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RESEARCH ARTICLE

Associations of air pollution with peripheral inflammation and cardiac autonomic physiology in children

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Abstract

Climate change-related disasters have drawn increased attention to the impact of air pollution on health. 122 children ages 9–11 years old, $M(SD)$ = 9.91(.56), participated. Levels of particulate matter (PM2.5) near participants' homes were obtained from the Environmental Protection Agency. Cytokines were assayed from 100 child serum samples: IL-6, IL-8, IL-10, and TNFα. Autonomic physiology was indexed by pre-ejection period (PEP), respiratory sinus arrhythmia (RSA), cardiac autonomic regulation (CAR), and cardiac autonomic balance (CAB). IL-6 was positively related to daily PM2.5 (r = .26, p = .009). IL-8 was negatively associated with monthly PM2.5 (r = −.23, p = .02). PEP was positively related to daily (r = .29, p = .001) and monthly PM2.5 (r = .18, p = .044). CAR was negatively associated with daily PM2.5 (r = −.29, p = .001). IL-10, TNFα, RSA, and CAB were not associated with PM2.5. Air pollution may increase risk of inflammation in children.

KEYWORDS
air pollution, cardiac autonomic regulation, children, inflammation, interleukin-6

1 | INTRODUCTION

Climate change, increasing prevalence of wildfires, and environmental justice efforts have drawn increased attention to the impact of air pollution on children's health. Global climate change has led to worsening of overall air quality and episodes of high air pollution due to wildfires (Kan et al., 2012; Liu et al., 2016). Furthermore, the COVID-19 pandemic has exacerbated the impacts of air pollution on human health, as one study of 3,089 counties in the United States found that counties with higher air pollution had higher COVID-19 mortality rates, adjusting for confounders (Wu et al., 2020). Children in particular are at increased risk of negative health effects due to air pollution, although they have only recently been studied in relation to these environmental phenomena (Currie & Deschênes, 2016; Leffers, 2021; Trentacosta & Mulligan, 2020). Biologically, children's developing organs and systems are highly susceptible to the effects of air pollution (Salvi, 2007). Children's vulnerability and under-representation in studies of air pollution motivated the current study. We examined associations between air pollution and children's physiology, including peripheral inflammation and autonomic nervous system (ANS) physiology, as both have links to lifelong health outcomes.

1.1 | Air pollution and children's health

The impact of environmental contaminants, such as air pollution, on children's development has become a concern of developmental researchers (Trentacosta et al., 2016). Burgeoning research and calls to action aim to elucidate how contaminants may impact later development and long-term health (Trentacosta & Mulligan, 2020). In adults, air pollution exposure has been linked to an increased risk of physical health problems with inflammatory underpinnings, such as asthma and heart disease (Brunekeef & Holgate, 2002). Children may be especially susceptible to the effects of air pollution, given that, compared to adults, they have a higher intake of contaminants and greater lung surface area relative to their body weight (Salvi, 2007; Schwartz, 2004). Air pollution consists of pollutants and particulates. One index of air pollution is fine particulate matter (PM2.5), which reflects fine particles in the air that are 2.5 microns or less in width. These fine particles which are emitted into the air can penetrate into the lungs and pass into the bloodstream, subsequently affecting lung and heart function (Larr & Neidell, 2016). In addition, exposure to pollutants may have a greater influence on lung function and respiratory health in children, because their lungs are not yet fully developed (Esposito et al., 2014).

Previous studies with children have shown significant associations between ambient air pollution and allergic sensitization, respiratory symptoms, ultra-structural cellular changes to children's airways, and lung growth (for a review, see Salvi, 2007). In a large study of over 4,000 children during the first 4 years of life, elevated traffic-related pollution was associated with higher risk of physician-diagnosed asthma and self-reported respiratory illness (ear/nose/throat infections, flu, serious colds; Brauer et al., 2007). In a subgroup of the study ($n = 713$), pollution was associated with an increased prevalence of immunoglobulin E-mediated sensitization to common food allergens (Brauer et al., 2007). In another study, exposure to sulphur dioxide from an oil refinery was associated with reduced lung function and increased airway inflammation in children aged 8–14 years old (Barbone et al., 2019). A large cohort in the UK found that increases in monthly ozone levels were associated with increases in concurrent respiratory treatments in children 2–6 years of age (Beatty & Shimshack, 2014). In youth enrolled in the California Children's Health Study

($N = 6{,}424$), greater exposure to wildfire smoke was associated with an increase in eye and respiratory symptoms, medication use, and physician visits (Künzli et al., 2006). The effects of air pollution on children are thought to depend on developmental timing. That is, similar levels of pollution may have a greater effect earlier in development compared to later (Larr & Neidell, 2016).

Effects of air pollution can arise from pre- and perinatal exposure, with greater levels of air pollution being associated with outcomes including intrauterine mortality, increased preterm birth, and lower birth weights (Bobak et al., 2001; Pereira et al. 1998; Xu et al., 1995). A large birth cohort study of over 5,000 births demonstrated increased air pollutant exposure was associated with lower birth weight, controlling for a variety of social and economic factors (Bobak et al., 2001). Recently, a systematic review of 58 studies, with a total of over 32.7 million births, found an association of air pollution (PM2.5 or ozone) and climate change (heat exposure) with adverse birth outcomes such as preterm birth, low birth weight, and stillbirth (Bekkar et al., 2020). In a large prospective cohort study, infants who lived closer to a major roadway or had higher prenatal exposure to PM2.5 and ozone were at increased likelihood for developmental delays (Ha et al., 2019). This work illustrates the multigenerational process in which environmental contaminants impact child health outcomes (Trentacosta et al., 2016).

1.2 | Air pollution, oxidative stress, and inflammation in children

The biological mechanisms by which air pollution impacts children's health are actively investigated and thought to involve oxidative stress, inflammation, and tissue remodeling (Esposito et al., 2014; Schraufnagel et al., 2019; Schwartz, 2004). Oxidative stress involves an imbalance between reactive oxygen species and the mechanisms that detoxify and repair damage of reactive intermediates, resulting in the breakdown of protective antioxidant mechanisms (Madl et al., 2014). This process also entails pro-inflammatory signaling, setting off a cascade that may affect multiple organ systems (Schraufnagel et al., 2019). Nanoparticles, while much smaller than PM2.5, give rise to inflammation and oxidative stress (Madl et al., 2014). In general, air pollution has been linked to increased inflammation in the body, in both adults and children (Schwartz, 2004), though the specific biological mechanisms by which air pollution increases inflammation are still being uncovered. One mechanism implicates endotoxin, as studies have documented the presence of endotoxin in PM2.5 particulate matter (Heinrich et al., 2003; Xin et al., 2021). Endotoxin is a bacterial product present in our environment and known to be a strong modulator of immune responses, inducing increased production of cytokines such as interleukin-6 (IL-6), tumor necrosis factor alpha (TNFα), and others (Cavaillon, 2018). One study that exposed human cell lines in vitro to PM2.5 samples collected from different locations with varying traffic densities in China has shown that in vitro cytokine production by cells was closely correlated with endotoxin content in the PM2.5 samples (Xin et al., 2021). Consistent with this finding, another study cultured human monocytic cell lines with PM2.5 samples from different sites and different seasons of the year in Mexico City and found higher levels of in vitro cytokine production for samples from the rainy-warm season, which had higher endotoxin content (Manzano-León et al., 2016). More research is needed to examine links between endotoxin content and in vivo production of cytokines and inflammatory responses in humans. In addition to this mechanism, greater exposure to traffic-related air pollutants has been found to be associated with airway inflammation and airway tissue remodeling, indicative of oxidative stress (Berhane et al., 2011; Brown et al., 2012; Esposito et al., 2014).

Markers of systemic inflammation such as IL-6 or C-reactive protein (CRP) have been posited as useful early biomarkers of health in children (Bernard et al., 2019; Doom et al., 2021; Lourenço et al., 2014) and are increasingly being examined in association with air pollution exposure. Some research has begun examining the association between air pollution exposure and inflammation in children. Pilot studies in Mexico City found that children aged 5–7 years old ($N = 35$) with exposure to urban air pollution showed higher concentrations of IL-6, reduced levels of neutrophils, and increased levels of monocytes than children in cities with lower pollution (Calderón-Garcidueñas et al., 2013). An earlier study found that 8-year-old children in Mexico City ($N = 52$) exposed to higher PM2.5 levels had significant increases in inflammatory markers and vasoconstrictors such as TNFα, prostaglandin E2, CRP, interleukin-1β, and endothelin-1, compared to those from a city with low levels of pollutants (Calderón-Garcidueñas et al., 2008). In addition, cumulative levels of PM2.5 were negatively associated with white blood cell count in highly exposed children (Calderón-Garcidueñas et al., 2008). For these children, systemic inflammation has been linked to immunodysregulation, oxidative stress, neuroinflammation, small blood vessel pathology, along with the early signs of Alzheimer's and Parkinson's diseases (Calderón-Garcidueñas et al., 2015). In a study in China, school children who were chronically exposed to pollution had decreased B lymphocyte count and immunoglobulin C3 and C4 levels, and increased monocyte count and CD8+ lymphocyte proportion compared to control children (Li et al., 2019). In a recent study in California, children who were exposed to a nearby wildfire that was associated with increases in PM2.5 exhibited a significant reduction in pro-inflammatory Th1 cells, and a trend towards more wheezing episodes and more asthma exacerbations in those with prior asthma, compared to children exposed to a more limited, controlled fire (Prunicki et al., 2019). Together, these findings suggest that air pollution may impact children's immune functioning. In addition, there are lasting effects of early-life pollutant exposure on inflammatory markers. A cohort study ($N = 670$) of 8-year-old children indicated that increases in exposure to nitrogen dioxide (NO_2) during infancy was associated with a 13.6% increase in IL-6 levels, and a 27.8% increase in interleukin-10 (IL-10) in children with asthma (Gruzieva et al., 2017).

