5			
Basic model		0.01 (-0.02,0.04)	0.50
Basic model + demographics		0.01 (-0.02,0.04)	0.40
Basic model + demographics + diabetes management		0.00 (-0.02,0.03)	0.74
Basic model + demographics + diabetes management + lifestyle		0.00 (-0.02,0.03)	0.78
Basic model + demographics + diabetes management + lifestyle + SES		0.00 (-0.03,0.03)	0.88
12-month PM2.5			
Basic model		0.11 (0.06,0.16)	<0.01*
Basic model + demographics		0.08 (0.03,0.13)	<0.01*
Basic model + demographics + diabetes management		0.06 (0.01,0.11)	0.01*
Basic model + demographics + diabetes management + lifestyle		0.06 (0.01,0.11)	<0.01*
Basic model + demographics + diabetes management + lifestyle + SES		0.06 (0.01,0.10)	0.02*
Distance to road A1			
Basic model	<=150	0.51 (-0.10,1.12)	0.10
	>150 (ref)		
Basic model + demographics	<=150	0.41 (-0.18,1.00)	0.17
	>150 (ref)		
Basic model + demographics + diabetes management	<=150	0.32 (-0.24,0.88)	0.27
	>150 (ref)		
Basic model + demographics + diabetes management + lifestyle	<=150	0.33 (-0.24,0.89)	0.26
	>150 (ref)		
Basic model + demographics + diabetes management + lifestyle + SES	<=150	0.30 (-0.27,0.86)	0.30
	>150 (ref)		
Distance to road A1			
Basic model	<=200 m	0.36 (-0.09,0.81)	0.10
	200-400 m	0.34 (-0.09,0.77)	
	>400 m (ref)		
Basic model + demographics	<=200 m	0.34 (-0.09,0.78)	0.19
	200-400 m	0.21 (-0.20,0.63)	
	>400 m (ref)		
Basic model + demographics + diabetes management	<=200 m	0.28 (-0.14,0.70)	0.33
	200-400 m	0.15 (-0.25,0.55)	
	>400 m (ref)		
Basic model + demographics + diabetes management + lifestyle	<=200 m	0.30 (-0.11,0.72)	0.34
	200-400 m	0.08 (-0.31,0.48)	

	>400 m (ref)		
Basic model + demographics + diabetes management + lifestyle + SES	<=200 m	0.28 (-0.14,0.69)	0.42
	200-400 m	0.06 (-0.35,0.46)	
	>400 m (ref)		
Distance to road A2			
Basic model	<=150	0.41 (-0.02,0.84)	0.06
	>150 (ref)		
Basic model + demographics	<=150	0.29 (-0.13,0.71)	0.18
	>150 (ref)		
Basic model + demographics + diabetes management	<=150	0.29 (-0.12,0.69)	0.17
	>150 (ref)		
Basic model + demographics + diabetes management + lifestyle	<=150	0.27 (-0.13,0.68)	0.18
	>150 (ref)		
Basic model + demographics + diabetes management + lifestyle + SES	<=150	0.26 (-0.14,0.67)	0.20
	>150 (ref)		
Distance to road A2			
Basic model	<=200 m	0.23 (-0.14,0.60)	0.31
	200-400 m	-0.14 (-0.44,0.17)	
	>400 m (ref)		
Basic model + demographics	<=200 m	0.14 (-0.22,0.49)	0.40
	200-400 m	-0.16 (-0.45,0.13)	
	>400 m (ref)		
Basic model + demographics + diabetes management	<=200 m	0.14 (-0.21,0.48)	0.34
	200-400 m	-0.17 (-0.45,0.11)	
	>400 m (ref)		
Basic model + demographics + diabetes management + lifestyle	<=200 m	0.13 (-0.21,0.47)	0.35
	200-400 m	-0.17 (-0.45,0.11)	
	>400 m (ref)		
Basic model + demographics + diabetes management + lifestyle + SES	<=200 m	0.11 (-0.23,0.46)	0.28
	200-400 m	-0.20 (-0.49,0.08)	
	>400 m (ref)		
Distance to road A3			
Basic model	<50	0.39 (0.15,0.63)	<0.01*
	50-200	0.24 (0.06,0.42)	
	>200 (ref)		
Basic model + demographics	<50	0.31 (0.08,0.54)	0.01*
	50-200	0.17 (-0.01,0.34)	
	>200 (ref)		
Basic model + demographics + diabetes management	<50	0.28 (0.06,0.50)	0.02*
	50-200	0.16 (-0.01,0.33)	

	>200 (ref)		
Basic model + demographics + diabetes management + lifestyle	<50	0.26 (0.04,0.48)	0.02*
	50-200	0.16 (-0.01,0.32)	
	>200 (ref)		
Basic model + demographics + diabetes management + lifestyle + SES	<50	0.25 (0.03,0.47)	0.03*
	50-200	0.15 (-0.01,0.32)	
	>200 (ref)		
Distance to road A4			
Basic model	<=50	-0.26 (-0.58,0.07)	0.12
	>50 (ref)		
Basic model + demographics	<=50	-0.28 (-0.59,0.04)	0.08
	>50 (ref)		
Basic model + demographics + diabetes management	<=50	-0.25 (-0.55,0.04)	0.10
	>50 (ref)		
Basic model + demographics + diabetes management + lifestyle	<=50	-0.22 (-0.52,0.08)	0.14
	>50 (ref)		
Basic model + demographics + diabetes management + lifestyle + SES	<=50	-0.23 (-0.52,0.07)	0.14
	>50 (ref)		
Distance to road A1-A3			
Basic model	<50	0.35 (0.12,0.58)	<0.01*
	50-200	0.28 (0.11,0.45)	
	>200 (ref)		
Basic model + demographics	<50	0.26 (0.05,0.48)	<0.01*
	50-200	0.21 (0.04,0.37)	
	>200 (ref)		
Basic model + demographics + diabetes management	<50	0.24 (0.03,0.45)	0.02*
	50-200	0.19 (0.03,0.35)	
	>200 (ref)		
Basic model + demographics + diabetes management + lifestyle	<50	0.22 (0.01,0.43)	0.02*
	50-200	0.19 (0.03,0.35)	
	>200 (ref)		
Basic model + demographics + diabetes management + lifestyle + SES	<50	0.21 (0.00,0.42)	0.03*
	50-200	0.18 (0.02,0.34)	
	>200 (ref)		
Distance to road A1-A3			
Basic model	<50 m	0.34 (0.10,0.57)	<0.01*
	50-100 m	0.36 (0.07,0.64)	
	100-200 m	0.22 (0.01,0.44)	
	200-400 m	-0.04 (-0.22,0.15)	
	>=400 (ref)		

Basic model + demographics	<50 m	0.22 (-0.01,0.45)	0.03*
	50-100 m	0.22 (-0.06,0.50)	
	100-200 m	0.14 (-0.07,0.34)	
	200-400 m	-0.10 (-0.28,0.08)	
	>=400 (ref)		
Basic model + demographics + diabetes management	<50 m	0.20 (-0.02,0.42)	0.04*
	50-100 m	0.20 (-0.07,0.47)	
	100-200 m	0.12 (-0.08,0.32)	
	200-400 m	-0.10 (-0.27,0.07)	
	>=400 (ref)		
Basic model + demographics + diabetes management + lifestyle	<50 m	0.18 (-0.04,0.40)	0.04*
	50-100 m	0.19 (-0.08,0.45)	
	100-200 m	0.12 (-0.07,0.32)	
	200-400 m	-0.11 (-0.28,0.06)	
	>=400 (ref)		
Basic model + demographics + diabetes management + lifestyle + SES	<50 m	0.16 (-0.07,0.38)	0.06
	50-100 m	0.17 (-0.09,0.44)	
	100-200 m	0.11 (-0.09,0.30)	
	200-400 m	-0.12 (-0.29,0.05)	
	>=400 (ref)		
AADT-A1			
Basic model	highest tertile	0.31 (0.11,0.51)	0.01*
	medium tertile	0.11 (-0.07,0.30)	
	lowest tertile(ref)		
Basic model + demographics	highest tertile	0.24 (0.04,0.44)	0.06
	medium tertile	0.09 (-0.09,0.28)	
	lowest tertile(ref)		
Basic model + demographics + diabetes management	highest tertile	0.17 (0.00,0.34)	0.08
	medium tertile	0.01 (-0.16,0.18)	
	lowest tertile(ref)		
Basic model + demographics + diabetes management + lifestyle	highest tertile	0.19 (0.02,0.36)	0.07
	medium tertile	0.05 (-0.12,0.22)	
	lowest tertile(ref)		
Basic model + demographics + diabetes management + lifestyle + SES	highest tertile	0.20 (0.05,0.34)	0.07
	medium tertile	0.06 (-0.07,0.20)	
	lowest tertile(ref)		
AADT-A2			
Basic model	highest tertile	0.30 (0.10,0.49)	<0.01*
	medium tertile	0.11 (-0.07,0.30)	
	lowest tertile(ref)		
Basic model + demographics	highest tertile	0.22 (0.03,0.41)	0.05

	medium tertile	0.05 (-0.13,0.23)	
	lowest tertile(ref)		
Basic model + demographics + diabetes management	highest tertile	0.18 (0.01,0.34)	0.05
	medium tertile	0.00 (-0.17,0.16)	
	lowest tertile(ref)		
Basic model + demographics + diabetes management + lifestyle	highest tertile	0.19 (0.03,0.36)	0.05*
	medium tertile	0.03 (-0.14,0.20)	
	lowest tertile(ref)		
Basic model + demographics + diabetes management + lifestyle + SES	highest tertile	0.20 (0.03,0.37)	0.04*
	medium tertile	0.04 (-0.12,0.21)	
	lowest tertile(ref)		
AADT-A3			
Basic model	highest tertile	0.22 (0.03,0.42)	0.07
	medium tertile	0.14 (-0.04,0.32)	
	lowest tertile(ref)		
Basic model + demographics	highest tertile	0.20 (0.01,0.39)	0.12
	medium tertile	0.10 (-0.07,0.28)	
	lowest tertile(ref)		
Basic model + demographics + diabetes management	highest tertile	0.13 (-0.04,0.30)	0.33
	medium tertile	0.05 (-0.11,0.22)	
	lowest tertile(ref)		
Basic model + demographics + diabetes management + lifestyle	highest tertile	0.15 (-0.02,0.32)	0.23
	medium tertile	0.07 (-0.09,0.24)	
	lowest tertile(ref)		
Basic model + demographics + diabetes management + lifestyle + SES	highest tertile	0.15 (-0.02,0.32)	0.22
	medium tertile	0.08 (-0.09,0.24)	
	lowest tertile(ref)		
AADT-A4			
Basic model	highest tertile	0.35 (0.16,0.53)	<0.01*
	medium tertile	0.22 (0.04,0.41)	
	lowest tertile(ref)		
Basic model + demographics	highest tertile	0.33 (0.15,0.51)	<0.01*
	medium tertile	0.22 (0.04,0.40)	
	lowest tertile(ref)		
Basic model + demographics + diabetes management	highest tertile	0.27 (0.10,0.44)	<0.01*
	medium tertile	0.17 (0.00,0.34)	
	lowest tertile(ref)		
Basic model + demographics + diabetes management + lifestyle	highest tertile	0.27 (0.11,0.44)	<0.01*
	medium tertile	0.17 (0.01,0.34)	
	lowest tertile(ref)		

Basic model + demographics + diabetes management + lifestyle + SES	highest tertile	0.29 (0.12,0.46)	<0.01*
	medium tertile	0.19 (0.02,0.35)	
	lowest tertile(ref)		

* P value <0.05

Basic model: air pollution exposure + random effect study sites

Demographics: age at enrollment, sex and race/ethnicity; diabetes management factors: type of insulin regimen, diabetes duration (in years) and body mass index z score (BMI z score); lifestyle factors: physical activity (days exercised at least 20 minutes that sweated, time spent on computer and time spent watching TV), smoking(ever smoke and days smoked in the past 30 days); area level socioeconomic status: percent below poverty at Census Block 2000.

