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Duration-sensitive association between air pollution exposure and changes in cardiometabolic biomarkers: Evidence from a predominantly African American cohort

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A B S T R A C T

Background: Ambient fine particulate matter ($PM_{2.5}$) exposure has been related to cardiometabolic diseases, but the underlying biological pathways remain unclear at the population level.
Objective: To investigate the effect of $PM_{2.5}$ exposure on changes in multiple cardiometabolic biomarkers across different exposure durations.
Method: Data from a prospective cohort study were analyzed. Ten cardiometabolic biomarkers were measured, including ghrelin, resistin, leptin, C-peptide, creatine kinase myocardial band (CK-MB), monocyte chemoattractant protein-1 (MCP-1), tumor necrosis factor alpha (TNF-alpha), N-terminal pro B-type natriuretic peptide (NT-proBNP), troponin, and interleukin-6 (IL-6). $PM_{2.5}$ levels across exposure durations from 1 to 36 months were assessed. Mixed effect model was used to estimate changes in biomarker levels against 1 $\mu g/m^3$ increase in $PM_{2.5}$ level across different exposure durations.
Results: Totally, 641 participants were included. The average $PM_{2.5}$ exposure level was 9 $\mu g/m^3$. $PM_{2.5}$ exposure was inversely associated with ghrelin, and positively associated with all other biomarkers. The magnitudes of these associations were duration-sensitive and exhibited a U-shaped or inverted-U-shaped trend. For example, the association of resistin were $\beta = 0.05$ (95% CI: 0.00, 0.09) for 1-month duration, strengthened to $\beta = 0.27$ (95% CI: 0.14, 0.41) for 13-month duration, and weakened to $\beta = 0.12$ (95% CI: −0.03, 0.26) for 24-month duration. Similar patterns were observed for other biomarkers except for CK-MB, of which the association direction switched from negative to positive as the duration increased. Resistin, leptin, MCP-1, TNF-alpha, and troponin had a sensitive exposure duration of nearly 12 months. Ghrelin and C-peptide were more sensitive to longer-term exposure (>18 months), while NT-proBNP and IL-6 were more sensitive to shorter-term exposure (<6 months).
Conclusion: $PM_{2.5}$ exposure was associated with elevated levels in cardiometabolic biomarkers related to insulin resistance, inflammation, and heart injury. The magnitudes of these associations depended on the exposure duration. The most sensitive exposure durations of different biomarkers varied.

1. Introduction

Ambient air pollution exposure, especially to fine particulate matter ($PM_{2.5}$), is recognized as a leading cause of global mortality and morbidity (Landrigan et al., 2018). Causal associations between $PM_{2.5}$ exposure and cardiometabolic diseases, including heart attack, congestive heart failure, diabetes, and obesity has been established (Rajagopalan et al., 2018a; An et al., 2018; Cosselman et al., 2015; Brook et al., 2018; Liu et al., 2019; Bowe et al., 2018; Di et al., 2017). It is estimated that $PM_{2.5}$ exposure is responsible for nearly four million deaths annually, of which more than half are related to cardiometabolic diseases (Cohen et al., 2017).

Several population studies have estimated the effect of $PM_{2.5}$ exposure on biomarkers of metabolism and inflammation, to understand the

Abbreviations: CI, confidence interval; CK-MB, creatine kinase myocardial band; COMPASS, Chicago Multiethnic Prevention and Surveillance Study; MCP-1, monocyte chemoattractant protein-1; IL-6, interleukin-6; NT-proBNP, pro B-type natriuretic peptide; OR, odds ratio; SES, socioeconomic status; TNF-alpha, tumor necrosis factor alpha.