1.3 | Air pollution and autonomic physiology

Greater exposure to air pollutants is also theorized to lead to autonomic imbalance, characterized by reduced parasympathetic nervous system (PNS) and/or increased sympathetic nervous system (SNS) activity at rest (Brook & Rajagopalan, 2021). Physiological profiles of autonomic imbalance are associated with increased risk for disease (e.g., cardiovascular disease; Thayer et al., 2010). This is one potential mechanism that might explain the robust associations between air pollution and cardiovascular morbidity and mortality (Rajagopalan et al., 2018). Several pathways have been proposed to explain how air pollution might influence autonomic activity. At the acute level, pollutants may augment autonomic activity by activating irritant receptors in the lungs, which has been found to lead to increased sympathetic activity in rodents (Rajagopalan et al., 2018). Pollutants can also have direct effects on cardiac ion channels, impacting subsequent cardiac activity (Rajagopalan et al., 2018). At a chronic level, exposure to air pollutants may lead to autonomic imbalance by promoting systemic inflammation, which can upregulate SNS activity (Andersson & Tracey, 2012) or by altering the microbiome and the gut-brain axis (Brook & Rajagopalan, 2021). Further, a recent meta-analysis found that air pollution was associated with an increased risk of childhood obesity (Parasin et al., 2021), which is associated with reduced cardiac indices of PNS activity (Eyre et al., 2014) and can potentiate inflammation

(Hotamisligil, 2006). Importantly, the immune system, the autonomic nervous system, the gut microbiome, and adiposity, are all theorized to be tightly interconnected through bidirectional pathways of influence (Dantzer et al., 2018). Thus, the effects of air pollution on each of these systems may be amplified as they influence one another.

A complete theoretical model for how air pollution may affect the autonomic nervous system (ANS) is still lacking. However, increasing evidence is linking air pollution exposure to individual differences in autonomic activity. Several studies have documented negative associations between exposure to ambient pollutants and resting parasympathetic modulation of cardiac activity, as indexed through heart rate variability (HRV). In a recent meta-analysis of studies of older adults, robust inverse associations were observed between exposure to PM2.5 and several indices of HRV (Wang et al., 2020; but see also contrary evidence in Pope et al., 1999). Relatively fewer studies have tested relations between air pollution and sympathetic activity. In one study, experimental exposure to diesel exhaust pollution led to increased sympathetic activity, as indexed through peripheral muscle sympathetic nerve activity, in adult males (Rankin et al., 2021). One study of children ages 9–11 years observed positive, though non-significant, associations between air concentrations of the metal cadmium and sympathetic activity, as indexed through pre-ejection period (PEP), though no relations were observed between PEP and either lead or mercury (Hill et al., 2021). Another recent study with a youth sample found no associations between neighborhood levels of PM2.5 and either parasympathetic or sympathetic activity at rest, as indexed through HRV and skin conductance level respectively, in 144 adolescents ages 9.5–15.5 years old (Miller et al., 2019).

Importantly, the parasympathetic and sympathetic branches of the ANS do not always act in coordination with one another (Berntson et al., 2008). As such, autonomic imbalance cannot be easily approximated from individual markers of PNS and SNS activity in isolation. Berntson and colleagues developed two basic measures of autonomic space that can be used to understand the simultaneous influence of both ANS branches: (1) cardiac autonomic balance (CAB) and (2) cardiac autonomic regulation (CAR; Berntson et al., 2008). CAB is a measure of the relative influence of the PNS and SNS on heart activity, with larger values reflecting greater parasympathetic and less sympathetic influence. CAR is a measure of the combined influence of PNS and SNS over heart activity, with larger CAR values indicating greater overall autonomic regulation of heart activity. In adults, both of these measures have been linked to health outcomes: lower CAB was associated with concurrent diabetes, and lower CAR was associated with a history of a heart attack (Berntson et al., 2008). The only study we are aware of to test relations between air pollution and a measure of autonomic space found no significant associations between air pollution and autonomic imbalance at rest but did find that higher neighborhood PM2.5 levels were associated with greater reductions in autonomic balance during an acute stressor (Miller et al., 2019).

In sum, theoretical models propose autonomic imbalance as a potential biological mediator of the link between air pollution and health. However, the literature has been almost entirely limited to the use of PNS and SNS measures in isolation from one another with a predominant focus on the PNS. In addition, very few studies have investigated links between air pollution and ANS functioning in youth samples.

1.4 | Present study

In the present study, we examined the association between air pollution, indexed by PM2.5, and serum measures of peripheral inflammation and autonomic nervous system physiology in children. Additionally, we aimed to examine the extent to which these associations

are independent of the effects of family income, child age, sex, and body mass index (BMI). Families' addresses were recorded and used to obtain measures of air pollution for their neighborhood on the day of their laboratory visit, using records from the Environmental Protection Agency. Blood samples were collected from participants after arrival to the research laboratory and serum was assayed for four cytokines: IL-6, interleukin-8 (IL-8), IL-10, and TNFα. ANS data was collected during a resting baseline period and included the measures of respiratory sinus arrhythmia (RSA), pre-ejection period (PEP), CAR, and CAB. The goal of this study was to examine biomarkers that may explain links between air pollution and children's health. Specifically, we examined peripheral inflammation and ANS physiology as possible correlates of exposure to air pollution in children.

2 | METHODS

2.1 | Participants

The study involved 130 participants who lived in the Greater Sacramento area for which air pollution data was available. Of these, 122 participants had ANS data ($n = 8$ participants were missing PEP or RSA data due to: excessive, uncleanable noise ($n = 4$), ECG technical malfunction ($n = 3$), or missing data file ($n = 1$)). Of the 130 participants with air pollution data, 100 participants provided a blood sample. Missing blood samples were due to child refusal ($n = 12$), phlebotomist unavailability ($n = 17$), and insufficient blood ($n = 1$). Therefore, 100 participants have both inflammation and air pollution data.

Demographics for the 122 participants with ANS data were as follows: children were 9–11 years old ($M = 9.91$, $SD = .56$); 56 participants identified as female (46%) and 66 identified as male (54%). Regarding race/ethnicity, 53.2% of participants identified as White (Non-Hispanic), 26.2% identified as biracial or multiracial (or multiethnic), 12.3% identified as White-Hispanic, 5% identified as Hispanic/Latinx, 2.5% identified as Asian, .8% identified as Native American/Alaska Native. Median household income was \$125,500 ($SD = 56{,}000$). Median income adjusted for family size was \$31,250 ($SD = 18{,}150$). The majority of participating parents (43.22%) had a 4-year college degree, .84% had less than a high school diploma, 12.71% had completed high school, 12.71% completed some college or had a 2-year college degree, 21.20% had a graduate degree, and 9.32% had a doctoral degree.

Demographics for the 100 participants with inflammation data were as follows: participants were 9–11 years old ($M = 9.91$ years old, $SD = .57$); 43% identified as female and 57% identified as male. Regarding race/ethnicity, 50% of participants identified as White (Non-Hispanic), 28% were biracial or multiracial (or multiethnic), 12% identified as White-Hispanic, 4% identified as Asian, 3% identified as Hispanic/Latinx, 1% identified as Native American/Alaska Native, and 1% identified as Black/African American; ($n = 1$ was missing race data). Median household income was \$125,000 ($SD = 58{,}000$). Median income adjusted for family size was \$31,250 ($SD = 20{,}500$). The majority of participating parents had a 4-year college degree (42%), 1% had less than a high school diploma, 13% had completed high school, 14% had completed some college of had a 2-year college degree, 23% had a graduate degree, and 7% had a doctoral degree.

Participants were screened for eligibility via a phone interview with a parent. Participant exclusion criteria included having a chronic health condition, developmental disorder, a speech or language disorder that would prohibit study activities, or a current psychotropic or steroid medication regimen. In addition, if participants had been ill in the past two weeks, study visits were scheduled two weeks after their child's symptoms subsided.