Table 4.5 b Regression results of the association between exposure to air pollution and glucose homeostasis (study site OH and CA, n=949)

air pollutant		β (95% CI)	P value
1-month PM2.5			
Basic model		0.00 (-0.01,0.02)	0.62
Basic model + demographics		0.00 (-0.02,0.01)	0.66
Basic model + demographics + diabetes management		0.00 (-0.02,0.01)	0.68
Basic model + demographics + diabetes management + lifestyle		0.00 (-0.02,0.01)	0.81
Basic model + demographics + diabetes management + lifestyle + SES		0.00 (-0.02,0.01)	0.74
12-month PM2.5		0.00 (0.00,0.00)	
Basic model		-0.01 (-0.03,0.01)	0.41
Basic model + demographics		-0.02 (-0.05,0.00)	0.05
Basic model + demographics + diabetes management		-0.02 (-0.04,0.00)	0.13
Basic model + demographics + diabetes management + lifestyle		-0.01 (-0.04,0.01)	0.23
Basic model + demographics + diabetes management + lifestyle + SES		-0.02 (-0.04,0.00)	0.11
Distance to road A1			
Basic model	<=150	0.31 (-0.30,0.92)	0.32
	>150 (ref)		
Basic model + demographics	<=150	0.27 (-0.32,0.87)	0.37
	>150 (ref)		
Basic model + demographics + diabetes management	<=150	0.26 (-0.31,0.84)	0.37
	>150 (ref)		
Basic model + demographics + diabetes management + lifestyle	<=150	0.24 (-0.33,0.82)	0.40
	>150 (ref)		
Basic model + demographics + diabetes management + lifestyle + SES	<=150	0.16 (-0.41,0.73)	0.58
	>150 (ref)		
Distance to road A1			
Basic model	<=200 m	0.20 (-0.36,0.75)	0.70
	200-400 m	-0.10 (-0.52,0.33)	
	>400 m (ref)		
Basic model + demographics	<=200 m	0.17 (-0.37,0.71)	0.48
	200-400 m	-0.21 (-0.63,0.20)	
	>400 m (ref)		
Basic model + demographics + diabetes management	<=200 m	0.15 (-0.36,0.67)	0.38
	200-400 m	-0.25 (-0.65,0.15)	
	>400 m (ref)		
Basic model + demographics + diabetes management + lifestyle	<=200 m	0.14 (-0.37,0.66)	0.34
	200-400 m	-0.27 (-0.66,0.13)	

	>400 m (ref)		
Basic model + demographics + diabetes management + lifestyle + SES	<=200 m	0.08 (-0.43,0.59)	0.21
	200-400 m	-0.36 (-0.75,0.04)	
	>400 m (ref)		
Distance to road A2			
Basic model	<=150	0.39 (-0.21,0.99)	0.20
	>150 (ref)		
Basic model + demographics	<=150	0.46 (-0.12,1.04)	0.12
	>150 (ref)		
Basic model + demographics + diabetes management	<=150	0.52 (-0.04,1.08)	0.07
	>150 (ref)		
Basic model + demographics + diabetes management + lifestyle	<=150	0.47 (-0.09,1.03)	0.10
	>150 (ref)		
Basic model + demographics + diabetes management + lifestyle + SES	<=150	0.38 (-0.18,0.93)	0.19
	>150 (ref)		
Distance to road A2			
Basic model	<=200 m	0.25 (-0.25,0.76)	0.47
	200-400 m	0.19 (-0.29,0.67)	
	>400 m (ref)		
Basic model + demographics	<=200 m	0.36 (-0.13,0.85)	0.33
	200-400 m	0.10 (-0.36,0.57)	
	>400 m (ref)		
Basic model + demographics + diabetes management	<=200 m	0.42 (-0.06,0.89)	0.21
	200-400 m	0.11 (-0.34,0.56)	
	>400 m (ref)		
Basic model + demographics + diabetes management + lifestyle	<=200 m	0.33 (-0.14,0.80)	0.39
	200-400 m	0.07 (-0.38,0.52)	
	>400 m (ref)		
Basic model + demographics + diabetes management + lifestyle + SES	<=200 m	0.23 (-0.25,0.70)	0.64
	200-400 m	-0.03 (-0.48,0.42)	
	>400 m (ref)		
Distance to road A3			
Basic model	<50	0.34 (0.03,0.65)	0.02*
	50-200	0.26 (0.02,0.51)	
	>200 (ref)		
Basic model + demographics	<50	0.23 (-0.07,0.53)	0.12
	50-200	0.21 (-0.03,0.46)	
	>200 (ref)		
Basic model + demographics + diabetes management	<50	0.28 (-0.01,0.57)	0.03*
	50-200	0.26 (0.02,0.50)	

	>200 (ref)		
Basic model + demographics + diabetes management + lifestyle	<50	0.24 (-0.05,0.53)	0.05*
	50-200	0.26 (0.02,0.50)	
	>200 (ref)		
Basic model + demographics + diabetes management + lifestyle + SES	<50	0.18 (-0.11,0.47)	0.23
	50-200	0.18 (-0.06,0.42)	
	>200 (ref)		
Distance to road A4			
Basic model	<=50	0.19 (-0.18,0.56)	0.31
	>50 (ref)		
Basic model + demographics	<=50	0.23 (-0.13,0.59)	0.21
	>50 (ref)		
Basic model + demographics + diabetes management	<=50	0.12 (-0.23,0.46)	0.52
	>50 (ref)		
Basic model + demographics + diabetes management + lifestyle	<=50	0.14 (-0.21,0.48)	0.44
	>50 (ref)		
Basic model + demographics + diabetes management + lifestyle + SES	<=50	0.13 (-0.21,0.48)	0.44
	>50 (ref)		
Distance to road A1-A3			
Basic model	<50	0.35 (0.05,0.65)	<0.01*
	50-200	0.30 (0.07,0.54)	
	>200 (ref)		
Basic model + demographics	<50	0.26 (-0.04,0.55)	0.04*
	50-200	0.27 (0.04,0.51)	
	>200 (ref)		
Basic model + demographics + diabetes management	<50	0.31 (0.03,0.60)	<0.01*
	50-200	0.31 (0.09,0.54)	
	>200 (ref)		
Basic model + demographics + diabetes management + lifestyle	<50	0.27 (-0.01,0.55)	0.01*
	50-200	0.30 (0.07,0.52)	
	>200 (ref)		
Basic model + demographics + diabetes management + lifestyle + SES	<50	0.20 (-0.08,0.48)	0.10
	50-200	0.22 (-0.01,0.45)	
	>200 (ref)		
Distance to road A1-A3			
Basic model	<50 m	0.27 (-0.05,0.59)	0.02*
	50-100 m	0.12 (-0.25,0.49)	
	100-200 m	0.28 (-0.02,0.58)	
	200-400 m	-0.19 (-0.44,0.07)	
	>=400 (ref)		

Basic model + demographics	<50 m	0.15 (-0.17,0.46)	0.02*
	50-100 m	0.02 (-0.34,0.38)	
	100-200 m	0.25 (-0.05,0.55)	
	200-400 m	-0.24 (-0.49,0.01)	
	>=400 (ref)		
Basic model + demographics + diabetes management	<50 m	0.20 (-0.11,0.50)	<0.01*
	50-100 m	0.06 (-0.29,0.41)	
	100-200 m	0.28 (-0.01,0.56)	
	200-400 m	-0.26 (-0.50,-0.02)	
	>=400 (ref)		
Basic model + demographics + diabetes management + lifestyle	<50 m	0.15 (-0.15,0.45)	<0.01*
	50-100 m	0.06 (-0.29,0.41)	
	100-200 m	0.25 (-0.04,0.54)	
	200-400 m	-0.26 (-0.50,-0.03)	
	>=400 (ref)		
Basic model + demographics + diabetes management + lifestyle + SES	<50 m	0.06 (-0.24,0.37)	0.02*
	50-100 m	-0.03 (-0.38,0.32)	
	100-200 m	0.15 (-0.14,0.44)	
	200-400 m	-0.30 (-0.54,-0.06)	
	>=400 (ref)		
AADT-A1			
Basic model	highest tertile	0.04 (-0.20,0.29)	0.69
	medium tertile	-0.06 (-0.31,0.18)	
	lowest tertile(ref)		
Basic model + demographics	highest tertile	-0.19 (-0.45,0.07)	0.17
	medium tertile	-0.22 (-0.46,0.03)	
	lowest tertile(ref)		
Basic model + demographics + diabetes management	highest tertile	-0.08 (-0.33,0.18)	0.24
	medium tertile	-0.20 (-0.43,0.03)	
	lowest tertile(ref)		
Basic model + demographics + diabetes management + lifestyle	highest tertile	-0.05 (-0.30,0.21)	0.15
	medium tertile	-0.22 (-0.45,0.01)	
	lowest tertile(ref)		
Basic model + demographics + diabetes management + lifestyle + SES	highest tertile	-0.10 (-0.35,0.16)	0.11
	medium tertile	-0.24 (-0.47,-0.01)	
	lowest tertile(ref)		
AADT-A2			
Basic model	highest tertile	0.25 (0.01,0.49)	0.06
	medium tertile	-0.01 (-0.25,0.23)	
	lowest tertile(ref)		
Basic model + demographics	highest tertile	0.08 (-0.16,0.33)	0.52

	medium tertile	-0.06 (-0.30,0.18)	
	lowest tertile(ref)		
Basic model + demographics + diabetes management	highest tertile	0.17 (-0.07,0.41)	0.17
	medium tertile	-0.05 (-0.28,0.18)	
	lowest tertile(ref)		
Basic model + demographics + diabetes management + lifestyle	highest tertile	0.14 (-0.10,0.38)	0.27
	medium tertile	-0.05 (-0.28,0.18)	
	lowest tertile(ref)		
Basic model + demographics + diabetes management + lifestyle + SES	highest tertile	0.05 (-0.19,0.29)	0.79
	medium tertile	-0.03 (-0.26,0.19)	
	lowest tertile(ref)		
AADT-A3			
Basic model	highest tertile	0.11 (-0.13,0.36)	0.09
	medium tertile	-0.21 (-0.45,0.04)	
	lowest tertile(ref)		
Basic model + demographics	highest tertile	-0.07 (-0.31,0.18)	0.15
	medium tertile	-0.23 (-0.47,0.01)	
	lowest tertile(ref)		
Basic model + demographics + diabetes management	highest tertile	0.02 (-0.22,0.26)	0.10
	medium tertile	-0.21 (-0.44,0.02)	
	lowest tertile(ref)		
Basic model + demographics + diabetes management + lifestyle	highest tertile	0.00 (-0.24,0.24)	0.13
	medium tertile	-0.20 (-0.43,0.02)	
	lowest tertile(ref)		
Basic model + demographics + diabetes management + lifestyle + SES	highest tertile	-0.07 (-0.31,0.18)	0.31
	medium tertile	-0.17 (-0.40,0.05)	
	lowest tertile(ref)		
AADT-A4			
Basic model	highest tertile	-0.03 (-0.27,0.22)	0.47
	medium tertile	0.12 (-0.13,0.36)	
	lowest tertile(ref)		
Basic model + demographics	highest tertile	-0.14 (-0.38,0.11)	0.53
	medium tertile	-0.06 (-0.31,0.19)	
	lowest tertile(ref)		
Basic model + demographics + diabetes management	highest tertile	-0.09 (-0.32,0.15)	0.78
	medium tertile	-0.05 (-0.30,0.19)	
	lowest tertile(ref)		
Basic model + demographics + diabetes management + lifestyle	highest tertile	-0.07 (-0.31,0.16)	0.83
	medium tertile	-0.03 (-0.27,0.21)	
	lowest tertile(ref)		

Basic model + demographics + diabetes management + lifestyle + SES	highest tertile	-0.06 (-0.29,0.18)	0.69
	medium tertile	-0.11 (-0.35,0.14)	
	lowest tertile(ref)		

* P value <0.05

Basic model: air pollution exposure + random effect study sites

Demographics: age at enrollment, sex and race/ethnicity; diabetes management factors: type of insulin regimen, diabetes duration (in years) and body mass index z score (BMI z score); lifestyle factors: physical activity (days exercised at least 20 minutes that sweated, time spent on computer and time spent watching TV), smoking(ever smoke and days smoked in the past 30 days); area level socioeconomic status: percent below poverty at Census Block 2000.

Table 4. 6 Sensitivity analyses

Table 4.6 a Sensitivity analysis for youth were fasting at baseline and youth aged over 10 (study site SC, CO and WA)

Youth who were fasting on the day of blood draw (N=1764)			
air pollutant		**β (95% CI)**	**P value**
1-month PM2.5			
Fully adjusted model[1]		0.01 (-0.02,0.04)	0.62
12-month PM2.5			
Fully adjusted model		0.07 (0.02,0.12)	<0.01*
Distance to road A1			
Fully adjusted model	<=150	0.31 (-0.28,0.90)	0.31
	>150 (ref)		
Distance to road A1			
Fully adjusted model	<=200 m	0.30 (-0.13,0.73)	0.32
	200-400 m	0.16 (-0.27,0.59)	
	>400 m (ref)		
Distance to road A2			
Fully adjusted model	<=150	0.32 (-0.11,0.74)	0.15
	>150 (ref)		
Distance to road A2			
Fully adjusted model	<=200 m	0.16 (-0.21,0.52)	0.24
	200-400 m	-0.22 (-0.52,0.09)	
	>400 m (ref)		
Distance to road A3			
Fully adjusted model	<50	0.26 (0.03,0.49)	0.03*
	50-200	0.17 (0.00,0.35)	
	>200 (ref)		
Distance to road A4			
Fully adjusted model	<=50	-0.18 (-0.49,0.13)	0.26
	>50 (ref)		
Distance to road A1-A3			
Fully adjusted model	<50	0.24 (0.02,0.46)	0.02*
	50-200	0.20 (0.04,0.37)	
	>200 (ref)		
Distance to road A1-A3			
Fully adjusted model	<50 m	0.20 (-0.04,0.43)	0.04*
	50-100 m	0.26 (-0.02,0.53)	
	100-200 m	0.11 (-0.09,0.32)	
	200-400 m	-0.09 (-0.28,0.09)	
	>=400 (ref)		
AADT-A1			
Fully adjusted model	highest tertile	0.19 (0.01,0.36)	0.10
	medium tertile	0.05 (-0.13,0.22)	
	lowest tertile(ref)		
AADT-A2			
Fully adjusted model	highest tertile	0.17 (-0.01,0.35)	0.10
	medium tertile	0.00 (-0.18,0.18)	
	lowest tertile(ref)		
AADT-A3			
Fully adjusted model	highest tertile	0.13 (-0.06,0.31)	0.39
	medium tertile	0.06 (-0.12,0.23)	
	lowest tertile(ref)		
AADT-A4			