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underlying biological pathways for the adverse health effects of $PM_{2.5}$ exposure (Chen et al., 2015, 2016; Zhang et al., 2017; Green et al., 2016; Hajat et al., 2015; Lanki et al., 2015; Dabass et al., 2016; Wyatt et al., 2022; Viehmann et al., 2015; Brook et al., 2016; Dadvand et al., 2014). Despite inconsistent results, findings from prior studies supported associations of $PM_{2.5}$ exposure with an elevated level of inflammation biomarker C-reactive protein (CRP) (Chen et al., 2015, 2016; Zhang et al., 2017; Green et al., 2016; Hajat et al., 2015; Lanki et al., 2015; Dabass et al., 2016; Wyatt et al., 2022; Viehmann et al., 2015) and a higher risk for insulin resistance (Chen et al., 2016; Brook et al., 2013, 2016; Thiering et al., 2013; Kim and Hong, 2012). A meta-analysis of eleven studies also suggests that $PM_{2.5}$ exposure increases the circulating level of interleukin-6 (IL-6), a key mediator of inflammation (Zhu et al., 2021). Apart from these commonly investigated biomarkers, evidence of involvement of other crucial cardiometabolic biomarkers, such as tumor necrosis factor alpha (TNF-alpha), troponin, and monocyte chemoattractant protein-1 (MCP-1), is sparse in population studies, although animal studies suggest that these pathways play key roles in observed adverse health effects of $PM_{2.5}$ exposure (Wang et al., 2015; Zhang et al., 2018; Sun et al., 2009). To our knowledge, few population studies have included cardiometabolic biomarkers other than insulin, CRP, and IL-6 (Wyatt et al., 2022; Chen et al., 2015; Dadvand et al., 2014; Zhang et al., 2022; Xia et al., 2019; Tseng et al., 2022).

Another key gap in the literature relevant for public health is how the duration of exposure to air pollution impacts biology. Both short- and long-term $PM_{2.5}$ exposures have been investigated in relation to cardiometabolic biomarkers, with exposure durations ranging from several days (Green et al., 2016; Hajat et al., 2015; Dabass et al., 2016; Wyatt et al., 2022; Chen et al., 2015; Viehmann et al., 2015; Brook et al., 2016) to one month (Chen et al., 2016; Green et al., 2016; Dabass et al., 2016) and up to one (Chen et al., 2016; Green et al., 2016; Hajat et al., 2015; Lanki et al., 2015; Dabass et al., 2016; Viehmann et al., 2015) and two years (Zhang et al., 2017). Researchers have observed differing associations with short- and long-term exposures. For example, Hajat et al. reported a positive association between IL-6 and long-term $PM_{2.5}$ exposure (one-year average concentration), but not with short-term exposure (up to five-day average) (Hajat et al., 2015). Chen et al. concluded that short- (up to 58-day average) and long-term (one-year average) $PM_{2.5}$ exposures were associated with changes in different biomarkers related to energy metabolism (Chen et al., 2016). Overall, most studies support the association between long-term $PM_{2.5}$ exposure and changes in cardiometabolic biomarkers (Chen et al., 2016; Zhang et al., 2017; Green et al., 2016; Hajat et al., 2015; Lanki et al., 2015; Dabass et al., 2016; Viehmann et al., 2015), while some limited evidence for short-term $PM_{2.5}$ exposure was noted (Wyatt et al., 2022; Chen et al., 2015; Brook et al., 2016). The inconsistencies raised a question on whether sensitive time windows for these cardiometabolic biomarkers vary, warranting a more comprehensive investigation of different $PM_{2.5}$ exposure durations.

Additionally, African Americans, an under-represented population in biomedical research, bear a disproportionate burden of air pollution and cardiometabolic diseases in the US. The racial/ethnical disparities in air pollution exposure are most pronounced in urban areas with high levels of residential segregation (Woo et al., 2019). It is also well-established that African Americans have higher prevalence of cardiometabolic diseases, and these disparities persist even after accounting for differences in age, sex, socioeconomic status (SES), and other factors (Graham, 2015; Benjamin et al., 2019; Cefalu and Golden, 2015). A synergistic interaction of disparities in air pollution and disease prevalence has led to a stronger adverse effect of $PM_{2.5}$ exposure. It is estimated that African Americans have a 1.5 times higher rate of cardiometabolic diseases and all-cause mortality than Caucasians that was only explained by higher exposure to $PM_{2.5}$ (Erqou et al., 2018).