2.2 | Procedure & measures

Children arrived at the laboratory with their parent or guardian to participate in a larger study examining the social buffering of stress and psychobiological functioning in children (Alen et al., 2020; Parenteau et al., 2020). As part of the larger study, participants were asked to provide two blood samples, one at baseline and the second sample later in the study session (100 min after undergoing a social stressor or control condition, Parenteau et al., 2020). The study data were collected between August 2017 and September 2019. Air pollution has not been previously analyzed in any publications from this study. For the current study, only the baseline blood sample was used in analyses to maximize sample size. Parents and children completed questionnaires prior to and following the first blood sample. Height and weight of the children were recorded in the laboratory using a mechanical beam scale and used to compute BMI.

2.3 | Blood sample collection: cytokine measures

Baseline blood samples were collected from participants 30 min after arrival to the research laboratory and serum was assayed for four cytokines, IL-6, IL-8, IL-10, and TNFα. The first blood draw occurred after arrival at the laboratory to allow children to acclimate to the novel environment, before administration of the experimental study protocol (greater detail can be found in Alen et al., 2020 and Parenteau et al., 2020). Blood draws were performed by trained and certified phlebotomists with previous experience in pediatric samples. Further detail regarding blood draws can be found in Alen et al., 2020.

Cytokine assays were conducted in the Foundations of Health Research Center at Northwestern University using the following procedure: serum aliquots were thawed, then they were assayed in triplicate for the following cytokines: IL-6, IL-8, IL-10, and TNFα. The assays were performed with a custom four-plex assay on the Simple-Plex Platform (Protein Simple, San Jose, CA). This integrated system conducts automated fluorescence immunoassays using disposable microfluidic cartridges. It yields data with high levels of accuracy and reproducibility (Aldo et al., 2016). In the present study, mean intra-assay coefficients of variability for triplicate runs were: 4.89% for IL-6, 4.70% for TNFα, 3.41% for IL-10, and 2.33% for IL-8. Mean inter-assay coefficients of variability were: 6.36% for IL-6, 5.84% for TNFα, 7.01% for IL-10, and 8.53% for IL-8.

Outliers (defined as 3 *SD* above or below the mean) in IL-6, IL-8, and IL-10 were Winsorized to the closest value within 3 *SD* of the mean existing in the data. This included 1 outlier value for IL-6, 2 outliers for IL-8, and three outliers for IL-10. TNFα did not exhibit any outliers and therefore did not need to be Winsorized. Consistent with common practice, variables were then natural log-transformed to ensure a normal distribution. We log-transformed TNFα to be consistent with the other cytokine analyses. Across all analyses, results were consistent when using untransformed (not log-transformed) inflammatory markers and when Winsorized to 4 *SD* rather than 3 *SD* from the mean (log or untransformed).

2.4 | Autonomic nervous system (ANS) physiology data collection

2.4.1 | Respiratory sinus arrhythmia

Respiratory sinus arrhythmia (RSA) was used as a marker of parasympathetic nervous system (PNS) modulation of cardiac activity (Laborde et al., 2017). RSA was collected with a

MindWare ambulatory electrocardiogram (ECG; MindWare, Westerville, OH), using three silver electrodes attached to the child's chest in Einthoven's triangle configuration. RSA data were collected during a resting 5-min baseline period, as part of a larger ECG data collection procedure (Alen et al., 2020, 2022). The current analysis focused on the baseline period, during which children were in a seated position on a comfortable couch in the company of a parent or caregiver. Participants were instructed to attempt to relax, refrain from speaking to their parent, and not engage in any activity for the 5-min duration. Interbeat Interval data were calculated using an automated algorithm in the MindWare Biolab acquisition software. A high-frequency band pass filter set at 0.23–0.50 Hz was used to correspond to the average breathing rate of this age group (Shader et al., 2018). Sampling rate was set at 500 Hz. R-peaks were inspected and cleaned for artifacts by trained researchers using MindWare Heart Rate Variability software (version 3.1.5). For further details regarding the RSA data processing, please see (Alen et al., 2020, 2022). RSA during the individual 60-s epochs were then averaged together, producing a mean resting RSA value.

2.4.2 | Pre-ejection period

Pre-ejection period (PEP) was used as a marker of sympathetic nervous system (SNS) activity, where shorter PEP reflects greater SNS modulation of cardiac activity (Berntson et al., 2004). We obtained PEP from cardiac impedance data using a MindWare ambulatory device (MindWare, Westerville, OH). We attached four silver electrodes with a 7% chloride wet gel to the child's back and chest in the standard configuration (Sherwood et al., 1990), including two on the back and two on the chest. For further details about the impedance data, see (Alen et al., 2020). The current analysis focused on a 5-min resting baseline measure of PEP. In a robustness check, results were identical in direction and significance when including or when excluding five participants with usable yet noisy data.

2.4.3 | Cardiac autonomic balance and regulation

Cardiac autonomic balance (CAB) and cardiac autonomic regulation (CAR) were calculated as the relative contribution (difference) of PNS to SNS modulation of cardiovascular activity, and the combined contribution of PNS and SNS modulation of cardiovascular activity, respectively, using formulas from Berntson et al. (2008). RSA reflects parasympathetic modulation of cardiovascular activity whereas PEP reflects sympathetic modulation of cardiovascular activity. Because the two indices were scaled differently, we z-scored the values (zRSA and zPEP). CAB was calculated as: CAB = zRSA – (–zPEP), and CAR was calculated as: CAR = zRSA + (–zPEP), as previously recommended by Berntson et al. (2008). Due to missingness in RSA and PEP, as described above, CAB and CAR values were available for $n = 122$ participants who also had air pollution data available.

2.5 | Air pollution variables

To obtain air pollution values, we used the Environmental Protection Agency (EPA)'s Air Quality System Data Mart database which hosts various measures of air quality in multiple cities across the United States for each day of the year. Specifically, we used pre-generated data files maintained by the EPA which have daily air quality summary information from

each outdoor monitor in the country. Data can be downloaded from: https://aqs.epa.gov/aqsweb/airdata/download_files.html. Files were downloaded for the years the study was conducted (2017–2019). The EPA database included air quality measures from two types of monitors: devices using the Federal Reference Method (FRM), which have undergone rigorous testing and analysis, and devices using the Federal Equivalent Method (FEM/non-FRM), which met compliance for the National Ambient Air Quality Standards (NAAQS; Hall et al., 2014). For the present analyses, FRM monitor values were used because FRM monitors were closer in distance to participants' homes ($M = 6.72$ miles, $SD = 4.36$) than non-FRM monitors ($M = 7.98$ miles, $SD = 8.34$).

The EPA files contain the following variables of interest: arithmetic mean (the average concentration of PM2.5) and daily air quality index (AQI). In order to determine which EPA monitors were closest to a participant's current residential address, the EPA ArcGIS map application was used (https://epa.maps.arcgis.com/apps/webappviewer/index.html). For each participant session date, we retrieved the daily AQI and average PM2.5 concentration for the monitor in the closest available location to the family's current place of residence. Monthly PM2.5 was calculated by averaging the PM2.5 levels for the preceding 30 days.

AQI is a measure of daily air quality calculated from levels of ground-level ozone, particulate matter, carbon monoxide, sulfur dioxide, and nitrogen dioxide. The higher the AQI, the more health effects people may experience (AirNow.gov, U.S. EPA, 2016). AQI is a unitless summary value of six different criteria air pollutants. One of these criteria pollutants is PM2.5, emitted from power plants, industrial processes, vehicle tailpipes, wood stoves, and wildfires (AirNow.gov, U.S. EPA, 2016). PM2.5 is an important indicator of air pollution to understand when certain air conditions are hazardous for health. The smaller the particles, the deeper the pollutants can move into the lungs, with effects being more serious especially in children or elderly populations (Oehha.ca.gov, CA OEHHA, 2021).

2.5.1 | Daily PM2.5

Daily PM2.5 was the "daily arithmetic mean" for the monitor closest to participants' home address, on the day the participant visited the laboratory. In cases when PM2.5 was not available for that day, values from the previous day(s) were used. Thirty participants' values are from the day prior to the study visit, with 21 participants' values being from 2 to 5 days prior to the study visit. Daily PM2.5 values were Winsorized to 3 *SD* above the mean, with 1 outlier (149.9) being Winsorized to the highest value within 3 *SD*, 33.9. Note: this participant had a session during the Camp Fire in November 2018 (approximately 100 miles from the laboratory). We Winsorized instead of excluding this data point because the increased PM2.5 for this participant reflects a true increase in air pollution. Compared to state averages, the sample's mean daily PM2.5 (14.42) was not significantly different than the state of California's mean in 2017 (10.33; $p = .12$). However, the sample mean daily PM2.5 (9.27) was less than the state average (11.39; $p = .001$) in 2018 and 2019 (sample = 5.13, state = 7.74; $p = .02$). Compared to national averages, the sample's 2017 mean daily PM2.5 was significantly higher than the national average (8.06; $p = .03$). In 2018, the sample's mean daily PM2.5 was not significantly different than the national average, and was significantly lower than the national average in 2019 (sample = 5.13, national = 7.63; $p = .02$).