Fully adjusted model	highest tertile medium tertile lowest tertile(ref)	0.28 (0.10,0.46) 0.19 (0.02,0.36)	<0.01*
Youth aged over 10 (N=1342)			
air pollutant		**β (95% CI)**	**P value**
1-month PM2.5			
Fully adjusted model		0.00 (-0.03,0.04)	0.82
12-month PM2.5			
Fully adjusted model		0.06 (0.00,0.12)	0.05
Distance to road A1			
Fully adjusted model	<=150 >150 (ref)	0.43 (-0.30,1.16)	0.25
Distance to road A1			
Fully adjusted model	<=200 m 200-400 m >400 m (ref)	0.37 (-0.20,0.93) 0.15 (-0.35,0.65)	0.38
Distance to road A2			
Fully adjusted model	<=150 >150 (ref)	-0.01 (-0.55,0.53)	0.98
Distance to road A2			
Fully adjusted model	<=200 m 200-400 m >400 m (ref)	-0.08 (-0.56,0.39) -0.12 (-0.50,0.25)	0.77
Distance to road A3			
Fully adjusted model	<50 50-200 >200 (ref)	0.35 (0.07,0.63) 0.12 (-0.10,0.33)	0.04*
Distance to road A4			
Fully adjusted model	<=50 >50 (ref)	-0.29 (-0.68,0.09)	0.13
Distance to road A1-A3			
Fully adjusted model	<50 50-200 >200 (ref)	0.27 (0.00,0.54) 0.14 (-0.07,0.34)	0.10
Distance to road A1-A3			
Fully adjusted model	<50 m 50-100 m 100-200 m 200-400 m >=400 (ref)	0.25 (-0.03,0.54) 0.18 (-0.17,0.54) 0.09 (-0.16,0.34) -0.05 (-0.27,0.18)	0.28
AADT-A1			
Fully adjusted model	highest tertile medium tertile lowest tertile(ref)	0.26 (0.04,0.48) 0.15 (-0.07,0.37)	0.06
AADT-A2			
Fully adjusted model	highest tertile medium tertile lowest tertile(ref)	0.26 (0.04,0.47) 0.04 (-0.18,0.26)	0.04*
AADT-A3			
Fully adjusted model	highest tertile medium tertile lowest tertile(ref)	0.21 (-0.01,0.43) 0.09 (-0.12,0.31)	0.18
AADT-A4			

Fully adjusted model	highest tertile	0.32 (0.11,0.54)	0.01*
	medium tertile	0.20 (-0.01,0.42)	
	lowest tertile(ref)		

* P value <0.05

[1.] Fully adjusted model controlled for age at enrollment, sex and race/ethnicity, diabetes management factors including type of insulin regimen, diabetes duration (in years) and body mass index z score (BMI z score), lifestyle factors including physical activity (days exercised at least 20 minutes that sweated, time spent on computer and time spent watching TV), smoking(ever smoke and days smoked in the past 30 days) as well as area level socioeconomic status (percent below poverty at Census Block 2000).

Table 4.6 b Sensitivity analysis for youth were fasting at baseline and youth aged over 10 (study site OH and CA)

Youth who were fasting on the day of blood draw (N=799)			
air pollutant		**β (95% CI)**	**P value**
1-month PM2.5			
Fully adjusted model[1]		0.00 (-0.02,0.02)	0.93
12-month PM2.5			
Fully adjusted model		-0.01 (-0.04,0.01)	0.30
Distance to road A1			
Fully adjusted model	<=150	0.34 (-0.29,0.97)	0.29
	>150 (ref)		
Distance to road A1			
Fully adjusted model	<=200 m	0.21 (-0.35,0.77)	0.09
	200-400 m	-0.48 (-0.95,-0.02)	
	>400 m (ref)		
Distance to road A2			
Fully adjusted model	<=150	0.44 (-0.15,1.03)	0.15
	>150 (ref)		
Distance to road A2			
Fully adjusted model	<=200 m	0.26 (-0.24,0.76)	0.60
	200-400 m	0.01 (-0.48,0.49)	
	>400 m (ref)		
Distance to road A3			
Fully adjusted model	<50	0.10 (-0.22,0.41)	0.45
	50-200	0.17 (-0.10,0.45)	
	>200 (ref)		
Distance to road A4			
Fully adjusted model	<=50	0.27 (-0.10,0.64)	0.16
	>50 (ref)		
Distance to road A1-A3			
Fully adjusted model	<50	0.13 (-0.18,0.44)	0.18
	50-200	0.24 (-0.02,0.50)	
	>200 (ref)		
Distance to road A1-A3			
Fully adjusted model	<50 m	-0.01 (-0.34,0.31)	0.05*
	50-100 m	0.01 (-0.39,0.41)	
	100-200 m	0.15 (-0.18,0.47)	
	200-400 m	-0.33 (-0.59,-0.06)	
	>=400 (ref)		
AADT-A1			
Fully adjusted model	highest tertile	-0.03 (-0.32,0.26)	0.21
	medium tertile	-0.21 (-0.46,0.04)	
	lowest tertile(ref)		
AADT-A2			

Fully adjusted model	highest tertile	0.09 (-0.18,0.36)	0.48
	medium tertile	-0.08 (-0.33,0.17)	
	lowest tertile(ref)		
AADT-A3			
Fully adjusted model	highest tertile	-0.11 (-0.38,0.16)	0.28
	medium tertile	-0.20 (-0.45,0.05)	
	lowest tertile(ref)		
AADT-A4			
Fully adjusted model	highest tertile	-0.08 (-0.34,0.17)	0.74
	medium tertile	-0.10 (-0.36,0.17)	
	lowest tertile(ref)		

Youth aged over 10 (N=699)			
air pollutant		**β (95% CI)**	**P value**
1-month PM2.5			
Fully adjusted model		0.00 (-0.02,0.02)	0.81
12-month PM2.5			
Fully adjusted model		-0.02 (-0.05,0.00)	0.09
Distance to road A1			
Fully adjusted model	<=150	0.28 (-0.47,1.03)	0.46
	>150 (ref)		
Distance to road A1			
Fully adjusted model	<=200 m	0.21 (-0.47,0.88)	0.11
	200-400 m	-0.48 (-0.96,-0.01)	
	>400 m (ref)		
Distance to road A2			
Fully adjusted model	<=150	0.47 (-0.26,1.19)	0.21
	>150 (ref)		
Distance to road A2			
Fully adjusted model	<=200 m	0.24 (-0.34,0.82)	0.57
	200-400 m	-0.18 (-0.72,0.37)	
	>400 m (ref)		
Distance to road A3			
Fully adjusted model	<50	0.17 (-0.20,0.54)	0.66
	50-200	0.02 (-0.30,0.33)	
	>200 (ref)		
Distance to road A4			
Fully adjusted model	<=50	0.01 (-0.43,0.45)	0.96
	>50 (ref)		
Distance to road A1-A3			
Fully adjusted model	<50	0.21 (-0.15,0.57)	0.45
	50-200	0.12 (-0.17,0.42)	
	>200 (ref)		
Distance to road A1-A3			
Fully adjusted model	<50 m	0.01 (-0.37,0.40)	0.05*
	50-100 m	-0.20 (-0.64,0.25)	
	100-200 m	0.00 (-0.38,0.38)	
	200-400 m	-0.42 (-0.72,-0.12)	
	>=400 (ref)		
AADT-A1			

Fully adjusted model	highest tertile	-0.33 (-0.66,0.00)	0.05
	medium tertile	-0.33 (-0.63,-0.04)	
	lowest tertile(ref)		
AADT-A2			
Fully adjusted model	highest tertile	-0.09 (-0.40,0.21)	0.83
	medium tertile	-0.06 (-0.35,0.23)	
	lowest tertile(ref)		
AADT-A3			
Fully adjusted model	highest tertile	-0.22 (-0.53,0.08)	0.17
	medium tertile	-0.26 (-0.55,0.03)	
	lowest tertile(ref)		
AADT-A4			
Fully adjusted model	highest tertile	-0.14 (-0.44,0.15)	0.56
	medium tertile	-0.15 (-0.45,0.16)	
	lowest tertile(ref)		

* P value <0.05

[1.] Fully adjusted model controlled for age at enrollment, sex and race/ethnicity, diabetes management factors including type of insulin regimen, diabetes duration (in years) and body mass index z score (BMI z score), lifestyle factors including physical activity (days exercised at least 20 minutes that sweated, time spent on computer and time spent watching TV), smoking(ever smoke and days smoked in the past 30 days) as well as area level socioeconomic status (percent below poverty at Census Block 2000).

Table 4. 7 Stratified analyses by race/ethnicity in study site SC, CO and WA

Study site SC, CO and WA	Black (N=147)	Hispanic (N=149)	Other race (N=49)	White (N=1551)
	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
Distance to road A3				
<50	-0.05 (-1.20, 1.09)	1.16 (0.12, 2.19)*	-0.39 (-1.43, 0.65)	0.24 (0.01, 0.46)*
50-200	0.74 (-0.19, 1.67)	0.22 (-0.46, 0.90)	0.68 (-0.12, 1.48)	0.08 (-0.09, 0.25)
>200 (ref)				

Models adjusted for study site (random effect), age, sex, BMI Z score, duration of diabetes, type of insulin regime, smoking, exercise and area level percent below poverty

* P< 0.05

Chapter 5: The association between air pollution and subclinical cardiovascular disease (CVD) markers in youth living with type I diabetes

Abstract

The associations between acute exposure to air pollution and adverse cardiovascular events have been well established. However, the effects of acute exposure to air pollution on subclinical cardiovascular disease (CVD) markers are less studied and findings from existing studies are mixed. We examined the associations between acute exposure to air pollution and markers of arterial stiffness in youth living with type I diabetes in this study.

Youth living with type I diabetes were recruited from SEARCH CVD, an ancillary study of SEARCH for Diabetes in Youth Study. Youth who have two assessments of markers of arterial stiffness from the Ohio study site were included. Arterial stiffness, measured by pulse wave velocity (PWV), augmentation index (AIx), and brachial distensibility (BrachD) were the outcomes. Acute exposure to air pollution, including $PM_{2.5}$ on the day of assessment, on each of the 7 days prior to assessment and moving averages for 2- to 5- days prior to assessment, as well as a weekly average for $PM_{2.5}$ and weekly average $PM_{2.5}$ elemental carbon (EC) were obtained from spatio-temporal generalized additive mixed models (GAMMs). Separate linear mixed models were used to model the relationship between each measure of acute air pollution exposure and each marker of subclinical CVD.

A total of 137 participants were included in the analyses. Mean age for participants was 14.1 (SD:2.8) years and the mean follow-up time between SEARCH CVD visits was 5.25 (SD:0.47) years. Generally, air pollution exposures were decreasing over the follow-up period. A 1 $\mu g/m^3$ reduction in $PM_{2.5}$ 1-day prior to assessment was associated with 0.194 (95% Confidence Interval (CI): 0.021, 0.367) lower AIx adjusted for age, sex, race/ethnicity, mean arterial pressure (MAP), body mass index (BMI) Z score, hemoglobin A1c (HbA1c), smoking status and area level percent below poverty. $PM_{2.5}$ 1-day prior to assessment at SEARCH CVD visit 1 was not associated with AIx (-0.060, 95% CI:-0.239, 0.120) in the fully adjusted model. Changes in acute exposure to air pollution and acute exposure to air pollution at visit 1 were not associated with either PWV or BrachD in fully adjusted models.

Our results found that reduction in acute exposure to air pollution on the day prior to assessment may be associated with vascular function represented by lower AIx in youth living with type I diabetes. Acute exposure to air pollution were not associated with central artery stiffness and peripheral artery stiffness represented by PWV and BrachD, respectively. The biological pathways linking acute exposure to air pollution and the three CVD markers may vary by markers among those with diabetes. Future studies with larger sample size and extensive information on medical profile are needed to validate our results. The effects of air pollution on vascular alterations needs to be further studied to refute or confirm our results in other populations and geographic areas with other air pollution mixtures.

Introduction

The associations between acute exposure to air pollution and cardiovascular events have been well established [2]. Acute exposure to air pollution significantly increased the risk of myocardial infarction [254], heart failure [255], stroke [256] and arrhythmia [257]. Evidence suggests that acute exposure to air pollution enhances cardiovascular risk among susceptible populations including older populations, people with existing cardiovascular structural or functional conditions and people with diabetes mellitus [52,189,258].

People living with diabetes (both type I and type II) are at greater risk of developing cardiovascular disease (CVD) when exposed to elevated levels of air pollution. Researchers found exposure to air pollution was associated with enhanced inflammation, vascular dysfunction, coagulation and insulin resistance in animal models induced with type I and type II diabetes [70,74,97] and was associated with enhanced susceptibility for inflammation, impairment in vascular function and adverse cardiovascular events for people living with diabetes [52,53,259,260].