Within this context, we conducted this study to investigate the association between ambient $PM_{2.5}$ exposure and cardiometabolic biomarkers that were less frequently investigated in prior studies, including ghrelin, resistin, leptin, C-peptide, creatine kinase myocardial band (CK-MB), MCP-1, TNF-alpha, N-terminal pro B-type natriuretic peptide (NT-proBNP), troponin, and IL-6. We further examined the associations with cumulative average $PM_{2.5}$ over different exposure durations from 1 month to 36 months, aiming to elucidate how different exposure durations influence the impact of $PM_{2.5}$ exposure. Notably, the study leverages data from the Chicago Multiethnic Prevention and Surveillance Study (COMPASS), a predominantly African American cohort that seeks to uncover the causes of health disparities.

2. Method

2.1. Study population

COMPASS is a large, longitudinal cohort study. A more detailed description of the study design can be found elsewhere (Aschebrook-Kilfoy et al., 2020). Briefly, eligibility for COMPASS includes: 1) age 18 or older at the time of enrollment; 2) ability to consent and provide survey data in English or Spanish; 3) willingness to provide blood, urine, and saliva samples as well as electronic health record access. COMPASS has employed multiple recruitment modalities, including a population-based approach, a community-based approach, and a hospital/clinic-based approach. During their first visit to the research clinic, participants completed a survey questionnaire. Anthropometry and blood pressure are then measured. The COMPASS questionnaire codebook can be found at https://compass.uchicago.edu/research/self-reported-questionnaire-data/. The residential address of each participant was geocoded and ascertained by our research staff. All participants in this study had valid residential addresses.

From an initial sample size of 7409 eligible participants, blood samples of 650 participants were randomly selected for measurement of cardiometabolic biomarkers. The population analyzed in this study were enrolled into COMPASS between 2015 and 2019, thus were not impacted by COVID-19. All the participants lived in their current addresses for more than three years.

3.2. Cardiometabolic biomarker measurement

Plasma levels of C-peptide, CKMB, ghrelin, IL-6, leptin, MCP-1, NT-proBNP, resistin, TNF-alpha and troponin I were analyzed by multiplex assays using Human Custom ProcartaPlex 12-Plex immunoassay (Life Technologies Corp, CA, USA). Briefly, plasma samples were vortexed and spun down. Twenty-five microliters of the plasma and standards were added to each well of a 96-well plate. Then assay buffer and multiplexed bead solution were added as per manufacturer's protocol. After a 2-h incubation at room temperature, the detection Antibody mixtures were added to the plate followed by addition of Streptavidin-Phycoerythrin solution. After incubation and washing, the plate was analyzed on a Luminex 200 instrument (Luminex Corporation, Austin, Texas). The median fluorescent intensity (MFI) was used to determine the concentration of the analytes against the standard curve. Four parameter logistic (4 PL) curve was used to generate the standard curve. All the measures were in pg/mL.

3.3. $PM_{2.5}$ exposure assessment

Ambient $PM_{2.5}$ exposure data was obtained from the Atmospheric Composition Analysis Group at Washington University at St. Louis. Monthly surface $PM_{2.5}$ levels for 1998–2021 were estimated by combining Aerosol Optical Depth retrievals from the NASA Moderate Resolution Imaging Spectroradiometer (MODIS), Multi-angle Imaging SpectroRadiometer (MISR), and Sea-viewing Wide Field-of-view Sensor (SeaWiFS) instruments with the GEOS-Chem chemical transport model, and subsequently calibrating to global and North America ground-based observations using a Geographically Weighted Regression (Van Donkelaar et al., 2019, 2021; Hammer et al., 2020). The most updated high

resolution (0.01° × 0.01°) datasets for surface $PM_{2.5}$ levels in North America can be obtained on the website: https://sites.wustl.edu/acag/datasets/surface-pm2-5/. No missing values were reported in our exposure assessment.