2.5.2 | Monthly PM2.5

Monthly concentrations of PM2.5 were calculated from the 30 days prior to the date of data collection. For example, if a participant visited the laboratory on February 12, the

arithmetic means of PM2.5 were averaged between January 12 and February 12 to arrive at an average value of PM2.5 exposure in the month prior to study participation. Monthly PM2.5 values were Winsorized to 3 *SD* from the mean, resulting in three values being Winsorized to the closest value within 3 *SD* from the mean (24.49).

2.5.3 | Wildfire season

As noted, a participant with a high PM2.5 value participated in the research study during the Camp Fire (November 2018). This prompted us to more closely examine whether nearby wildfires may impact levels of PM2.5 in the study sample. We created a binary variable coded 0 or 1, with 1 representing a wildfire month (October 2017; July, August, November 2018; September 2019). In total, 27 (out of 122) participants came into the lab during wildfire months. The majority of these participants ($n = 21$) came to the lab in July or August 2018 while the Mendocino Complex Fire was active, approximately 100 miles from the laboratory. Wildfire months showed a trend towards having higher levels of monthly PM2.5 than non-wildfire months (M wildfire = 10.9, M non-wildfire = 8.9, $t(40) = 1.83$, $p = .075$), and wildfire month was not related to differences in mean daily PM2.5 ($t(32) = 1.41$, $p = .17$). Results were similar in the sub-sample of participants ($n = 100$) with inflammation data.

2.6 | Data analysis plan

Statistical analyses were run in RStudio version 1.3.959, running R version 4.0.0 (R Core Team, 2020; RStudio Team, 2020). First, bivariate Pearson correlations were calculated between the main study variables. The main analyses involve individual linear regressions in which inflammation and ANS physiology were regressed onto air pollution, unadjusted for covariates. Next, multiple regression analyses were conducted to include covariates in each model (age, sex, BMI, and income). Sensitivity analyses were conducted to determine whether there were differences in findings if AQI was used as a predictor instead of PM2.5.

3 | RESULTS

3.1 | Bivariate correlations

3.1.1 | Air pollution and inflammation

Pearson correlations between study variables are reported in Table 1. IL-6 was significantly positively correlated with daily PM2.5, $r(98) = .26$, $p = .009$, and daily AQI, $r(92) = .27$, $p = .009$, but was not significantly correlated with monthly PM2.5, $r(97) = .17$, $p = .088$. IL-10 and TNFα were not significantly correlated with measures of air pollution (p's > .43). IL-8 was significantly negatively correlated with monthly PM2.5, $r(97) = -.23$, $p = .023$. However, IL-8 was not significantly correlated with daily PM2.5 or AQI (p's > .24).

3.1.2 | Air pollution and autonomic nervous system

CAR and CAB

CAR was significantly negatively correlated with daily PM2.5, $r(120) = -.29$, $p = .001$, daily AQI, $r(110) = -.27$, $p = .004$, and monthly PM2.5, $r(120) = -.23$, $p = .01$. CAB was not correlated with measures of air pollution (p's > .18).

TABLE 1 Means, Standard Deviations, and Pearson Correlations

Variable	*M*	*SD*	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1. Daily PM2.5	9.00	6.36																
2. Daily AQI	36.18	19.60	.98**															
3. Monthly PM2.5	9.35	4.90	.56**	.56**														
4. lnIL-6	0.08	0.55	.26**	.27**	.17													
5. lnIL-8	1.91	0.27	−.12	−.10	−.23*	−.03												
6. lnIL-10	0.80	0.32	.01	−.01	−.05	.22*	.08											
7. lnTNFα	1.79	0.22	−.06	−.08	−.01	.13	.08	.38**										
8. CAR	−0.03	1.37	−.29**	−.27**	−.23*	−.02	.10	−.03	−.09									
9. CAB	0.06	1.44	.12	.10	.04	.07	−.03	.21*	.20	−.03								
10. RSA	6.34	1.21	−.11	−.12	−.13	.04	.08	.12	.07	.68**	.71**							
11. PEP	80.23	10.14	.29**	.27**	.18*	.07	−.09	.17	.20	−.70**	.73**	.04						
12. Sex	0.54	0.50	−.08	−.11	.01	−.00	−.06	.07	.14	.12	.05	.12	−.05					
12. Age	9.91	0.56	.10	.12	−.02	.01	.09	.05	−.02	.04	.09	−.03	−.01					
14. Annual Income ($)	125608	56166	.11	.13	.13	.12	.17	−.15	−.13	.02	−.05	−.03	−.05	−.08	−.01			
15. Race	0.34	0.48	−.01	−.04	.05	−.08	−.04	.01	.11	−.27**	.04	−.16	.21*	−.23**	.05	−.32**		
16. BMI	17.63	2.83	−.02	−.06	.02	.32**	.06	.15	−.01	−.14	.09	−.03	.09	.16	−.01	.11	−.03	.07

Note. PM2.5 = particulate matter, AQI = Air Quality Index, lnIL-6 = log-transformed interleukin-6, lnIL-8 = log-transformed interleukin-8, lnIL-10 = log-transformed interleukin-10, lnTNFα = log-transformed tumor necrosis factor alpha, CAR = cardiac autonomic regulation, CAB = cardiac autonomic balance, RSA = respiratory sinus arrhythmia, PEP = pre-ejection period, BMI = body mass index. Sex was coded as a binary variable, with female = 0 and male = 1. Race was coded as a binary variable, with white coded as 0 and races other than white coded as 1. Correlations are reported on a sample size of 122 unless they involve inflammation variables, in which case $n = 100$. * $p < .05$. ** $p < .01$

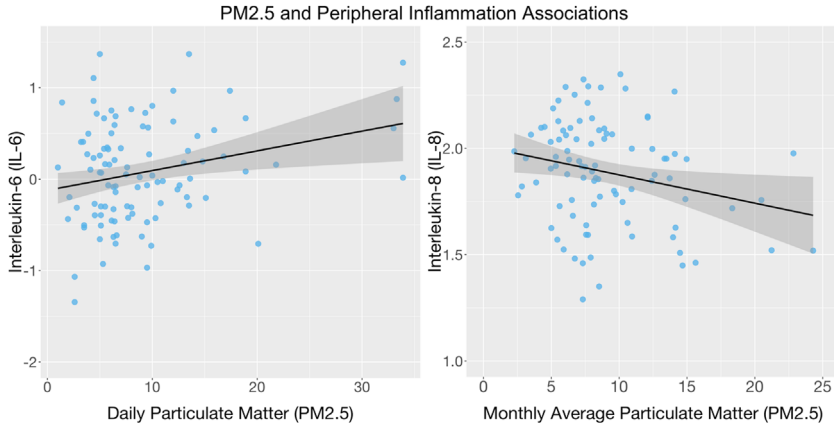

FIGURE 1 Associations between air pollution (PM2.5) and peripheral inflammation. This figure illustrates the associations between PM2.5 and IL-6 (left) and IL-8 (right). Regression lines are in black, with the gray shaded area representing the 95% confidence interval.

PEP and RSA

In an exploratory analysis, longer PEP was correlated with higher daily PM2.5, $r(120) = .29$, $p = .001$, and monthly PM2.5, $r(120) = .18$, $p = .044$. RSA was not correlated with daily or monthly PM2.5 (p's $> .14$).

Of note, daily PM2.5 and daily AQI were highly correlated (due to PM2.5 contributing to AQI), $r(110) = .98$, $p < .0001$. For the remaining analyses, measures of PM2.5 were used, as these quantifiable concentrations have been strongly linked to health outcomes. Sensitivity analyses were conducted to determine if any differences emerge when using AQI as the air pollution metric. In addition, monthly PM2.5 was significantly correlated with daily PM2.5, $r(97) = .53$, $p < .0001$, and daily AQI, $r(92) = .53$, $p < .0001$.

3.1.3 | Monitor distance

To examine if there was any spatial variability in the PM2.5 concentrations in our sample, monitor distance from a participant's home was considered. Monitor distance was calculated using the point-to-point distance between a participant's home address and the nearest FRM monitor address. Monitor distance from the home was not correlated with daily PM2.5, $r(120) = -.12$, $p = .18$, or monthly PM2.5, $r(120) = -.01$, $p = .89$. Therefore, levels of PM2.5 did not differ on average for participants who lived closer or further away from a monitor.