Type I and type II diabetes are different in pathology, where people living with type I do not have insulin-producing beta cells due to autoimmune destruction in contrast to people with type II diabetes who produce insulin but could not use them properly. However, both type I and type II diabetes patients are more likely to live with cardiovascular risk factors and they are more vulnerable to cardiovascular diseases [98-100]. There are very few studies focused on the impact of exposure to air pollution on subclinical CVD biomarkers. We are not aware of any studies

investigating the association between acute exposure to air pollution and subclinical CVD markers in youth living with type I diabetes.

Arterial stiffness is an early sign of vascular alterations, and it is associated with cardiovascular risk factors, as well as CVD risks [140,141,261]. Pulse Wave Velocity (PWV), Augmentation Index (AIx) and Brachial Distensibility (BrachD) are measures related to arterial stiffness. Carotid-femoral PWV is a "golden standard" marker of arterial stiffness [153,262]. AIx is an indirect measure. BrachD, although less frequently used, is a useful marker to detect subclinical vascular changes in relation to arteriosclerosis [155,261].

Few studies have focused on the relationship between acute exposure to air pollution and arterial stiffness and findings from existing studies are mixed. Prior studies have found short-term exposure to air pollution was associated with increased AIx among welders in a case-crossover study [110], among healthy men in an experimental study [263] and among males in a repeated measures study [112]. However, acute exposure to diesel exhaust was not associated with PWV in a double-blinded experiment in young healthy men [263]. To the best of our knowledge, no studies have been conducted on exposure to ambient air pollution and BrachD. Thus, there is a knowledge gap in understanding the associations between acute exposure to air pollution and subclinical CVD markers in youth living with type I diabetes.

In this study, we performed repeated measures analyses for youth who have two assessments of subclinical CVD markers to examine the associations between acute exposure to air pollution (e.g. particulate matter <2.5 μm in aerodynamic diameter ($PM_{2.5}$) and $PM_{2.5}$ elemental carbon (EC)) and subclinical CVD markers of

arterial stiffness including PWV, AIx and BrachD in youth living with type I diabetes. Air pollution is a modifiable risk factor for CVD. It is important to understand the functional changes of subclinical CVD markers following exposure to air pollution, especially in youth living with type I diabetes. The results of our study may provide evidence for early prevention of cardiovascular complications via reducing exposures to air pollution for youth living with type I diabetes.

Methods

Study Population

Initiated in 2000, SEARCH for Diabetes in Youth is a multi-center observational study that focused on physician-diagnosed diabetes in youth aged under 20 from 6 study sites (South Carolina, Ohio, Colorado, Washington, Southern California and Hawaii) [156]. In Phase 1, youth were asked to participate in an in-person baseline visit for demographics, health behaviors, medical history, anthropometric measures and blood samples. Parents/legal guardian were asked to complete family history questionnaires. SEARCH CVD is an ancillary study to SEARCH for Diabetes in Youth Study for youth diagnosed with type I diabetes in Colorado and Ohio study sites [161,162]. Participants were aged over 10 at SEARCH baseline visit in 2004-2005 and had data collected on cardiovascular structure and function measures. A follow-up SEARCH CVD visit was conducted in 2009-2011 on eligible participants, where demographics, anthropometric, laboratory data and cardiovascular structure and function measures were obtained. In our study, youth were eligible if they had two assessments of subclinical CVD markers from SEARCH

CVD. We only included youth from Ohio because very few youth from the Colorado site had two assessments of CVD markers. We excluded youth on anti-hypertensive medication (n=1) since anti-hypertensive medication may differentially affect cardiometabolic responses to air pollution exposures [158]. Youth with missing information in baseline hemoglobin A1c (HbA1c) and area level percent of poverty were excluded (n=2). One participant with extreme augmentation index was excluded. A total of 137 participants were included in the analyses.

Outcome

Subclinical CVD markers included pulse wave velocity (PWV), augmentation index (AIx) and branchial artery distensibility (BrachD). All three measures are non-invasive. Assessment of vascular function was conducted following a 5 minutes' rest in supine position. BrachD was measured using a non-invasive DynaPulse Pathway instrument (Pulse Metric, Inc., San Diego, California). This instrument calculates brachial artery distensibility utilizing arterial pressure signals obtained from a standard cuff sphygmomanometer. Three measures were taken and the average BrachD was used in our study. The coefficients of variability were less than 9% [264]. PWV measured by a SphygmoCor SCOR-PVx System (Atcor Medical, Sydney, Australia) is the differences in the carotid-to-distal artery length divided by the difference in R-wave-waveform foot times. In this study, we utilized carotid-femoral PWV, a "golden standard" measure of arterial stiffness in the analysis [153]. A tonometer was used to collect carotid and femoral arterial waveforms gated by R-wave recorded on electrocardiogram simultaneously. Ten successive measures were used to cover a complete respiratory circle and the whole process was repeated three

times to obtain the mean PWV trunk measure for each participant. The coefficients of variability were <7% [264]. AIx was calculated by the difference between the primary and the reflected wave of the central arterial waveform and was then adjusted to a standard heart rate of 75 beats per minute because it is affected by heart rate. The SphygmoCortonometer was used to measure 3 radial pulse waves and then analyze the pulse waves to calculate central aortic pressure waves. The intraclass correlation coefficients were between 0.7 and 0.9 [264]. Higher PWV and AIx indicate higher arterial stiffness while lower BrachD suggests higher stiffness.

Exposure

Particulate matter <2.5 μm in aerodynamic diameter ($PM_{2.5}$) and $PM_{2.5}$ elemental carbon (EC) were measures of exposure to air pollution [222]. We constructed single day estimates on the day of assessment and for each of the 7 days prior to assessment and then constructed moving averages for 2- to 5- day prior to assessment, as well as a weekly average for $PM_{2.5}$ based on 24-hour estimates obtained from spatio-temporal generalized additive mixed models (GAMMs) [222]. The day of assessment was defined as lag day 0 and each of the 7 days prior to assessment was defined as lag day 1-7, respectively. A weekly average was constructed for $PM_{2.5}$ EC based on 24-hour estimates from GAMM. We only included a weekly average for $PM_{2.5}$ EC because 24-hour EC was only available on every third and fourth day from January 1, 1999 and every third day after August 2001.

We geocoded the residential address of each participant at both SEARCH CVD visit 1 and visit 2 and assigned the modeled air pollution exposures ($PM_{2.5}$, $PM_{2.5}$ EC) to each participant by residential location. ArcGIS 9.3 software (ESRI

2008) and the TIGER 2000 and 2006 Road Network Files were used for geocoding and we applied a 30 m offset to account for residential distance from the road. We reached a street-segment rate greater than 94%.

The GAMM included air pollution monitor measurements, meteorological factors that are influential to air pollution dispersion, geographic information system (GIS)-based time invariant spatial characteristics and traffic-related PM. Twenty-four hour average $PM_{2.5}$ concentration data were obtained from the US Environmental Protection Agency (USEPA) Air Quality System (AQS), from the Interagency Monitoring of Protected Visual Environments (IMPROVE) network, and from the Southern Aerosol Research and Characterization Study (SEARCH) network. $PM_{2.5}$ EC measures were from the AQS (parameter code 88380) and IMPROVE (parameter code 88321) networks on every third and fourth day from January 1, 1999 and every third day after August 2001. The meteorological factors including wind speed and direction, sensible heat flux, planetary boundary layer height, air temperature, total precipitation, and total snowfall were collected as the same period of air pollution measures from the MERRA project [265]. Data on county-level population density (in persons m^{-2}) from the 2000 US Census [223] were obtained from ESRI Data and Maps 10.1, and elevation data were obtained from the USGS National Elevation Dataset [238]. Traffic-related PM by road classes were derived from Atmospheric Dispersion Modeling System (ADMS)-Roads software (CERC; Cambridge, England).

The general form of the model is:

$$y_{i,t} = \alpha + \alpha_t + \sum_q d_q(X_{i,q}) + \sum_p f_p(Z_{i,t,p}) + g_t(s_i) + g(s_i) + b_i + e_{i,t};$$

$$b_i \sim N(0, \sigma^2{}_b); \;\; e_{i,t} \sim N(0, \sigma^2{}_{e\,t})$$

where $y_{i,t}$ is the air pollution measures at monitor site i (i=1 to I sites) and time t (t=1 to T 24-hour time periods), s_i is the pair of projected coordinates at site i. $X_{i,q}$ are GIS-based time-invariant spatial characteristics for q=1…Q, $Z_{i,t,p}$ are spatio-temporal characteristics for p=1…P, α_t is an intercept representing the adjusted mean across all sites on a given day. d_q are penalized spline smooth functions of Q GIS-based time-invariant spatial characteristics, $f_p$are penalized spline smooth functions of P spatio-temporal characteristics $g_t(s_i)$ accounts for residual spatial variability in the 24-hr particulate matter values, and $g(s_i)$ accounts for time-invariant spatial variability across the contiguous US. The site-specific random effect b_i represents unexplained location-specific variability.

Covariates

Demographics including age, sex, race/ethnicity (non-Hispanic white vs. others), medical profile including mean arterial pressure (MAP), body mass index (BMI) Z score, hemoglobin A1c (HbA1c), as well as smoking (current smoker vs. non-current smoker) and percent below poverty at Census Block of residence from the US Census 2000 [240] were included as covariates. All the covariates were measured at SEARCH CVD visits except that HbA1c was measured at SEARCH baseline visit.

Statistical Analyses

Linear mixed effect models with random intercepts for each subject were used for the regression analyses. Separate models were fit for each air pollutant and each outcome. First, we fit a basic model with air pollutant at SEARCH CVD visit 1, time-varying air pollutant. We then additionally adjusted for age at visit 1, time-varying age, sex and race/ethnicity, MAP at visit 1, time-varying MAP, BMI Z score at visit 1, HbA1c at baseline, smoking at visit 1, time-varying smoking and area level percent below poverty at visit 1 and time-varying area level percent below poverty. We were able to assess both cross-sectional effect and longitudinal effect of air pollution using this model. Sensitivity analyses were performed for youth whose residential address can be geocoded at a street match (n=128). SAS 9.4 (SAS Institute Inc., Cary, NC, USA) was used for all the statistical analyses.

Results

Descriptive statistics at SEARCH CVD visit 1 and at SEARCH baseline visit are presented in Table 5.1. Mean age for participants was 14.1 (SD:2.8) years and 59 (40.9%) were females. Most of the participants were white (N=121, 88.3%). The mean follow-up time between the two SEARCH CVD visits was 5.25 (SD:0.47) years. The distributions of air pollution exposures by SEARCH CVD visits are presented in Table 5.2. Air pollution exposures decreased over the follow-up period. The mean differences between two visits was 249.9 ng/m^3 (SD:308.8) for weekly average $PM_{2.5}$ EC and was 4.2 $\mu g/m^3$ (SD:5.8) for weekly average $PM_{2.5}$. The distributions of markers of arterial stiffness by SEARCH CVD visits are presented in Table 5.3.

In basic models, weekly average $PM_{2.5}$ EC, weekly average $PM_{2.5}$, $PM_{2.5}$ on lag day 0 to lag day 7 and $PM_{2.5}$ moving averages for 2- to 5-day prior to assessment were associated with increased AIx (Table 5.4). However, only $PM_{2.5}$ 1-day prior to assessment (lag day 1) was associated with AIx after controlling for both time-varying and time-invariant covariates in the fully adjusted model. A 1 $\mu g/m^3$ reduction in $PM_{2.5}$ 1-day prior to assessment was associated with 0.194 (95% Confidence Interval (CI): 0.021, 0.367) lower AIx in the fully adjusted model. $PM_{2.5}$ 1-day prior to assessment at SEARCH CVD visit 1 was not associated with AIx (-0.060, 95% CI:-0.239, 0.120) in the fully adjusted model.

Weekly average $PM_{2.5}$ EC, weekly average $PM_{2.5}$, $PM_{2.5}$ on lag day 0 to lag 5, and $PM_{2.5}$ moving averages for 2- to 5-day prior to assessment were negatively associated with PWV in basic models (Table 5.5). None of the air pollution exposures were associated with PWV in fully adjusted models.

We did not observe associations between any of the air pollution exposures and BrachD either in basic models or in fully adjusted models (Table 5.6).

The associations were similar in sensitivity analyses restricted to youth whose residential address can be geocoded at street match (Table 5.7-5.9).

Discussion

In summary, changes in $PM_{2.5}$ 1-day prior to assessment was associated with AIx, but not associated with PWV and BrachD. AIx, PWV and BrachD are markers of arterial stiffness, where higher AIx and PWV as well as lower BrachD indicated arterial stiffness. We expected the associations between acute exposure to air pollution and subclinical CVD markers to be different because AIx, PWV and

BrachD measured vascular functions differently and because we did not adjust for heart rate in PWV and BrachD models. AIx, a measure of wave reflection, is a mixed measure of central and peripheral arterial stiffness [266]. Compared to PWV, the golden standard [153], AIx may capture arterial stiffening not represented by PWV and information concerning wave reflection. Evidence suggested acute systemic inflammation was associated with increased PWV and decreased AIx in healthy people [142]. Although the mechanisms are not fully understood, reduced incident wave reflected at peripheral arteries, possibly caused by vasodilation activated by Interleukin-1, may partially explain the differences [267]. We observed positive associations between acute exposure to air pollution and AIx at several lags but negative associations for PWV at the same lag periods in basic models. Although the associations did not exist in fully adjusted models for both biomarkers except lag 1 for AIx, results from basic models may suggest that the biological pathways linking air pollution to AIx and linking air pollution to PWV could be different. BrachD is a measure of peripheral arterial stiffness. Prior research found cardiac autonomic dysfunction was associated with central and peripheral arterial stiffness indicated by higher PWV and lower BrachD but was not associated with AIx in youth living with type I diabetes [268]. We are not aware that to what extent AIx represents peripheral arterial stiffness and how AIx and BrachD are linked. We assessed changes in markers of arterial stiffness between 2 SEARCH visits. Mean AIx was lower at visit 2 which coincided with the decreased air pollution at visit 2. PWV was slightly higher and BrachD did not change at visit 2.