We retrospectively assigned the $PM_{2.5}$ exposure to each participant according to their residential addresses. The cumulative average $PM_{2.5}$ levels were generated over different exposure durations, from 1 month to 36 months prior to the date when the blood sample was collected.

3.4. Potential confounders

Based on prior publications in this cohort (Luo et al., 2022, 2023), we constructed a causal directed acyclic graph to select potential confounders (supplemental figure S1). Accordingly, potential confounders adjusted in the final analysis included age (≤35, 36–45, 46–55, 56–65, >65), race/ethnicity (non-Hispanic White, non-Hispanic Black, other), gender (male, female), education (less than high school, high school, some college, college or more), household income (<$15,000, $15,000 - $34,999, $35,000 - $69,999 and >$69,999), neighborhood area deprivation index (ADI, in quartiles), body mass index (BMI; <25, 25–29.9, 30–39.9, >39.9), seasonality (January–March, April–June, July–September, October–December), smoking (never, former, current), measured hypertension (yes, no), heart attack history (yes, no), and type 2 diabetes (yes, no). Age, race/ethnicity, gender, education, household income, and heart attack history were collected through questionnaires. ADI is a composite score to measure neighborhood disadvantages and was retrieved at the census tract level based on participants' residential address (Kind and Buckingham, 2018). BMI, hypertension, and type 2 diabetes were measured and ascertained when participants visited our research clinic. Heart attack history was retrieved from the electronic health record. We also retrieved self-report hypertension medication use, given its influence on cardiometabolic profiles (Smith et al., 2014). However, since the hypertension medication variable was not on the backdoor pathway and had many missing values, we adjusted for this variable in the sensitivity analysis instead of our main analysis.

3.5. Statistical analysis

Among the ten cardiometabolic biomarkers in this study, four (ghrelin, resistin, leptin, and CK-MB) were measured in all participants, two (C-peptide and MCP-1) were under limit of detection (LOD) in <15% participants, and the remaining four (TNF-alpha, NT-proBNP, troponin, and IL-6) were under LOD in >40% participants (Table 1), leading to missing values in these biomarkers. Missing values in C-peptide and MCP-1 were imputed using LOD divided by $\sqrt{2}$ as suggested by prior practices (Richardson and Ciampi, 2003). Since the distributions of ghrelin, resistin, leptin, CK-MB, C-peptide, and MCP-1 were right-skewed, the concentrations of these six biomarkers were log-transformed and treated as continuous variables in analysis to mitigate the influence of extreme values. TNF-alpha (Li et al., 2018), NT-proBNP (Welsh et al., 2022), troponin (Dionne et al., 2020), and IL-6 (Mouawad et al., 1996) were grouped into binary variables using a cutoff of 8.1, 125, 0.04, 10 pg/mL, respectively, as suggested by clinical practices. Missing values in these four biomarkers were considered as below the cutoff.

We used mixed effect models to estimate the association between $PM_{2.5}$ exposure and the cardiometabolic biomarkers. Linear regression was used for continuous biomarker variables to estimate the average change (β) in the log-transformed level and the corresponding 95% confidence interval (CI). Logistic regression was used for binary biomarker variables to estimate the odds ratio (OR) for the high-level group and the corresponding 95% CI. The average $PM_{2.5}$ exposure concentration level was treated as a continuous variable in the model; therefore, the results should be interpreted against 1 $\mu g/m^3$ increase in $PM_{2.5}$ level. The average $PM_{2.5}$ concentration levels of different exposure durations were put in the model separately. To further eliminate potential confounding arising from spatial variations, we included random effects of residential zip codes for intercept in the model. We then described the trend of effect estimates across different exposure durations using a smoothing line generated from LOESS (Cleveland, 1979).