3.2 | Regression analyses

3.2.1 | Air pollution and peripheral inflammation

To further examine the significant positive association between air pollution (daily PM2.5) and IL-6 ($\beta = .26$, $p = .009$), a linear regression was conducted, which explained 6.8% of the variance in IL-6 ($R^2 = .068$). This model is illustrated in Figure 1. To control for covariates, a multiple regression model including age, sex, family income, and BMI was conducted. The association remained significant when adjusting for these covariates ($\beta = .27$, $p = .005$). In

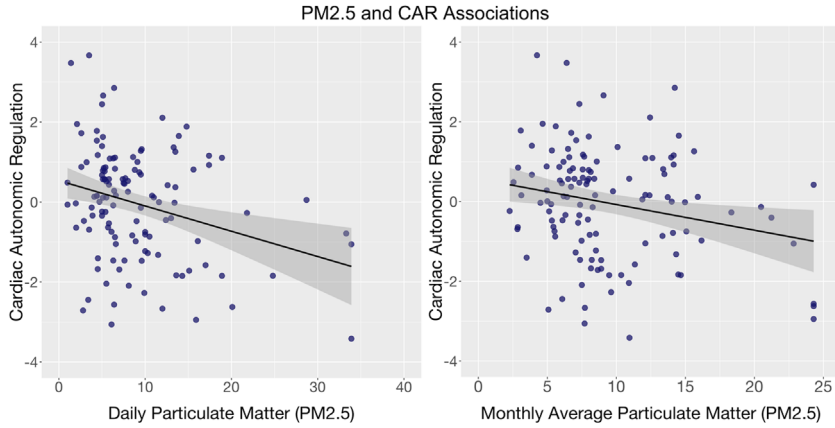

FIGURE 2 Associations between air pollution (PM2.5) and cardiac autonomic regulation (CAR). This figure illustrates the associations between PM2.5 and CAR. Regression lines are in black, with the gray shaded area representing the 95% confidence interval.

the model, BMI explained 10.6% of the variance in IL-6; PM2.5 explained 6.85% of the variance in IL-6, independently of BMI and the other covariates. Overall, this model explained 19% of the variance in IL-6 ($R^2 = .189$).

To further examine the significant negative association between monthly air pollution (monthly PM2.5) and IL-8 ($\beta = -.23$, $p = .02$), a linear regression was conducted, which explained 5% of the variance in IL-8 ($R^2 = .051$). A multiple regression including covariates was conducted, and monthly PM2.5 was significantly associated with IL-8 ($\beta = -.23$, $p = .005$) with the inclusion of covariates in the model. Daily PM2.5 and monthly PM2.5 were not significantly associated with IL-10 or TNFα in models with or without covariates (p's > .52). Sensitivity analyses showed that the associations with inflammation (IL-6, IL-8) and air pollution were consistent when using daily PM2.5 or daily AQI as a measure of air pollution. All inflammation regression analyses with daily values of PM2.5 can be found in Table 2 and regressions with monthly values are in Table 3.

3.2.2 | Air pollution and autonomic nervous system

CAR and CAB

To examine the negative association between daily air pollution values and CAR, a linear regression was conducted for CAR and daily PM2.5 ($\beta = -.29$, $p = .001$), explaining 8.5% of the variance in CAR ($R^2 = .085$). This model is illustrated in Figure 2. To control for covariates, a multiple regression model including age, sex, family income, and BMI was conducted, and explained 13.6% of the variance in CAR ($R^2 = .136$). In the model, daily PM2.5 was a significant predictor of CAR ($\beta = -.30$, $p = .001$), and explained 7.8% of the variance in CAR. None of the covariates significantly predicted CAR. Next, a linear regression model was conducted to examine the association between CAR and monthly PM2.5 ($\beta = -.23$, $p = .01$), which explained 5% of the variance in CAR ($R^2 = .05$). A multiple regression model including covariates was conducted, explaining 10% of the variance in CAR ($R^2 = .096$). The association between CAR and PM2.5 remained significant when adjusting for covariates ($\beta = -.22$, $p = .02$). In the covariate model, PM2.5 explained 4.6% of the variance in CAR. Daily PM2.5 and monthly PM2.5 were not significantly associated with CAB. Sensitivity analyses showed that the associations between air pollution and CAR or CAB were

TABLE 2 Regression Analyses: Daily Air Pollution and Peripheral Inflammation

	Predictor	*b*	*b* 95% CI [LL, UL]	*beta*	*beta* 95% CI [LL, UL]	*SE*	*p*	Fit
IL-6 Model								R^2 = .068** 95% CI[.00,.18]
	Intercept	−0.12	[−0.30, 0.06]			0.10	.19	
	DailyPM2.5	0.02**	[0.01, 0.04]	0.26	[0.07, 0.45]	0.008	.009**	
IL-6 Covariate Model								R^2 = .189** 95% CI[.03,.29]
	Intercept	−0.74	[−2.64, 1.16]			0.96	.44	
	DailyPM2.5	0.02**	[0.01, 0.04]	0.27	[0.08, 0.47]	0.08	.005**	
	BMI	0.07**	[0.03, 0.10]	0.34	[0.15, 0.53]	0.18	.001**	
	Age	−0.07	[−0.26, 0.12]	−0.07	[−0.26, 0.12]	0.09	.46	
	Sex	0.06	[−0.15, 0.26]	0.05	[−0.14, 0.24]	0.11	.60	
	Income	0.00	[−0.00, 0.00]	0.09	[−0.10, 0.28]	0.00	.38	
IL-8 Model								R^2 = .013 95% CI[.00,.09]
	Intercept	1.95**	[1.86, 2.04]			0.04	.001**	
	DailyPM2.5	−0.00	[−0.01, 0.00]	−0.12	[−0.31, 0.08]	0.004	.25	
IL-8 Covariate Model								R^2 = .077 95% CI[.00,.15]
	Intercept	1.07*	[0.10, 2.05]			0.49	.03*	
	DailyPM2.5	−0.01	[−0.01, 0.00]	−0.16	[−0.37, 0.04]	0.004	.11	
	BMI	0.00	[−0.02, 0.02]	0.02	[−0.19, 0.22]	0.009	.88	
	Age	0.08	[−0.02, 0.17]	0.17	[−0.04, 0.37]	0.05	.11	
	Sex	−0.03	[−0.14, 0.08]	−0.06	[−0.26, 0.14]	0.05	.55	
	Income	0.00	[−0.00, 0.00]	0.20	[−0.01, 0.40]	0.00	.06	

(Continues)

TABLE 2 (Continued)

	Predictor	*b*	*b* 95% CI [LL, UL]	*beta*	*beta* 95% CI [LL, UL]	*SE*	*p*	Fit
IL-10 Model								R^2 = .000 95% CI[.00,.03]
	Intercept	0.79**	[0.68, 0.90]			0.05	.000**	
	DailyPM2.5	0.00	[−0.01, 0.01]	0.01	[−0.19, 0.21]	0.005	.91	
IL-10 Covariate Model								R^2 = .051 95% CI[.00,.11]
	Intercept	0.46	[−0.73, 1.65]			0.60	.45	
	DailyPM2.5	0.00	[−0.01, 0.01]	0.03	[−0.17, 0.24]	0.10	.76	
	BMI	0.02	[−0.01, 0.04]	0.16	[−0.04, 0.36]	0.01	.13	
	Age	0.01	[−0.11, 0.13]	0.01	[−0.19, 0.22]	0.06	.89	
	Sex	0.04	[−0.09, 0.17]	0.07	[−0.14, 0.27]	0.07	.52	
	Income	−0.00	[−0.00, 0.00]	−0.14	[−0.34, 0.07]	0.000	.19	
TNFα Model								R^2 = .004 95% CI[.00,.06]
	Intercept	1.81**	[1.74, 1.89]			0.03	.000**	
	DailyPM2.5	−0.00	[−0.01, 0.00]	−0.06	[−0.26, 0.14]	0.003	.52	
TNFα Covariate Model								R^2 = .032 95% CI[.00,.07]
	Intercept	1.88**	[1.04, 2.72]			0.42	.000**	
	DailyPM2.5	−0.00	[−0.01, 0.01]	−0.04	[−0.25, 0.17]	0.003	.68	
	BMI	−0.00	[−0.02, 0.02]	−0.00	[−0.21, 0.20]	0.008	.97	
	Age	−0.00	[−0.09, 0.08]	−0.01	[−0.22, 0.20]	0.04	.91	
	Sex	0.05	[−0.04, 0.15]	0.12	[−0.08, 0.33]	0.05	.25	
	Income	−0.00	[−0.00, 0.00]	−0.10	[−0.31, 0.10]	0.00	.33	

Note. A significant *b*-weight indicates the beta-weight. *b* represents unstandardized regression weights. *beta* indicates the standardized regression weights. *LL* and *UL* indicate the lower and upper limits of a confidence interval, respectively. *SE* indicate the standard error of an estimate. IL-6 = interleukin-6, IL-8 = interleukin-8, IL-10 = interleukin-10, TNFα = tumor necrosis factor alpha, PM2.5 = particulate matter. Analyses in the table were conducted using a sample of 100 participants.* $p < .05$. ** $p < .01$.