In the analyses, AIx has been adjusted to a standard heart rate of 75 beats per minute, however, the measures of PWV and BrachD were not adjusted for heart rate. We did not control heart rate as a potential confounder for PWV and BrachD in regression analyses due to the limited data availability. Hence, heart rate, although less compelling to be a reason for the different results due to the fact that the 3 markers measured vascular functions differently, may account for some variations when comparing the results for 3 biomarkers of arterial stiffness.

We observed unexpected associations between acute exposure to air pollution at visit 1 and AIx in some of the basic models, where acute exposure to air pollution at several lags were associated with less stiffness indicated by lower AIx. The unexpected associations may be caused by limited sample size and limited geographical variation for the study population. Acute exposure to air pollution at visit 1 were not associated with either PWV or BrachD. The study population in our study lived with CVD risk factors and they were at higher risk having cardiovascular dysfunction. The cross-sectional associations between acute exposure to air pollution and arterial stiffness need to be further investigated.

Our study results were consistent with the welder's study, where additional welding on the day prior to monitoring was associated with greater augmentation index (5.1%, 95% CI: 0.8, 9.5) [110]. The study concluded that exposure to metal-rich air pollution may alter vascular function. In terms of the chemical composition of air pollution, our study has weekly average $PM_{2.5}$ EC but do not have single day estimates for $PM_{2.5}$ EC to compare with the results from $PM_{2.5}$ single day estimates. EC exposure on the day prior to assessment could be associated with AIx since acute

exposure to EC was associated with cardiovascular outcomes hospitalization [269,270]. In a randomized controlled study, augmentation index increased by 7.8% for healthy volunteers exposed to diesel exhaust compared to healthy volunteers exposed to filter air for 1 hour [263]. No effect on PWV was observed. Researchers argued that PWV was measured 40 minutes after acute exposure to air pollution, a time when augmentation index and augmentation pressure have returned to baseline levels. A repeated measures study on short-term exposure to air pollution and arterial stiffness was conducted in elderly men from Veterans Affairs Normative Aging study [112]. The study found 3.6 $\mu g/m^3$ increase in 3-day average exposure to $PM_{2.5}$ was associated with 0.8% (95% CI: 0.2, 1.4) increase in AIx. Very limited studies used PWV as measure of arterial stiffness in prior research. A 10 $\mu g/m^3$ increase in $PM_{2.5}$ at 1-day lag was associated with 2.1% (95% CI: 0.7, 3.6) higher brachial-ankle PWV in healthy adults [109]. Exposure to long-term $PM_{2.5}$ was not associated with carotid-femoral PWV in young adults [113]. However, another study assessing the effect of long-term exposure to PM_{10} on brachial-ankle PWV found positive association in patients undergoing hemodialysis [114]. We are not aware of any studies examined the effect of exposure to air pollution on BrachD.

Inflammation is a plausible mechanism linking acute exposure to air pollution and arterial stiffening. Weng and colleagues observed a positive correlation between brachial-ankle PWV and C-reactive protein (CRP) in patients undergoing hemodialysis [114]. A randomized double blinded trial found acute systemic inflammation was associated with large-artery stiffening [142]. In addition, endothelial dysfunction, associated with both exposure to air pollution [2] and arterial

stiffness [147,148], might explain part of the changes in arterial stiffness caused by air pollution.

Though the association between acute exposure to air pollution and arterial stiffness was not confirmed by PWV and BrachD in our study, changes in AIx may have implications for vulnerable population including youth living with type I diabetes. AIx was linked to endothelial dysfunction in healthy people [147] and was associated with increased risk of adverse CVD events and all-cause mortality independent of blood pressure and heart rate [271]. Acute exposure to $PM_{2.5}$ may induce immediate endothelial dysfunction in people living with type II diabetes [53]. Other studies suggested that long-term exposure to air pollution was associated with structural changes of CVD markers in adults and in adults living with diabetes [272,273]. Arterial stiffening may occur prior to structural changes of CVD in pediatric population [274]. Hence, evidence suggested the possibility of changes of functional CVD markers in response to exposure to air pollution for vulnerable populations.

There are limitations in this study. We had a small sample size and only included 137 youth with two assessments of CVD markers. We were not able to include some possible confounders including lipid profile and were not able to assess effect-modification by sex, race/ethnicity and smoking status due to limited sample size. More information on medical profile are needed. For example, HbA1c used in the study was measured at SEARCH baseline instead of SEARCH CVD visits and heart rate is missing in our study. Additionally, the analyses were performed for

youth recruited from only 1 study site, thus the generalizability to other geographic areas which may differ in the speciation of air pollution, is compromised.

Our study also has strengths. We were able to assess the effects of time-varying acute exposure to air pollution on subclinical CVD markers in a repeated measures design. The study focused on youth living with type I diabetes, which are highly vulnerable to CVD when exposed to elevated levels of ambient air pollution. Results of our study add some scientific evidence on the current air pollution research for this under-investigated population. In addition, we obtained novel subclinical CVD markers including PWV, AIx and BrachD as measures of arterial stiffness and obtained highly specific air pollution measures including $PM_{2.5}$ and $PM_{2.5}$ EC derived from spatio-temporal GAMMs. We performed sensitivity analyses for youth whose residential addresses can be geocoded at street match. Results from sensitivity analyses were consistent with the results from main analyses.

Conclusion

Our results found that reduction in acute exposure to air pollution on the day prior to assessment may be associated with vascular function represented by AIx in youth living with type I diabetes. Acute exposure to air pollution were not associated with central artery stiffness and peripheral artery stiffness represented by PWV and BrachD, respectively. The biological pathways linking acute exposure to air pollution and the three CVD markers seem to vary by marker. Future studies with larger sample size and extensive information on medical profile are needed to validate our results. The effects of air pollution on vascular alterations needs to be further studied

to refute or confirm our results in other populations and geographic areas with other air pollution mixtures.

Table 5. 1 Basic characteristics of the study population

Characteristics at SEARH CVD visit 1 (N=137)		Mean(SD)/ N(%)
Age in years		14.1 (2.8)
Race/Ethnicity		
White		121 (88.3%)
Nonwhite		16 (11.7%)
Sex	Female	56 (40.9%)
	Male	81 (59.1%)
Current smoker		4 (2.9%)
BMI Z score		0.65 (0.89)
Follow up time in years		5.25 (0.47)
Mean arterial pressure(MAP)		82.9 (6.3)
Percent below poverty for census tract of residence		1.0% (1.0)
Characteristics at SEARCH baseline visit		Mean(SD)/ N(%)
Waist circumference >= 90th percentile[1]		18 (13.1%)
Hypertensive youth[2]		5 (3.7%)
High LDL[3]		51 (38.4%)
High triglycerides[4]		11 (8.3%)
HbA1c		7.9 (1.4)
HbA1c 3 level	good	79 (57.7%)
	intermediate	44 (32.1%)
	poor	14 (10.2%)
Insurance	None	2 (1.5%)
	Medicaid/Medicare	19 (14.0%)
	Private	115 (84.6%)
Insulin regime	Pump	37 (27.0%)
	Long + short/rapid insulin, 3 or more times a day	40 (29.2%)
	Long + any other combination, 2 or more times a day	1 (0.7%)
	Any combination of insulins excluding long, 3 or more times/day	10 (7.3%)
	Any insulin(s) taken 1x/day, or any insulin combination excluding long 2x/day	49 (35.8%)

1. Waist circumference >= 90th percentile for age and gender
2. Hypertensive (Systolic blood pressure or diastolic blood pressure >=95th percentile for age and height
3. High low-density lipoprotein (LDL) >=100 mg/dl
4. High triglycerides >=100mg/dl

Table 5. 2 Distributions of air pollution exposures by SEARCH CVD visits

	Mean (SD)		
Air pollutant	SEARCH CVD visit 1	SEARCH CVD visit 2	Mean difference
Weekly average EC	803.8 (314.3)	554.0 (223.4)	249.9 (308.8)*
Weekly average $PM_{2.5}$	15.5 (5.6)	11.3 (3.2)	4.2 (5.8)*
$PM_{2.5}$ lag day 0	15.4 (6.7)	11.7 (4.8)	3.7 (7.9)*
$PM_{2.5}$ lag day 1	15.9 (8.1)	11.3 (5.1)	4.7 (9.9)*
$PM_{2.5}$ lag day 2	16.1 (8.6)	10.6 (4.8)	5.5 (10.3)*
$PM_{2.5}$ lag day 3	16.3 (7.9)	11.1 (4.8)	5.3 (8.2)*
$PM_{2.5}$ lag day 4	15.9 (7.8)	11.2 (4.9)	4.7 (8.8)*
$PM_{2.5}$ lag day 5	15.1 (7.8)	11.7 (5.3)	3.4 (9.4)*
$PM_{2.5}$ lag day 6	14.7 (7.3)	12.1 (5.3)	2.6 (7.8)*
$PM_{2.5}$ lag day 7	14.5 (6.5)	11.1 (5.1)	3.4 (7.9)*
$PM_{2.5}$ 2-day moving averages	15.7 (5.7)	11.3 (3.3)	4.5 (6.2)*
$PM_{2.5}$ 3-day moving averages	15.8 (5.9)	11.2 (3.3)	4.6 (6.4)*
$PM_{2.5}$ 4-day moving averages	15.8 (5.9)	11.2 (3.4)	4.6 (6.4)*
$PM_{2.5}$ 5-day moving averages	15.8 (5.9)	11.2 (3.3)	4.6 (6.4)*

*Paired t-test significant at $\alpha=0.05$

The unit of EC is ng/m^3 and the unit of $PM_{2.5}$ is $\mu g/m^3$

Table 5. 3 Distributions of arterial stiffness by SEARCH CVD visits

	Mean (SD)		
Outcomes	SEARCH CVD visit 1	SEARCH CVD visit 2	Mean difference
AIx	3.9 (8.9)	-2.6 (10.9)	6.5 (10.6)*
PWV	5.4 (0.7)	5.9 (0.9)	-0.5 (0.7)*
BrachD	6.0 (1.2)	6.0 (1.0)	0.1 (1.2)

*Paired t-test significant at α=0.05

Table 5. 4 Regression results for AIx

Outcome:AIx	Effect	Estimate (95% CI)
Basic model[1]	Time varying weekly average EC	0.011 (0.007,0.016)*
	Visit 1 weekly average EC	-0.006 (-0.011,0.000)*
Fully adjusted model[2]	Time varying weekly average EC	0.003 (-0.002,0.008)
	Visit 1 weekly average EC	-0.002 (-0.008,0.003)
Basic model	Time varying weekly average $PM_{2.5}$	0.561 (0.297,0.825)*
	Visit 1 weekly average $PM_{2.5}$	-0.349 (-0.645,-0.053)*
Fully adjusted model	Time varying weekly average $PM_{2.5}$	0.183 (-0.102,0.467)
	Visit 1 weekly average $PM_{2.5}$	-0.144 (-0.423,0.135)
Basic model	Time varying lag day 0 $PM_{2.5}$	0.363 (0.147,0.579)*
	Visit 1 lag day 0 $PM_{2.5}$	-0.063 (-0.303,0.178)
Fully adjusted model	Time varying lag day 0 $PM_{2.5}$	0.140 (-0.070,0.349)
	Visit 1 lag day 0 $PM_{2.5}$	0.032 (-0.193,0.258)
Basic model	Time varying lag day 1 $PM_{2.5}$	0.363 (0.188,0.538)*
	Visit 1 lag day 1 $PM_{2.5}$	-0.095 (-0.288,0.098)
Fully adjusted model	Time varying lag day 1 $PM_{2.5}$	0.194 (0.021,0.367)*
	Visit 1 lag day 1 $PM_{2.5}$	-0.060 (-0.239,0.120)
Basic model	Time varying lag day 2 $PM_{2.5}$	0.265 (0.096,0.433)*
	Visit 1 lag day 2 $PM_{2.5}$	-0.076 (-0.261,0.109)
Fully adjusted model	Time varying lag day 2 $PM_{2.5}$	0.060 (-0.107,0.228)
	Visit 1 lag day 2 $PM_{2.5}$	0.007 (-0.162,0.176)
Basic model	Time varying lag day 3 $PM_{2.5}$	0.314 (0.118,0.511)*
	Visit 1 lag day 3 $PM_{2.5}$	-0.216 (-0.431,-0.002)*
Fully adjusted model	Time varying lag day 3 $PM_{2.5}$	0.042 (-0.164,0.248)
	Visit 1 lag day 3 $PM_{2.5}$	-0.051 (-0.250,0.148)
Basic model	Time varying lag day 4 $PM_{2.5}$	0.263 (0.069,0.458)*
	Visit 1 lag day 4 $PM_{2.5}$	-0.253 (-0.463,-0.042)*
Fully adjusted model	Time varying lag day 4 $PM_{2.5}$	0.019 (-0.169,0.206)
	Visit 1 lag day 4 $PM_{2.5}$	-0.138 (-0.327,0.051)
Basic model	Time varying lag day 5 $PM_{2.5}$	0.199 (0.004,0.393)*
	Visit 1 lag day 5 $PM_{2.5}$	-0.165 (-0.374,0.043)
Fully adjusted model	Time varying lag day 5 $PM_{2.5}$	0.017 (-0.159,0.193)
	Visit 1 5-day prior $PM_{2.5}$	-0.052 (-0.239,0.136)
Basic model	Time varying lag day 6 $PM_{2.5}$	0.300 (0.071,0.528)*
	Visit 1 lag day 6 $PM_{2.5}$	-0.233 (-0.471,0.005)
Fully adjusted model	Time varying lag day 6 $PM_{2.5}$	0.130 (-0.078,0.337)
	Visit 1 lag day 6 $PM_{2.5}$	-0.128 (-0.342,0.086)
Basic model	Time varying lag day 7 $PM_{2.5}$	0.320 (0.100,0.540)*
	Visit 1 lag day 7 $PM_{2.5}$	-0.192 (-0.440,0.056)
Fully adjusted model	Time varying lag day 7 $PM_{2.5}$	0.095 (-0.112,0.301)
	Visit 1 lag day 7 $PM_{2.5}$	-0.021 (-0.249,0.207)
Basic model	Time varying 2-day moving average $PM_{2.5}$	0.522 (0.272,0.772)*
	Visit 1 2-day moving average $PM_{2.5}$	-0.295 (-0.578,-0.012)*