The models were adjusted for all aforementioned potential confounders. Missing values in potential confounders were assumed to be missing at random and then imputed using the non-parametric random forest imputation algorithm (Shah et al., 2014). Compared to traditional parametric imputation algorithms, such as multivariate imputation by chained equations, the non-parametric random forest imputation algorithm avoids model misspecification and outperforms traditional algorithms in complex scenarios that involves non-linearity and interactions (Shah et al., 2014). All variables were used to generate the imputed data. Ten complete datasets were generated via imputation, and we employed the established analytical procedure to combine the results.

In sensitivity analysis, we restricted our analysis to non-Hispanic Black people to avoid the influence of small sample size in other race/ethnicity groups. Additionally, we adjusted for hypertension medication use in the sensitivity analysis.

Statistical analysis in this study was performed using R 4.2.2 (R Core Team, Vienna, Austria). A two-tailed P-value< 0.05 was considered statistically significant.

3. Results

A total of 641 participants with valid measures of cardiometabolic biomarkers were analyzed in this study. The distributions of selected sociodemographic and medical characteristics are presented in Table 2. The study population was predominantly non-Hispanic Blacks (95.2%), more than 45% were above 55 years of age, over half reported an annual household income less than $15,000, and nearly 55% received high school education or less. The prevalence of obesity (BMI ≥30) and type 2 diabetes was 40.5% and 10.5%, respectively. Only 5.1% reported a heart

Table 1
Descriptive statistics of selected serum cardiometabolic biomarker levels in this study.

Biomarkers	Min	Q1	Median	Mean	Q3	Max	N under LOD	Cutoff value	N (%) above cutoff
Ghrelin (pg/mL)	76.99	1530.74	2701.57	3376.55	4584.90	17168.50	0	NA	
Resistin (pg/mL)	15.95	158.01	339.59	545.07	653.49	13588.20	0	NA	
Leptin (pg/mL)	3.98	976.85	2306.55	2897.62	4049.22	23015.40	0	NA	
C-peptide (pg/mL)	0.54	225.85	409.95	512.05	678.49	2901.25	62	NA	
CK-MB (pg/mL)	10.35	70.17	105.73	132.31	153.34	1805.77	0	NA	
MCP-1 (pg/mL)	0.02	3.34	8.82	17.49	20.60	450.96	99	NA	
TNF-alpha (pg/mL)	0.02	0.46	1.14	5.615	4.13	230.897	293	8.1	56 (8.7)
NT-proBNP (pg/mL)	0.07	4.55	11.18	22.83	25.45	272.91	254	125	10 (1.6)
Troponin (pg/mL)	1.46	63.78	144.04	258.54	249.96	1830.58	591	0.04	50 (7.8)
IL-6 (pg/mL)	0.05	4.423	11.025	32.468	23.99	688.98	551	10	48 (7.5)

CK-MB, creatine kinase myocardial band; IL-6, interleukin-6; LOD, limit of detection; MCP-1, monocyte chemoattractant protein-1; NT-proBNP, N-terminal pro B-type natriuretic peptide; TNF-alpha, tumor necrosis factor alpha.

Table 2
Distributions of selected sociodemographic and medical characteristics in the study population.

Selected characteristics	Study population (n = 641)
Age, n (%)	
≤35	9 (1.4)
36-45	115 (17.9)
46-55	222 (34.6)
56-65	219 (34.2)
>65	76 (11.9)
Race/ethnicity, n (%)	
Non-Hispanic Black	610 (95.2)
Non-Hispanic White	6 (0.9)
Hispanic	12 (1.9)
Other	12 (1.9)
Missing	1 (0.2)
Gender, n (%)	
Female	412 (64.3)
Male	229 (35.7)
Education, n (%)	
< High school	234 (36.5)
High school	179 (27.9)
Some college	184 (28.7)
College or more	44 (6.9)
Household income, n (%)	
< $15,000	370 (57.7)
$15,000 - $34,999	92 (14.4)
$35,000 - $69,999	25 (3.9)
> $69,999	51 (8.0)
Missing	103 (16.1)
BMI, n (%)	
<25	193 (30.1)
25–29.9	167 (26.1)
30–39.9	189 (29.5)
>39.9	59 (9.2)
Missing	33 (5.1)
Seasonality	
January–March	160 (25.0)
April–June	168 (26.2)
July–September	160 (25.0)
October–December	153 (23.9)
Smoking status	
Never	166 (25.9)
Former	78 (12.2)
Current	397 (61.9)
Measured hypertension	
No	303 (47.3)
Yes	338 (52.7)
Type 2 diabetes, n (%)	
No	574 (89.5)
Yes	67 (10.5)
Heart attack history, n (%)	
No	608 (94.9)
Yes	33 (5.1)
Area deprivation index national percentile	
Median (interquartile range)	70 (42–87)
Hypertension medication intake[a]	
No	261 (40.7)
Yes	205 (32.0)
Missing	175 (27.3)