TABLE 3 Regression Analyses: Monthly Air Pollution and Peripheral Inflammation

	Predictor	*b*	*b* 95% CI [LL, UL]	*beta*	*beta* 95% CI [LL, UL]	*SE*	*p*	Fit
IL-6 Model								R^2 = .030 95% CI[.00,.12]
	Intercept	−0.10	[−0.32, 0.13]			0.11	.39	
	Monthly PM2.5	0.02	[−0.00, 0.04]	0.17	[−0.02, 0.37]	0.01	.08	
IL-6 Covariate Model								R^2 = .139* 95% CI[.01,.23]
	Intercept	−1.25	[−3.20, 0.71]			0.98	.21	
	Monthly PM2.5	0.02	[−0.00, 0.04]	0.15	[−0.04, 0.34]	0.01	.13	
	BMI	0.06**	[0.02, 0.10]	0.32	[0.12, 0.51]	0.02	.002**	
	Age	−0.01	[−0.19, 0.18]	−0.01	[−0.20, 0.19]	0.09	.94	
	Sex	0.04	[−0.17, 0.26]	0.04	[−0.15, 0.23]	0.11	.69	
	Income	0.00	[−0.00, 0.00]	0.11	[−0.09, 0.30]	0.00	.29	
IL-8 Model								R^2 = .051* 95% CI[.00,.15]
	Intercept	2.02**	[1.91, 2.13]			0.05	.000**	
	Monthly PM2.5	−0.01*	[−0.02, −0.00]	−0.23	[−0.42, −0.03]	0.004	.02*	
IL-8 Covariate Model								R^2 = .105 95% CI[.00,.19]
	Intercept	1.30**	[0.34, 2.26]			0.48	.008**	
	Monthly PM2.5	−0.01*	[−0.02, −0.00]	−0.23	[−0.43, −0.04]	0.005	.02*	
	BMI	0.00	[−0.02, 0.02]	0.04	[−0.16, 0.23]	0.01	.72	
	Age	0.06	[−0.04, 0.15]	0.12	[−0.08, 0.32]	0.05	.22	
	Sex	−0.03	[−0.13, 0.08]	−0.05	[−0.25, 0.15]	0.05	.64	
	Income	0.00*	[0.00, 0.00]	0.20	[0.00, 0.40]	0.000	.04*	

(Continues)

TABLE 3 (Continued)

	Predictor	*b*	*b* 95% CI [LL, UL]	*beta*	*beta* 95% CI [LL, UL]	*SE*	*p*	Fit
IL-10 Model								R^2 = .003 95% CI[.00,.06]
	Intercept	0.83**	[0.70, 0.96]			0.07	.000**	
	Monthly PM2.5	−0.00	[−0.02, 0.01]	−0.05	[−0.25, 0.15]	0.006	.62	
IL-10 Covariate Model								R^2 = .051 95% CI[.00,.11]
	Intercept	0.46	[−0.73, 1.65]			0.59	.44	
	Monthly PM2.5	−0.00	[−0.01, 0.01]	−0.04	[−0.24, 0.16]	0.006	.69	
	BMI	0.02	[−0.00, 0.04]	0.16	[−0.04, 0.36]	0.01	.12	
	Age	0.01	[−0.10, 0.13]	0.02	[−0.18, 0.22]	0.06	.85	
	Sex	0.04	[−0.09, 0.18]	0.07	[−0.14, 0.27]	0.07	.51	
	Income	−0.00	[−0.00, 0.00]	−0.13	[−0.33, 0.08]	0.000	.22	
TNFα Model								R^2 = .000 95% CI[.00,.02]
	Intercept	1.80**	[1.71, 1.89]			0.05	.000**	
	Monthly PM2.5	−0.00	[−0.01, 0.01]	−0.01	[−0.21, 0.19]	0.004	.92	
TNFα Covariate Model								R^2 = .031 95% CI[.00,.07]
	Intercept	1.90**	[1.06, 2.74]			0.42	.000**	
	Monthly PM2.5	0.00	[−0.01, 0.01]	0.01	[−0.20, 0.21]	0.004	.96	
	BMI	−0.00	[−0.02, 0.02]	−0.00	[−0.21, 0.20]	0.008	.99	
	Age	−0.01	[−0.09, 0.07]	−0.02	[−0.23, 0.18]	0.04	.84	
	Sex	0.05	[−0.04, 0.15]	0.12	[−0.09, 0.33]	0.05	.25	
	Income	−0.00	[−0.00, 0.00]	−0.11	[−0.32, 0.10]	0.000	.29	

Note. A significant *b*-weight indicates the beta-weight. *b* represents unstandardized regression weights. *beta* indicates the standardized regression weights. *LL* and *UL* indicate the lower and upper limits of a confidence interval, respectively. *SE* indicate the standard error of an estimate. IL-6 = interleukin-6, IL-8 = interleukin-8, IL-10 = interleukin-10, TNFα = tumor necrosis factor alpha, PM2.5 = particulate matter. Analyses in the table were conducted using a sample of 100 participants.* $p < .05$. ** $p < .01$.

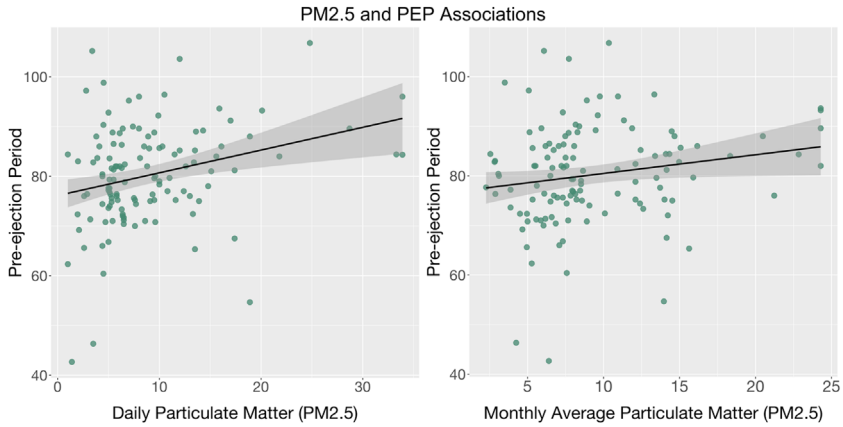

FIGURE 3 Associations between air pollution (PM2.5) and pre-ejection period (PEP). This figure illustrates the associations between PM2.5 and PEP. Regression lines are in black, with the gray shaded area representing the 95% confidence interval.

consistent when using daily PM2.5 or daily AQI as measures of air pollution. Daily PM2.5 and CAR and CAB regression analyses can be found in Table 4, and analyses using monthly PM2.5 can be found in Table 5.

PEP and RSA

To examine the positive association between daily air pollution and longer PEP ($\beta = .29$, $p = .001$), a linear regression was conducted, which explained 8.3% of the variance in PEP ($R^2 = .083$). This model is illustrated in Figure 3. A multiple regression model with covariates was also conducted, and the association remained significant ($\beta = .30$, $p = .001$). Daily PM2.5 explained 7.68% of the variance in PEP, and BMI explained 3% of variance in PEP. Next, a linear regression model was conducted to examine the association between PEP and monthly PM2.5 ($\beta = .18$, $p = .044$), and explained 3% of the variance in PEP ($R^2 = .033$). In a multiple regression model with covariates, monthly PM2.5 no longer predicted PEP at the .05 level ($\beta = .18$, $p = .056$). Daily PM2.5 and monthly PM2.5 were not significantly associated with RSA (p's > .14). Sensitivity analyses showed that the associations between air pollution and PEP or RSA were consistent when using daily PM2.5 or AQI as a predictor.

4 | DISCUSSION

In the present study, neighborhood levels of air pollution (PM2.5) were differentially associated with indices of children's peripheral inflammation (IL-6, IL-8) and autonomic physiology (CAR and PEP). Specifically, levels of daily PM2.5 on the day of (or prior to) coming to the laboratory were significantly associated with higher levels of IL-6 in children ages 9–11 years old. Conversely, higher monthly levels of PM2.5 (in the month leading up to the laboratory visit) were associated with lower levels of IL-8. Analyses revealed that IL-10 and TNFα were not significantly associated with daily or monthly levels of PM2.5.

Our findings are in line with previous research, which indicates that levels of air pollution are associated with elevations in markers of inflammation in children (Calderón-Garcidueñas et al., 2008, 2013; Li et al., 2019; Gruzieva et al., 2017). The current study adds to this growing evidence base and identifies IL-6 as an inflammatory marker that is potentially more sensitive to air pollution effects compared to IL-10 and TNFα.