Fully adjusted model	Time varying 2-day moving average $PM_{2.5}$	0.164 (-0.105,0.433)
	Visit 1 2-day moving average $PM_{2.5}$	-0.122 (-0.386,0.142)
Basic model	Time varying 3-day moving average $PM_{2.5}$	0.498 (0.254,0.742)*
	Visit 1 3-day moving average $PM_{2.5}$	-0.290 (-0.566,-0.014)*
Fully adjusted model	Time varying 3-day moving average $PM_{2.5}$	0.142 (-0.121,0.406)
	Visit 1 3-day moving average $PM_{2.5}$	-0.116 (-0.373,0.142)
Basic model	Time varying 4-day moving average $PM_{2.5}$	0.493 (0.250,0.735)*
	Visit 1 4-day moving average $PM_{2.5}$	-0.291 (-0.565,-0.016)*
Fully adjusted model	Time varying 4-day moving average $PM_{2.5}$	0.137 (-0.126,0.400)
	Visit 1 4-day moving average $PM_{2.5}$	-0.113 (-0.370,0.143)
Basic model	Time varying 5-day moving average $PM_{2.5}$	0.498 (0.254,0.742)*
	Visit 1 5-day moving average $PM_{2.5}$	-0.290 (-0.566,-0.014)*
Fully adjusted model	Time varying 5-day moving average $PM_{2.5}$	0.142 (-0.121,0.406)
	Visit 1 5-day moving average $PM_{2.5}$	-0.116 (-0.373,0.142)

*$P < 0.05$

[1.] Basic model included air pollutant at SEARCH CVD visit 1, time-varying air pollutant

[2.] Fully adjusted model additionally adjusted for age at visit 1, time-varying age, sex and race/ethnicity, MAP at visit 1, time-varying MAP, BMI Z score at visit 1, HbA1c at baseline, smoking at visit 1, time-varying smoking and area level percent below poverty at visit 1 and time-varying area level percent below poverty.

Table 5. 5 Regression results for PWV

Outcome:PWV	Effect	Estimate (95% CI)
Basic model[1]	Time varying weekly average EC	-0.001 (-0.001,0.000)*
	Visit 1 weekly average EC	0.000 (0.000,0.001)
Fully adjusted model[2]	Time varying weekly average EC	0.000 (0.000,0.000)
	Visit 1 weekly average EC	0.000 (-0.001,0.000)
Basic model	Time varying weekly average $PM_{2.5}$	-0.034 (-0.053,-0.014)*
	Visit 1 weekly average $PM_{2.5}$	0.002 (-0.021,0.026)
Fully adjusted model	Time varying weekly average $PM_{2.5}$	0.002 (-0.018,0.022)
	Visit 1 weekly average $PM_{2.5}$	-0.003 (-0.023,0.017)
Basic model	Time varying lag day 0 $PM_{2.5}$	-0.019 (-0.035,-0.003)*
	Visit 1 lag day 0 $PM_{2.5}$	-0.007 (-0.026,0.012)
Fully adjusted model	Time varying lag day 0 $PM_{2.5}$	0.002 (-0.013,0.017)
	Visit 1 lag day 0 $PM_{2.5}$	-0.004 (-0.021,0.012)
Basic model	Time varying lag day 1 $PM_{2.5}$	-0.018 (-0.031,-0.005)*
	Visit 1 lag day 1 $PM_{2.5}$	-0.003 (-0.018,0.013)
Fully adjusted model	Time varying lag day 1 $PM_{2.5}$	0.000 (-0.012,0.012)
	Visit 1 lag day 1 $PM_{2.5}$	-0.004 (-0.017,0.009)
Basic model	Time varying lag day 2 $PM_{2.5}$	-0.020 (-0.033,-0.008)*
	Visit 1 lag day 2 $PM_{2.5}$	-0.003 (-0.018,0.011)
Fully adjusted model	Time varying lag day 2 $PM_{2.5}$	-0.002 (-0.014,0.010)
	Visit 1 lag day 2 $PM_{2.5}$	-0.005 (-0.018,0.007)
Basic model	Time varying lag day 3 $PM_{2.5}$	-0.022 (-0.036,-0.007)*
	Visit 1 lag day 3 $PM_{2.5}$	0.001 (-0.016,0.017)
Fully adjusted model	Time varying lag day 3 $PM_{2.5}$	0.003 (-0.011,0.018)
	Visit 1 lag day 3 $PM_{2.5}$	-0.005 (-0.020,0.009)
Basic model	Time varying lag day 4 $PM_{2.5}$	-0.017 (-0.031,-0.003)*
	Visit 1 lag day 4 $PM_{2.5}$	0.004 (-0.012,0.021)
Fully adjusted model	Time varying lag day 4 $PM_{2.5}$	0.003 (-0.011,0.016)
	Visit 1 lag day 4 $PM_{2.5}$	-0.002 (-0.016,0.012)
Basic model	Time varying lag day 5 $PM_{2.5}$	-0.014 (-0.029,0.000)*
	Visit 1 lag day 5 $PM_{2.5}$	0.001 (-0.015,0.018)
Fully adjusted model	Time varying lag day 5 $PM_{2.5}$	-0.002 (-0.014,0.011)
	Visit 1 5-day prior $PM_{2.5}$	0.000 (-0.014,0.014)
Basic model	Time varying lag day 6 $PM_{2.5}$	-0.013 (-0.030,0.004)
	Visit 1 lag day 6 $PM_{2.5}$	0.005 (-0.014,0.024)
Fully adjusted model	Time varying lag day 6 $PM_{2.5}$	0.001 (-0.014,0.016)
	Visit 1 lag day 6 $PM_{2.5}$	0.005 (-0.011,0.020)
Basic model	Time varying lag day 7 $PM_{2.5}$	-0.016 (-0.032,0.000)
	Visit 1 lag day 7 $PM_{2.5}$	0.000 (-0.020,0.020)
Fully adjusted model	Time varying lag day 7 $PM_{2.5}$	0.003 (-0.011,0.018)
	Visit 1 lag day 7 $PM_{2.5}$	0.004 (-0.012,0.021)
Basic model	Time varying 2-day moving average $PM_{2.5}$	-0.033 (-0.051,-0.014)*
	Visit 1 2-day moving average $PM_{2.5}$	0.000 (-0.023,0.022)

Fully adjusted model	Time varying 2-day moving average $PM_{2.5}$	0.001 (-0.018,0.020)
	Visit 1 2-day moving average $PM_{2.5}$	-0.005 (-0.024,0.014)
Basic model	Time varying 3-day moving average $PM_{2.5}$	-0.032 (-0.050,-0.014)*
	Visit 1 3-day moving average $PM_{2.5}$	0.000 (-0.022,0.022)
Fully adjusted model	Time varying 3-day moving average $PM_{2.5}$	0.001 (-0.018,0.020)
	Visit 1 3-day moving average $PM_{2.5}$	-0.006 (-0.024,0.013)
Basic model	Time varying 4-day moving average $PM_{2.5}$	-0.032 (-0.050,-0.014)*
	Visit 1 4-day moving average $PM_{2.5}$	0.000 (-0.022,0.022)
Fully adjusted model	Time varying 4-day moving average $PM_{2.5}$	0.001 (-0.017,0.020)
	Visit 1 4-day moving average $PM_{2.5}$	-0.006 (-0.024,0.013)
Basic model	Time varying 5-day moving average $PM_{2.5}$	-0.032 (-0.050,-0.014)*
	Visit 1 5-day moving average $PM_{2.5}$	0.000 (-0.022,0.022)
Fully adjusted model	Time varying 5-day moving average $PM_{2.5}$	0.001 (-0.018,0.020)
	Visit 1 5-day moving average $PM_{2.5}$	-0.006 (-0.024,0.013)

*$P < 0.05$

[1.] Basic model included air pollutant at SEARCH CVD visit 1, time-varying air pollutant

[2.] Fully adjusted model additionally adjusted for age at visit 1, time-varying age, sex and race/ethnicity, MAP at visit 1, time-varying MAP, BMI Z score at visit 1, HbA1c at baseline, smoking at visit 1, time-varying smoking and area level percent below poverty at visit 1 and time-varying area level percent below poverty.

Table 5. 6 Regression Results for BrachD

Outcome:BrachD	Effect	Estimate (95% CI)
Basic model[1]	Time varying weekly average EC	0.000 (0.000,0.001)
	Visit 1 weekly average EC	0.000 (-0.001,0.001)
Fully adjusted model[2]	Time varying weekly average EC	0.000 (-0.001,0.001)
	Visit 1 weekly average EC	0.000 (-0.001,0.000)
Basic model	Time varying weekly average $PM_{2.5}$	0.015 (-0.012,0.042)
	Visit 1 weekly average $PM_{2.5}$	-0.010 (-0.042,0.023)
Fully adjusted model	Time varying weekly average $PM_{2.5}$	0.020 (-0.011,0.052)
	Visit 1 weekly average $PM_{2.5}$	-0.018 (-0.048,0.013)
Basic model	Time varying lag day 0 $PM_{2.5}$	0.011 (-0.010,0.033)
	Visit 1 lag day 0 $PM_{2.5}$	0.008 (-0.018,0.035)
Fully adjusted model	Time varying lag day 0 $PM_{2.5}$	0.012 (-0.011,0.035)
	Visit 1 lag day 0 $PM_{2.5}$	-0.005 (-0.030,0.020)
Basic model	Time varying lag day 1 $PM_{2.5}$	0.006 (-0.011,0.024)
	Visit 1 lag day 1 $PM_{2.5}$	0.000 (-0.021,0.022)
Fully adjusted model	Time varying lag day 1 $PM_{2.5}$	0.006 (-0.013,0.025)
	Visit 1 lag day 1 $PM_{2.5}$	-0.006 (-0.026,0.014)
Basic model	Time varying lag day 2 $PM_{2.5}$	0.004 (-0.013,0.021)
	Visit 1 lag day 2 $PM_{2.5}$	0.003 (-0.017,0.024)
Fully adjusted model	Time varying lag day 2 $PM_{2.5}$	0.006 (-0.012,0.025)
	Visit 1 lag day 2 $PM_{2.5}$	0.002 (-0.017,0.021)
Basic model	Time varying lag day 3 $PM_{2.5}$	0.011 (-0.009,0.031)
	Visit 1 lag day 3 $PM_{2.5}$	-0.002 (-0.025,0.022)
Fully adjusted model	Time varying lag day 3 $PM_{2.5}$	0.017 (-0.005,0.040)
	Visit 1 lag day 3 $PM_{2.5}$	-0.009 (-0.031,0.013)
Basic model	Time varying lag day 4 $PM_{2.5}$	0.007 (-0.012,0.026)
	Visit 1 lag day 4 $PM_{2.5}$	-0.012 (-0.035,0.011)
Fully adjusted model	Time varying lag day 4 $PM_{2.5}$	0.009 (-0.011,0.030)
	Visit 1 lag day 4 $PM_{2.5}$	-0.016 (-0.037,0.005)
Basic model	Time varying lag day 5 $PM_{2.5}$	0.007 (-0.012,0.027)
	Visit 1 lag day 5 $PM_{2.5}$	-0.008 (-0.031,0.015)
Fully adjusted model	Time varying lag day 5 $PM_{2.5}$	0.009 (-0.010,0.028)
	Visit 1 5-day prior $PM_{2.5}$	-0.007 (-0.028,0.013)
Basic model	Time varying lag day 6 $PM_{2.5}$	0.013 (-0.010,0.035)
	Visit 1 lag day 6 $PM_{2.5}$	-0.011 (-0.037,0.015)
Fully adjusted model	Time varying lag day 6 $PM_{2.5}$	0.010 (-0.013,0.033)
	Visit 1 lag day 6 $PM_{2.5}$	-0.011 (-0.035,0.012)
Basic model	Time varying lag day 7 $PM_{2.5}$	0.010 (-0.012,0.032)
	Visit 1 lag day 7 $PM_{2.5}$	-0.010 (-0.038,0.017)
Fully adjusted model	Time varying lag day 7 $PM_{2.5}$	0.006 (-0.017,0.028)
	Visit 1 lag day 7 $PM_{2.5}$	-0.012 (-0.038,0.013)
Basic model	Time varying 2-day moving average $PM_{2.5}$	0.013 (-0.012,0.039)
	Visit 1 2-day moving average $PM_{2.5}$	-0.005 (-0.037,0.026)
Fully adjusted model	Time varying 2-day moving average $PM_{2.5}$	0.020 (-0.010,0.049)

Basic model	Visit 1 2-day moving average $PM_{2.5}$	-0.015 (-0.044,0.015)
	Time varying 3-day moving average $PM_{2.5}$	0.013 (-0.012,0.037)
Fully adjusted model	Visit 1 3-day moving average $PM_{2.5}$	-0.005 (-0.036,0.025)
	Time varying 3-day moving average $PM_{2.5}$	0.019 (-0.010,0.048)
Basic model	Visit 1 3-day moving average $PM_{2.5}$	-0.014 (-0.042,0.015)
	Time varying 4-day moving average $PM_{2.5}$	0.013 (-0.012,0.037)
Fully adjusted model	Visit 1 4-day moving average $PM_{2.5}$	-0.005 (-0.035,0.026)
	Time varying 4-day moving average $PM_{2.5}$	0.020 (-0.009,0.048)
Basic model	Visit 1 4-day moving average $PM_{2.5}$	-0.014 (-0.042,0.014)
	Time varying 5-day moving average $PM_{2.5}$	0.013 (-0.012,0.037)
Fully adjusted model	Visit 1 5-day moving average $PM_{2.5}$	-0.005 (-0.036,0.025)
	Time varying 5-day moving average $PM_{2.5}$	0.019 (-0.010,0.048)
	Visit 1 5-day moving average $PM_{2.5}$	-0.014 (-0.042,0.015)

*$P < 0.05$

1. Basic model included air pollutant at SEARCH CVD visit 1, time-varying air pollutant

2. Fully adjusted model additionally adjusted for age at visit 1, time-varying age, sex and race/ethnicity, MAP at visit 1, time-varying MAP, BMI Z score at visit 1, HbA1c at baseline, smoking at visit 1, time-varying smoking and area level percent below poverty at visit 1 and time-varying area level percent below poverty.

Table 5. 7 Sensitivity analyses for youth whose residential addresses can be geocoded at street match, for outcome AIx

Outcome:AIx	Effect	Estimate (95% CI)
Basic model[1]	Time varying weekly average EC	0.012 (0.007,0.017)*
	Visit 1 weekly average EC	-0.007 (-0.012,-0.001)*
Fully adjusted model[2]	Time varying weekly average EC	0.003 (-0.003,0.008)
	Visit 1 weekly average EC	-0.002 (-0.007,0.004)
Basic model	Time varying weekly average $PM_{2.5}$	0.532 (0.263,0.802)*
	Visit 1 weekly average $PM_{2.5}$	-0.342 (-0.640,-0.043)*
Fully adjusted model	Time varying weekly average $PM_{2.5}$	0.117 (-0.168,0.403)
	Visit 1 weekly average $PM_{2.5}$	-0.112 (-0.399,0.174)
Basic model	Time varying lag day 0 $PM_{2.5}$	0.352 (0.130,0.573)*
	Visit 1 lag day 0 $PM_{2.5}$	-0.014 (-0.258,0.231)
Fully adjusted model	Time varying lag day 0 $PM_{2.5}$	0.098 (-0.112,0.307)
	Visit 1 lag day 0 $PM_{2.5}$	0.073 (-0.162,0.308)
Basic model	Time varying lag day 1 $PM_{2.5}$	0.379 (0.199,0.559)*
	Visit 1 lag day 1 $PM_{2.5}$	-0.107 (-0.303,0.090)
Fully adjusted model	Time varying lag day 1 $PM_{2.5}$	0.188 (0.015,0.360)*
	Visit 1 lag day 1 $PM_{2.5}$	-0.069 (-0.256,0.118)
Basic model	Time varying lag day 2 $PM_{2.5}$	0.248 (0.075,0.420)
	Visit 1 lag day 2 $PM_{2.5}$	-0.076 (-0.262,0.111)
Fully adjusted model	Time varying lag day 2 $PM_{2.5}$	0.024 (-0.143,0.191)
	Visit 1 lag day 2 $PM_{2.5}$	0.018 (-0.156,0.192)
Basic model	Time varying lag day 3 $PM_{2.5}$	0.280 (0.079,0.481)*
	Visit 1 lag day 3 $PM_{2.5}$	-0.204 (-0.420,0.011)
Fully adjusted model	Time varying lag day 3 $PM_{2.5}$	-0.018 (-0.223,0.188)
	Visit 1 lag day 3 $PM_{2.5}$	-0.009 (-0.213,0.194)
Basic model	Time varying lag day 4 $PM_{2.5}$	0.248 (0.049,0.446)*
	Visit 1 lag day 4 $PM_{2.5}$	-0.258 (-0.470,-0.047)*
Fully adjusted model	Time varying lag day 4 $PM_{2.5}$	-0.007 (-0.195,0.182)
	Visit 1 lag day 4 $PM_{2.5}$	-0.123 (-0.318,0.072)
Basic model	Time varying lag day 5 $PM_{2.5}$	0.186 (-0.013,0.385)
	Visit 1 lag day 5 $PM_{2.5}$	-0.165 (-0.376,0.045)
Fully adjusted model	Time varying lag day 5 $PM_{2.5}$	0.001 (-0.175,0.178)
	Visit 1 5-day prior $PM_{2.5}$	-0.056 (-0.250,0.138)
Basic model	Time varying lag day 6 $PM_{2.5}$	0.274 (0.040,0.509)*
	Visit 1 lag day 6 $PM_{2.5}$	-0.207 (-0.449,0.035)
Fully adjusted model	Time varying lag day 6 $PM_{2.5}$	0.099 (-0.110,0.309)
	Visit 1 lag day 6 $PM_{2.5}$	-0.107 (-0.330,0.115)
Basic model	Time varying lag day 7 $PM_{2.5}$	0.308 (0.082,0.535)*
	Visit 1 lag day 7 $PM_{2.5}$	-0.185 (-0.437,0.067)
Fully adjusted model	Time varying lag day 7 $PM_{2.5}$	0.057 (-0.151,0.266)
	Visit 1 lag day 7 $PM_{2.5}$	0.003 (-0.235,0.241)
Basic model	Time varying 2-day moving average $PM_{2.5}$	0.495 (0.240,0.750)*

Fully adjusted model	Visit 1 2-day moving average $PM_{2.5}$	-0.287 (-0.571,-0.003)*
	Time varying 2-day moving average $PM_{2.5}$	0.104 (-0.165,0.372)
Basic model	Visit 1 2-day moving average $PM_{2.5}$	-0.094 (-0.363,0.176)
	Time varying 3-day moving average $PM_{2.5}$	0.469 (0.220,0.718)*
Fully adjusted model	Visit 1 3-day moving average $PM_{2.5}$	-0.283 (-0.560,-0.005)*
	Time varying 3-day moving average $PM_{2.5}$	0.080 (-0.183,0.343)
Basic model	Visit 1 3-day moving average $PM_{2.5}$	-0.085 (-0.348,0.178)
	Time varying 4-day moving average $PM_{2.5}$	0.462 (0.215,0.709)*
Fully adjusted model	Visit 1 4-day moving average $PM_{2.5}$	-0.283 (-0.558,-0.007)*
	Time varying 4-day moving average $PM_{2.5}$	0.073 (-0.189,0.335)
Basic model	Visit 1 4-day moving average $PM_{2.5}$	-0.080 (-0.342,0.182)
	Time varying 5-day moving average $PM_{2.5}$	0.469 (0.220,0.718)*
Fully adjusted model	Visit 1 5-day moving average $PM_{2.5}$	-0.283 (-0.560,-0.005)*
	Time varying 5-day moving average $PM_{2.5}$	0.080 (-0.183,0.343)
	Visit 1 5-day moving average $PM_{2.5}$	-0.085 (-0.348,0.178)

*$P < 0.05$

[1.] Basic model included air pollutant at SEARCH CVD visit 1, time-varying air pollutant

[2.] Fully adjusted model additionally adjusted for age at visit 1, time-varying age, sex and race/ethnicity, MAP at visit 1, time-varying MAP, BMI Z score at visit 1, HbA1c at baseline, smoking at visit 1, time-varying smoking and area level percent below poverty at visit 1 and time-varying area level percent below poverty.

Table 5. 8 Sensitivity analyses for youth whose residential addresses can be geocoded at street match, for outcome PWV

Outcome:PWV	Effect	Estimate (95% CI)
Basic model[1]	Time varying weekly average EC	-0.001 (-0.001,0.000)*
	Visit 1 weekly average EC	0.000 (0.000,0.001)
Fully adjusted model[2]	Time varying weekly average EC	0.000 (-0.001,0.000)
	Visit 1 weekly average EC	0.000 (-0.001,0.000)
Basic model	Time varying weekly average $PM_{2.5}$	-0.033 (-0.052,-0.013)*
	Visit 1 weekly average $PM_{2.5}$	0.004 (-0.019,0.028)
Fully adjusted model	Time varying weekly average $PM_{2.5}$	-0.001 (-0.021,0.020)
	Visit 1 weekly average $PM_{2.5}$	0.001 (-0.020,0.021)
Basic model	Time varying lag day 0 $PM_{2.5}$	-0.016 (-0.032,0.000)*
	Visit 1 lag day 0 $PM_{2.5}$	-0.008 (-0.028,0.011)
Fully adjusted model	Time varying lag day 0 $PM_{2.5}$	0.003 (-0.012,0.018)
	Visit 1 lag day 0 $PM_{2.5}$	-0.005 (-0.022,0.012)
Basic model	Time varying lag day 1 $PM_{2.5}$	-0.015 (-0.028,-0.001)*
	Visit 1 lag day 1 $PM_{2.5}$	-0.005 (-0.020,0.011)
Fully adjusted model	Time varying lag day 1 $PM_{2.5}$	0.002 (-0.011,0.014)
	Visit 1 lag day 1 $PM_{2.5}$	-0.005 (-0.018,0.009)
Basic model	Time varying lag day 2 $PM_{2.5}$	-0.018 (-0.030,-0.006)*
	Visit 1 lag day 2 $PM_{2.5}$	-0.004 (-0.019,0.011)
Fully adjusted model	Time varying lag day 2 $PM_{2.5}$	-0.001 (-0.013,0.011)
	Visit 1 lag day 2 $PM_{2.5}$	-0.005 (-0.018,0.007)
Basic model	Time varying lag day 3 $PM_{2.5}$	-0.022 (-0.037,-0.008)*
	Visit 1 lag day 3 $PM_{2.5}$	0.001 (-0.015,0.018)
Fully adjusted model	Time varying lag day 3 $PM_{2.5}$	0.000 (-0.015,0.015)
	Visit 1 lag day 3 $PM_{2.5}$	-0.003 (-0.017,0.011)
Basic model	Time varying lag day 4 $PM_{2.5}$	-0.019 (-0.033,-0.005)*
	Visit 1 lag day 4 $PM_{2.5}$	0.006 (-0.011,0.023)
Fully adjusted model	Time varying lag day 4 $PM_{2.5}$	-0.001 (-0.015,0.012)
	Visit 1 lag day 4 $PM_{2.5}$	0.001 (-0.013,0.015)
Basic model	Time varying lag day 5 $PM_{2.5}$	-0.016 (-0.030,-0.001)*
	Visit 1 lag day 5 $PM_{2.5}$	0.004 (-0.012,0.021)
Fully adjusted model	Time varying lag day 5 $PM_{2.5}$	-0.004 (-0.017,0.008)
	Visit 1 5-day prior $PM_{2.5}$	0.004 (-0.010,0.018)
Basic model	Time varying lag day 6 $PM_{2.5}$	-0.015 (-0.032,0.002)
	Visit 1 lag day 6 $PM_{2.5}$	0.008 (-0.011,0.027)
Fully adjusted model	Time varying lag day 6 $PM_{2.5}$	-0.001 (-0.016,0.014)
	Visit 1 lag day 6 $PM_{2.5}$	0.008 (-0.007,0.024)
Basic model	Time varying lag day 7 $PM_{2.5}$	-0.017 (-0.033,-0.001)*
	Visit 1 lag day 7 $PM_{2.5}$	0.004 (-0.016,0.024)
Fully adjusted model	Time varying lag day 7 $PM_{2.5}$	0.002 (-0.013,0.017)
	Visit 1 lag day 7 $PM_{2.5}$	0.008 (-0.009,0.024)
Basic model	Time varying 2-day moving average $PM_{2.5}$	-0.031 (-0.049,-0.013)*

Fully adjusted model	Visit 1 2-day moving average $PM_{2.5}$	0.001 (-0.022,0.023)
	Time varying 2-day moving average $PM_{2.5}$	-0.001 (-0.020,0.018)
Basic model	Visit 1 2-day moving average $PM_{2.5}$	-0.002 (-0.021,0.017)
	Time varying 3-day moving average $PM_{2.5}$	-0.030 (-0.048,-0.013)*
Fully adjusted model	Visit 1 3-day moving average $PM_{2.5}$	0.001 (-0.021,0.023)
	Time varying 3-day moving average $PM_{2.5}$	-0.001 (-0.020,0.018)
Basic model	Visit 1 3-day moving average $PM_{2.5}$	-0.003 (-0.021,0.016)
	Time varying 4-day moving average $PM_{2.5}$	-0.030 (-0.048,-0.013)*
Fully adjusted model	Visit 1 4-day moving average $PM_{2.5}$	0.001 (-0.021,0.022)
	Time varying 4-day moving average $PM_{2.5}$	-0.001 (-0.020,0.018)
Basic model	Visit 1 4-day moving average $PM_{2.5}$	-0.003 (-0.021,0.016)
	Time varying 5-day moving average $PM_{2.5}$	-0.030 (-0.048,-0.013)*
Fully adjusted model	Visit 1 5-day moving average $PM_{2.5}$	0.001 (-0.021,0.023)
	Time varying 5-day moving average $PM_{2.5}$	-0.001 (-0.020,0.018)
	Visit 1 5-day moving average $PM_{2.5}$	-0.003 (-0.021,0.016)

*$P < 0.05$

[1.] Basic model included air pollutant at SEARCH CVD visit 1, time-varying air pollutant

[2.] Fully adjusted model additionally adjusted for age at visit 1, time-varying age, sex and race/ethnicity, MAP at visit 1, time-varying MAP, BMI Z score at visit 1, HbA1c at baseline, smoking at visit 1, time-varying smoking and area level percent below poverty at visit 1 and time-varying area level percent below poverty.