TABLE 4 Regression Analyses: Daily Air Pollution and Cardiac Autonomic Regulation (CAR) and Balance (CAB), Pre-ejection Period (PEP) and Respiratory Sinus Arrhythmia (RSA)

	Predictor	*b*	*b* 95% CI [LL, UL]	*beta*	*beta* 95% CI [LL, UL]	*SE*	*p*	Fit
CAR Model								R^2 = .085** 95% CI[.01,.19]
	Intercept	0.54*	[0.12, 0.95]			0.21	.001**	
	DailyPM2.5	−0.06**	[−0.10, −0.03]	−0.29	[−0.46, −0.12]	0.02	.001**	
CAR Covariate Model								R^2 = .136** 95% CI[.01,.22]
	Intercept	−2.11	[−6.58, 2.36]			2.25	.35	
	DailyPM2.5	−0.06**	[−0.10, −0.03]	−0.30	[−0.47, −0.12]	0.02	.001**	
	BMI	−0.08	[−0.17, 0.00]	−0.17	[−0.35, 0.01]	0.04	.06	
	Age	0.38	[−0.06, 0.82]	0.15	[−0.02, 0.33]	0.22	.09	
	Sex	0.25	[−0.23, 0.74]	0.09	[−0.08, 0.27]	0.25	.31	
	Income	0.00	[−0.00, 0.00]	0.06	[−0.12, 0.24]	0.000	.49	
CAB Model								R^2 = .015 95%CI[.00,.08]
	Intercept	−0.19	[−0.63, 0.26]			0.22	.41	
	DailyPM2.5	0.03	[−0.01, 0.07]	0.12	[−0.06, 0.30]	0.02	.18	
CAB Covariate Model								R^2 = .035 95% CI[.00,.08]
	Intercept	−1.29	[−6.17, 3.60]			2.46	.60	
	DailyPM2.5	0.03	[−0.01, 0.07]	0.13	[−0.05, 0.32]	0.02	.17	
	BMI	0.05	[−0.05, 0.14]	0.09	[−0.09, 0.28]	0.04	.32	
	Age	0.04	[−0.45, 0.52]	0.01	[−0.17, 0.20]	0.24	.88	
	Sex	0.23	[−0.30, 0.76]	0.08	[−0.11, 0.26]	0.29	.40	
	Income	−0.00	[−0.00, 0.00]	−0.07	[−0.25, 0.12]	0.000	.47	

(Continues)

TABLE 4 (Continued)

	Predictor	*b*	*b* 95% CI [LL, UL]	*beta*	*beta* 95% CI [LL, UL]	*SE*	*p*	Fit
RSA Model								R^2 = .013 95% CI[.00,.08]
	Intercept	6.54**	[6.17, 6.92]			0.19	.000**	
	DailyPM2.5	−0.02	[−0.06, 0.01]	−0.11	[−0.29, 0.06]	0.02	.21	
RSA Covariate Model								R^2 = .043 95% CI[.00,.09]
	Intercept	4.24*	[0.12, 8.36]			2.08	.04*	
	DailyPM2.5	−0.02	[−0.06, 0.01]	−0.11	[−0.30, 0.07]	0.02	.23	
	BMI	−0.02	[−0.10, 0.06]	−0.05	[−0.24, 0.13]	0.04	.59	
	Age	0.26	[−0.15, 0.66]	0.12	[−0.07, 0.30]	0.21	.21	
	Sex	0.29	[−0.15, 0.74]	0.12	[−0.06, 0.31]	0.23	.20	
	Income	0.00	[−0.00, 0.00]	0.06	[−0.12, 0.24]	0.000	.94	
PEP Model								R^2 = .083** 95% CI[.01,.19]
	Intercept	76.11**	[73.07, 79.15]			1.53	.000**	
	DailyPM2.5	0.46**	[0.18, 0.73]	0.29	[0.11, 0.46]	0.14	.001**	
PEP Covariate Model								R^2 = .123* 95% CI[.01,.21]
	Intercept	83.89**	[51.08, 116.70]			16.56	.000**	
	DailyPM2.5	0.47**	[0.19, 0.75]	0.30	[0.12, 0.48]	0.14	.001**	
	BMI	0.66*	[0.03, 1.29]	0.18	[0.01, 0.36]	0.32	.04*	
	Age	−1.75	[−4.99, 1.49]	−0.10	[−0.27, 0.08]	1.64	.29	
	Sex	−0.12	[−3.70, 3.45]	−0.01	[−0.18, 0.17]	1.80	.94	
	Income	−0.00	[−0.00, 0.00]	−0.09	[−0.27, 0.09]	0.000	.31	

Note. A significant *b*-weight indicates the beta-weight. *b* represents unstandardized regression weights. *beta* indicates the standardized regression weights. *LL* and *UL* indicate the lower and upper limits of a confidence interval, respectively. *SE* indicate the standard error of an estimate. CAR = cardiac autonomic regulation, CAB = cardiac autonomic balance, PM2.5 = particulate matter, RSA = respiratory sinus arrhythmia, PEP = pre-ejection period. Analyses in the table were conducted using a sample of 122 participants.* $p < .05$. ** $p < .01$.

TABLE 5 Regression Analyses: Monthly Air Pollution and Cardiac Autonomic Regulation (CAR) and Balance (CAB), Pre-ejection Period (PEP) and Respiratory Sinus Arrhythmia (RSA)

	Predictor	*b*	*b* 95% CI [LL, UL]	*beta*	*beta* 95% CI [LL, UL]	*SE*	*p*	Fit
CAR Model								R^2 = .052* 95% CI[.01,.15]
	Intercept	0.57*	[0.04, 1.09]			0.26	.034*	
	Monthly PM2.5	−0.06*	[−0.11, −0.01]	−0.23	[−0.40, −0.05]	0.03	.01*	
CAR Covariate Model								R^2 = .096* 95% CI[.00,.17]
	Intercept	−1.32	[−5.91, 3.27]			2.31	.57	
	Monthly PM2.5	−0.06*	[−0.11, −0.01]	−0.22	[−0.40, −0.04]	0.03	.02*	
	BMI	−0.08	[−0.16, 0.01]	−0.15	[−0.33, 0.03]	0.04	.09	
	Age	0.28	[−0.16, 0.73]	0.11	[−0.07, 0.29]	0.23	.21	
	Sex	0.33	[−0.17, 0.83]	0.12	[−0.06, 0.30]	0.25	.19	
	Income	0.00	[−0.00, 0.00]	0.06	[−0.12, 0.24]	0.000	.53	
CAB Model								R^2 = .001 95% CI[.00,.04]
	Intercept	−0.04	[−0.59, 0.52]			0.28	.90	
	Monthly PM2.5	0.01	[−0.04, 0.06]	0.04	[−0.14, 0.22]	0.03	.69	

(Continues)

TABLE 5 (Continued)

	Predictor	*b*	*b* 95% CI [LL, UL]	*beta*	*beta* 95% CI [LL, UL]	*SE*	*p*	Fit
CAB Covariate Model								R^2 = .020 95% CI[.00,.05]
	Intercept	−1.49	[−6.44, 3.46]			2.50	.55	
	Monthly PM2.5	0.01	[−0.04, 0.07]	0.04	[−0.15, 0.23]	0.03	.67	
	BMI	0.05	[−0.05, 0.14]	0.09	[−0.10, 0.28]	0.05	.35	
	Age	0.08	[−0.41, 0.56]	0.03	[−0.16, 0.22]	0.24	.76	
	Sex	0.20	[−0.34, 0.73]	0.07	[−0.12, 0.25]	0.27	.47	
	Income	−0.00	[−0.00, 0.00]	−0.06	[−0.25, 0.13]	0.000	.53	
RSA Model								R^2 = .018 95% CI[.00,.09]
	Intercept	6.65**	[6.19, 7.12]			0.23	.000**	
	Monthly PM2.5	−0.03	[−0.08, 0.01]	−0.13	[−0.31, 0.05]	0.02	.14	
RSA Covariate Model								R^2 = .045 95% CI[.00,.10]
	Intercept	4.60*	[0.47, 8.74]			2.08	.03*	
	Monthly PM2.5	−0.03	[−0.08, 0.02]	−0.12	[−0.31, 0.06]	0.02	.19	
	BMI	−0.02	[−0.10, 0.06]	−0.04	[−0.23, 0.14]	0.04	.64	
	Age	0.22	[−0.18, 0.63]	0.10	[−0.08, 0.29]	0.20	.28	
	Sex	0.32	[−0.12, 0.77]	0.13	[−0.05, 0.32]	0.23	.15	
	Income	−0.00	[−0.00, 0.00]	−0.00	[−0.19, 0.18]	0.000	.98	

(Continues)

TABLE 5 (Continued)

	Predictor	*b*	*b* 95% CI [LL, UL]	*beta*	*beta* 95% CI [LL, UL]	*SE*	*p*	Fit
PEP Model								R^2 = .033** 95% CI[.00,.12]
	Intercept	76.70**	[72.82, 80.58]			1.96	.000**	
	Monthly PM2.5	0.38*	[0.01, 0.75]	0.18	[0.00, 0.36]	0.18	.044*	
PEP Covariate Model								R^2 = .068 95% CI[.00,.13]
	Intercept	78.88**	[44.85, 112.91]			16.56	.000**	
	Monthly PM2.5	0.36	[−0.01, 0.74]	0.18	[−0.00, 0.36]	0.14	.056	
	BMI	0.61	[−0.05, 1.26]	0.17	[−0.01, 0.35]	0.32	.07	
	Age	−1.05	[−4.38, 2.28]	−0.06	[−0.24, 0.12]	1.64	.53	
	Sex	−0.68	[−4.36, 2.99]	−0.03	[−0.22, 0.15]	1.80	.71	
	Income	−0.00	[−0.00, 0.00]	−0.08	[−0.27, 0.10]	0.000	.38	

Note. A significant *b*-weight indicates the beta-weight. *b* represents unstandardized regression weights. *beta* indicates the standardized regression weights. *LL* and *UL* indicate the lower and upper limits of a confidence interval, respectively. *SE* indicate the standard error of an estimate. CAR = cardiac autonomic regulation, CAB = cardiac autonomic balance, PM2.5 = particulate matter, RSA = respiratory sinus arrhythmia, PEP = pre-ejection period. Analyses in the table were conducted using a sample of 122 participants.* $p < .05$. ** $p < .01$.

Of note, we found that levels of air pollution were associated with higher levels of IL-6 but lower levels of IL-8 in participants. This is somewhat consistent with studies conducted at the University of California-Davis National Primate Research Center, which found that monkeys with early life exposure to PM2.5 (born 3 months prior to a wildfire) had significantly higher expression of IL-6 as adults (8 years of age) compared to control monkeys born the following year. Interestingly, the offspring (1–2 years of age) of early-exposed mothers exhibited significantly reduced levels of IL-8 compared to control offspring (Miller, 2019). However, mothers produced increased levels of both IL-6 and IL-8 in response to lipopolysaccharide (LPS), while their offspring again displayed reduced production of IL-8 (but greater production of IL-6). Thus, exposed mothers had higher levels of both IL-6 and IL-8, while their offspring had higher levels of IL-6 and lower levels of IL-8, suggesting differential intergenerational effects (Miller, 2019). Our findings are in contrast to a study conducted with 10-year-old children in Taiwan (Chen et al., 2012), which found a positive association between PM2.5 and IL-8 levels, although these were measured in the nasal lavage on the day of exposure. Effects of air pollution may differ depending on the method of measurement and the presence of developmental effects over time.

These findings are important because exposure to pollutants released during wildfires has been related to numerous negative health outcomes in children, including asthma and decreased lung function, as well as neurodevelopmental outcomes like attention deficit hyperactivity disorder, autism, and deficits in school performance and memory (Holm et al., 2021; Oliveira et al., 2019; Suades-González et al., 2015). Mechanistically, it is thought that wildfire smoke impacts respiratory systems via direct inhalation, which leads to local oxidative stress, inflammation, and cell toxicity, potentially resulting in systemic effects (Adetona et al., 2016). Notably, particulate matter is the primary indicator of these adverse effects of wildfire pollution (Naeher et al., 2007). In addition, early life exposure to wildfire smoke and pollution may "program" structural, metabolic, and cellular signaling mechanisms that may result in lifelong metabolic impacts, such as obesity (Holm et al., 2021). This may explain past findings that greater exposure in utero to chemicals that occur in wildfire air pollution (polycyclic aromatic hydrocarbons; PAHs) is associated with higher body weight in children (Rundle et al., 2012).

We also found that daily and monthly levels of PM2.5 were associated with lower cardiac autonomic regulation (CAR) in our study sample. That is, children who experienced higher levels of air pollution in the day or month prior to the laboratory visit exhibited lower CAR during a baseline resting period in the laboratory. CAR is a measure that reflects the combined contribution of the PNS and SNS in modulating cardiovascular activity (Berntson et al., 2008). Greater values indicate greater overall autonomic regulation of heart activity. Previous work has suggested that greater autonomic control of the heart may be a positive factor in reducing risk for adverse cardiac health outcomes (Berntson et al., 2008; Thayer & Sternberg, 2006).

The literature on air pollution and ANS physiology, and in particular cardiac autonomic regulation (CAR) or balance (CAB), is rather limited. To our knowledge, only one previous study in children examined neighborhood PM2.5 in association with parasympathetic and sympathetic nervous system activity (Miller et al., 2019). While the study did not find any significant associations between PNS or SNS activity at rest and PM2.5, adolescents in neighborhoods with higher PM2.5 demonstrated higher autonomic reactivity to stress. Specifically, they exhibited greater reductions in autonomic balance during an acute stressor, indexed by heart rate variability and skin conductance (Miller et al., 2019). The current study found that, at rest, participants who lived in areas with greater PM2.5 concentrations exhibited lower CAR, which has been found to be indicative of later heart health problems (Berntson et al., 2008).

Results from our exploratory analysis of PEP and RSA suggest that the association with CAR may be driven by a negative relation between air pollution and sympathetic activity, as air pollution was not associated with resting parasympathetic activity in our sample. The lack of association between PM2.5 and RSA in our pediatric sample is inconsistent with findings from a recent meta-analysis of studies with older adults by Wang et al. (2020), which found that both short-term and long-term PM2.5 exposures were associated with decreased indices of HRV. However, our results are consistent with a study of 18 adults, which found that experimental exposure to air pollution did not impact measures of parasympathetic heart rate control, although it increased levels of circulating leucocytes (Heusser et al., 2019).

Greater exposure to PM2.5 was correlated with longer PEP, reflecting lower sympathetic influence on the heart (Berntson et al., 2004). This surprising finding is in contrast to theoretical models, based on evidence in adults, that air pollution can lead to upregulation of SNS activity and is associated with downregulation of PNS activity (Brook & Rajagopalan, 2021; Wang et al., 2020). The literature in youth samples is very limited. We are only aware of two recent studies that tested associations between pollutant exposure and resting ANS activity, and both studies found no significant associations (Hill et al., 2021; Miller et al., 2019). However, differences in results may also be due to the use of different methodologies, as SNS activity was measured via skin conductance by Miller and colleagues. In a study with rats, experimental exposure to diesel exhaust led to a reduction in sympathetic activity as indexed by prolonged PEP, consistent with our findings (Carll et al., 2013). Given the limited and mixed evidence so far, additional research in youth samples is needed before drawing strong conclusions. However, these findings suggest that air pollution may be differentially associated with resting ANS activity during childhood and adolescence, as compared to adulthood.

Of note, CAR has been significantly associated with general health indices and history of heart attacks (Berntson et al., 2008). Further, the maturation of cardiac autonomic control may be disrupted by childhood obesity, as indicated by reduced cardiac parasympathetic activity (Eyre et al., 2014). As mentioned, a recent meta-analysis of eight studies found that air pollution was associated with increased risk of childhood obesity (Parasin et al., 2021). Future work should examine the relationships between air pollution, autonomic regulation of the heart, and other cardiometabolic risk factors, to understand the impact of air pollution on children's health or risk for obesity.

4.1 | Strengths and limitations

The strengths of this study include the focus on children, an under-studied but vulnerable population; the concurrent measurement of multiple inflammatory markers along with cardiac autonomic physiology, and robustness of links between air pollution and these biomarkers after accounting for socioeconomic condition, BMI, and demographics. The study is not without limitations. First, the cross-sectional design provides useful preliminary evidence, but limits what we can infer from these associations. Longitudinal follow-up could shed light on the long-term health and psychological effects of air pollution. Second, inflammatory markers in general circulation should be complemented by more specific measures of airway inflammation and asthma symptoms in future studies to gain a more complete understanding of the full effects of air pollution on the body. Third, the sample size was relatively small and these findings will benefit from replication with larger samples. The sample size precluded the examination of more complex models including interaction effects to test the role of moderators, limiting the scope of the

analysis to main effects. Finally, the magnitude of effects captured in our Northern California study may not be representative of other geographic regions, thus replicating these effects with nationally-representative and international samples is an important future direction.

4.2 | Conclusion & future directions

As climate change continues to impact children and families, it is paramount to understand the impact of environmental contaminants such as air pollution on children's physiology. By examining daily and monthly levels of PM2.5 in relation to children's inflammation and autonomic physiology, this study further demonstrates the immediate consequences of exposure to air pollution, which may increase risk of future disease.

As discussed by Trentacosta and Mulligan, the future directions for research on environmental contaminants are plentiful (2020). The current study adds to the literature on air pollution exposure and childhood outcomes that may be linked to later life health problems; however, additional longitudinal work is needed. In addition, the current study only collected participants' current address and does not have information about how early-life air pollution exposure may have been related to children's current immune or autonomic functioning. Future research designs should also consider timepoints in development in which children may be particularly susceptible to the impacts of air pollution on health.

Air pollution exposure, as well as the effects of climate change, are an environmental justice issue. In the United States, PM2.5 pollutants disproportionately affect racial and ethnic minorities, such that regardless of income level, people of color have higher than average exposure to PM2.5 (Tessum et al., 2021). While minority race was not correlated with PM2.5 in the current study, future research and subsequent policy changes that seek to mitigate the effects of air pollution on children should address these disparities in exposure.

A promising future direction would be examining moderators or protective factors that may mitigate the effects of air pollution on children's development (Trentacosta & Mulligan, 2020). For example, with respect to the current study, research should examine ways to promote cardiac autonomic regulation in children as a potential protective factor in reducing risk of long-term cardiovascular impacts of pollution. Overall, policy changes that mitigate emissions have been estimated to produce significant improvements in children's wellbeing (Larr & Neidell, 2016). Continued developmental research on environmental contaminants can sound the alarm about the effects of air pollution and inform policy changes that could promote long-term population health.

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CONFLICT OF INTERESTS

The authors have no conflicts of interest to disclose.

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