Table 5. 9 Sensitivity analyses for youth whose residential addresses can be geocoded at street match, for outcome BrachD

Outcome:BrachD	Effect	Estimate (95% CI)
Basic model[1]	Time varying weekly average EC	0.000 (0.000,0.001)
	Visit 1 weekly average EC	0.000 (-0.001,0.001)
Fully adjusted model[2]	Time varying weekly average EC	0.000 (-0.001,0.001)
	Visit 1 weekly average EC	0.000 (-0.001,0.000)
Basic model	Time varying weekly average $PM_{2.5}$	0.014 (-0.013,0.042)
	Visit 1 weekly average $PM_{2.5}$	-0.011 (-0.045,0.022)
Fully adjusted model	Time varying weekly average $PM_{2.5}$	0.024 (-0.009,0.056)
	Visit 1 weekly average $PM_{2.5}$	-0.022 (-0.053,0.010)
Basic model	Time varying lag day 0 $PM_{2.5}$	0.009 (-0.013,0.031)
	Visit 1 lag day 0 $PM_{2.5}$	0.009 (-0.019,0.036)
Fully adjusted model	Time varying lag day 0 $PM_{2.5}$	0.011 (-0.013,0.034)
	Visit 1 lag day 0 $PM_{2.5}$	-0.008 (-0.034,0.018)
Basic model	Time varying lag day 1 $PM_{2.5}$	0.003 (-0.015,0.022)
	Visit 1 lag day 1 $PM_{2.5}$	0.003 (-0.019,0.026)
Fully adjusted model	Time varying lag day 1 $PM_{2.5}$	0.005 (-0.015,0.024)
	Visit 1 lag day 1 $PM_{2.5}$	-0.005 (-0.026,0.016)
Basic model	Time varying lag day 2 $PM_{2.5}$	0.002 (-0.015,0.019)
	Visit 1 lag day 2 $PM_{2.5}$	0.005 (-0.016,0.026)
Fully adjusted model	Time varying lag day 2 $PM_{2.5}$	0.005 (-0.014,0.024)
	Visit 1 lag day 2 $PM_{2.5}$	0.002 (-0.017,0.022)
Basic model	Time varying lag day 3 $PM_{2.5}$	0.012 (-0.008,0.032)
	Visit 1 lag day 3 $PM_{2.5}$	-0.005 (-0.029,0.019)
Fully adjusted model	Time varying lag day 3 $PM_{2.5}$	0.019 (-0.004,0.043)
	Visit 1 lag day 3 $PM_{2.5}$	-0.013 (-0.035,0.010)
Basic model	Time varying lag day 4 $PM_{2.5}$	0.009 (-0.011,0.028)
	Visit 1 lag day 4 $PM_{2.5}$	-0.016 (-0.040,0.008)
Fully adjusted model	Time varying lag day 4 $PM_{2.5}$	0.013 (-0.008,0.034)
	Visit 1 lag day 4 $PM_{2.5}$	-0.021 (-0.042,0.001)
Basic model	Time varying lag day 5 $PM_{2.5}$	0.010 (-0.010,0.030)
	Visit 1 lag day 5 $PM_{2.5}$	-0.011 (-0.034,0.013)
Fully adjusted model	Time varying lag day 5 $PM_{2.5}$	0.013 (-0.007,0.033)
	Visit 1 5-day prior $PM_{2.5}$	-0.011 (-0.032,0.010)
Basic model	Time varying lag day 6 $PM_{2.5}$	0.014 (-0.009,0.038)
	Visit 1 lag day 6 $PM_{2.5}$	-0.012 (-0.039,0.015)
Fully adjusted model	Time varying lag day 6 $PM_{2.5}$	0.014 (-0.010,0.038)
	Visit 1 lag day 6 $PM_{2.5}$	-0.015 (-0.039,0.010)
Basic model	Time varying lag day 7 $PM_{2.5}$	0.007 (-0.016,0.030)
	Visit 1 lag day 7 $PM_{2.5}$	-0.012 (-0.040,0.017)
Fully adjusted model	Time varying lag day 7 $PM_{2.5}$	0.005 (-0.019,0.028)
	Visit 1 lag day 7 $PM_{2.5}$	-0.016 (-0.042,0.010)
Basic model	Time varying 2-day moving average $PM_{2.5}$	0.013 (-0.013,0.039)

Fully adjusted model	Visit 1 2-day moving average $PM_{2.5}$	-0.007 (-0.039,0.025)
	Time varying 2-day moving average $PM_{2.5}$	0.022 (-0.008,0.053)
Basic model	Visit 1 2-day moving average $PM_{2.5}$	-0.018 (-0.048,0.012)
	Time varying 3-day moving average $PM_{2.5}$	0.012 (-0.013,0.037)
Fully adjusted model	Visit 1 3-day moving average $PM_{2.5}$	-0.007 (-0.038,0.024)
	Time varying 3-day moving average $PM_{2.5}$	0.022 (-0.008,0.051)
Basic model	Visit 1 3-day moving average $PM_{2.5}$	-0.017 (-0.046,0.011)
	Time varying 4-day moving average $PM_{2.5}$	0.012 (-0.013,0.038)
Fully adjusted model	Visit 1 4-day moving average $PM_{2.5}$	-0.007 (-0.038,0.024)
	Time varying 4-day moving average $PM_{2.5}$	0.022 (-0.007,0.052)
Basic model	Visit 1 4-day moving average $PM_{2.5}$	-0.017 (-0.046,0.011)
	Time varying 5-day moving average $PM_{2.5}$	0.012 (-0.013,0.037)
Fully adjusted model	Visit 1 5-day moving average $PM_{2.5}$	-0.007 (-0.038,0.024)
	Time varying 5-day moving average $PM_{2.5}$	0.022 (-0.008,0.051)
	Visit 1 5-day moving average $PM_{2.5}$	-0.017 (-0.046,0.011)

*P < 0.05

[1.] Basic model included air pollutant at SEARCH CVD visit 1, time-varying air pollutant

[2.] Fully adjusted model additionally adjusted for age at visit 1, time-varying age, sex and race/ethnicity, MAP at visit 1, time-varying MAP, BMI Z score at visit 1, HbA1c at baseline, smoking at visit 1, time-varying smoking and area level percent below poverty at visit 1 and time-varying area level percent below poverty.

Chapter 6: Conclusions

6.1 Social environment and cardiometabolic outcomes

Social environment in the neighborhood has been linked to health behaviors and chronic conditions through social learning theory and social norms. People adopt health behaviors through learning of "modeling" behaviors and through social reinforcement of learning [6]. Social norms of appropriate behaviors, shape individual's understanding towards health behaviors [275].

Social media, such as Twitter, can serve as a potential data source to characterize the social neighborhood environment. Unlike traditional indicators of neighborhood environment, Twitter indicators reflect an individual's perception and attitude towards the neighborhood environment, as well as an individual's utilization of the neighborhood resources [49]. Twitter data may also collect an individual's reaction to certain topics that are not captured in traditional survey studies due to the pressure to provide socially desired responses. Compared to existing neighborhood studies that mainly relied on the time-consuming neighborhood audits and expensive survey data collection within limited geographical areas, utilizing Twitter-derived indicators as proxy measures for neighborhood factors provides opportunities to conduct neighborhood studies at the national level economically and to study the impact of geographical factors on the association between neighborhood factors and health outcomes.

Social media platform, such as Twitter, can be used to characterize social neighborhood environment in the US. In manuscript 1, we investigated the relationships between Twitter-derived social neighborhood features and individual

level cardiometabolic outcomes in a nationally representative population. Findings suggested Twitter as a cost-effective data source for public health can be used understand the potential influence of social neighborhood context on cardiometabolic conditions including obesity and hypertension. Researchers may use Twitter as a public health surveillance tool to identify communities with greater risk of cardiometabolic outcomes. Public health practitioners could use Twitter as a platform for health education and social promotion of healthy behaviors aimed at reducing the burden for cardiometabolic outcomes.

6.2 Exposure to ambient air pollution and cardiometabolic outcomes

A substantial body of evidence has suggested that exposure to ambient air pollution is associated with increased risk of developing adverse chronic health outcomes, particularly cardiovascular disease (CVD) and mortality due to CVD [2,208-210]. Possible pathways linking air pollution to CVD morbidity and mortality include oxidative stress, inflammation, endothelial dysfunction and metabolic syndrome [2]. People living with diabetes are at higher risk of developing cardiovascular complications when exposed to air pollution [8,9,211,212]. Prior studies mainly focused on the effect of air pollution in adults living with type II diabetes. The impact of air pollution on CVD outcomes in youth living with type I diabetes is under-investigated.

Youth living with type I diabetes are more likely to live with CVD risk factors and thus having higher risk of CVD outcomes. Maintaining euglycemic blood glucose is an important task for people living with diabetes and failure to maintain a normal

range of blood glucose could lead to higher risks of developing diabetes-related cardiovascular complications [80-84,218,219].

As a highly vulnerable population, youth living with type I diabetes may have early CVD functional changes since prior studies suggested arterial stiffness was frequently found in people with diabetes and in people living with metabolic syndrome [105,106].

Manuscript 2 and manuscript 3 focused on the effects of exposure to ambient air pollution and cardiometabolic outcomes in youth living with type I diabetes, an under-investigated but highly vulnerable population. Manuscript 2 assessed long-term exposure to air pollution and glucose homeostasis in a cross-sectional design. Findings suggested long-term exposure to air pollution including $PM_{2.5}$, residential distance to highly trafficked roads and annual average daily traffic count may be associated with glucose homeostasis in youth living with type I diabetes in SC, CO and WA. Reducing exposure to ambient air pollution may have implications in prevention of CVD conditions for youth living with type I diabetes in certain areas. Differences in demographics and socioeconomic status may explain the differential responses to air pollution across study sites. Future studies may focus on the biological pathways linking air pollution and glycemic control in youth living with type I diabetes. The role of demographics, such as race/ethnicity, in the association between exposure to ambient air pollution and glucose homeostasis need to be further investigated.

Manuscript 3 assessed acute exposure to air pollution and subclinical CVD markers in a repeated measures design. Findings suggested changes in $PM_{2.5}$ on the

day prior to assessment may be associated with AIx. Acute exposure to ambient air pollution may not be associated with PWV and BrachD in this population of youth with type I diabetes living in OH. We expected different results from 3 subclinical CVD markers since AIx, PWV and BrachD measured arterial stiffness differently. The biological pathways linking acute exposure to air pollution and the three CVD markers may be different. Future studies with larger sample size and extensive information on medical profile are needed to validate our results. The effects of air pollution on vascular alterations needs to be further studied to refute or confirm our results in other populations and geographic areas with other air pollution mixtures. In general, both two studies found some evidence that exposure to ambient air pollution may be associated with cardiometabolic outcomes in youth living with type I diabetes. Youth living with type I diabetes have disproportionally higher risk of developing CVD. Reducing exposure to ambient air pollution may be beneficial in early prevention of cardiovascular conditions for this highly susceptible population.

6.3 Overall conclusion

In summary, this dissertation found some evidence between Twitter-derived social neighborhood characteristics and cardiometabolic outcomes in a nationally representative sample and found some evidence linking exposure to air pollution and cardiometabolic outcomes in youth living with type I diabetes. Reducing social stressors and reducing hazardous physical environmental factors may decrease the risk of cardiometabolic outcomes, providing possible directions for CVD prevention for public health practitioners.

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