[a] Not adjusted for in the main analysis.

attack history. Overall, the study population represents a population historically underrepresented in biomedical research.

The average $PM_{2.5}$ exposure concentration was 9 μg/m^3 across all exposure durations in this study (Fig. 1; original values in Supplemental Table S1). In most exposure durations, the average $PM_{2.5}$ concentrations ranged from 8 to 12 μg/m^3. The Pearson correlations between cardiometabolic biomarkers analyzed in this study is presented in supplemental figure S2.

3.1. Continuous cardiometabolic biomarkers

We observed significant associations of $PM_{2.5}$ exposure with all six continuous cardiometabolic biomarker variables (Fig. 2; original values in Supplemental Tables S2 and S3). Over the exposure durations of 1–36 months, the associations showed a two-stage change for ghrelin, C-peptide, MCP-1, resistin and leptin. Specifically, the association was strengthened as the exposure duration increased, and then weakened as the duration increased, presenting a U-shaped or inverted-U-shaped trend. However, these associations remained in the same direction. In contrast, the direction of association with CK-MB switch from negative to positive when exposure duration increased.

Ghrelin was inversely associated with $PM_{2.5}$ exposure across all exposure durations. The magnitude of the association exhibited a U-shaped trend across the exposure duration. This inverse association was steadily strengthened from $\beta = -0.03$ (95% CI: −0.06, 0.01) for 1-month exposure duration to $\beta = -0.46$ (95% CI: −0.57, −0.35) for 19-month exposure duration, the strongest association for ghrelin. Beyond 19 months, the association was attenuated as the exposure duration increased. However, a significant association ($\beta = -0.27$, 95% CI: −0.38, −0.17) was still observed for the 36-month exposure duration.

In contrast, $PM_{2.5}$ exposure was positively associated with resistin and leptin, and these associations exhibited an inverted-U-shaped trend across the exposure durations. At the beginning, the associations for 1-month exposure duration were $\beta = 0.05$ (95% CI: 0.00, 0.09) for resistin and $\beta = 0.01$ (95% CI: −0.03, 0.05) for leptin. These associations were steadily strengthened when the exposure duration increased. The exposure duration with the strongest associations for resistin and leptin were 13 months ($\beta = 0.27$, 95% CI: 0.13, 0.41) and 12 months ($\beta = 0.25$, 95% CI: 0.13, 0.38), respectively. Then these associations were attenuated as the exposure duration increased. The attenuation rate was higher for resistin than for leptin. Specifically, the associations became non-significant for resistin from a duration of 24 months ($\beta = 0.12$, 95% CI: −0.03, 0.26), and for leptin from a duration of 31 months ($\beta = 0.12$, 95% CI: −0.01, 0.22).

The association for C-peptide appeared to exhibit an inverted-U-shaped trend across these exposure durations as well. The association between C-peptide and 1-month exposure was null ($\beta = 0$, 95% CI: −0.10, 0.10), but then strengthened to be positive when exposure duration increased. C-peptide was not significantly associated with $PM_{2.5}$ exposure until 25 months ($\beta = 0.31$, 95% CI: 0.00, 0.63), and the significant associations were observed between durations of 25–27 months. After this period, the association weakened to non-significant.

$PM_{2.5}$ exposure was inversely associated with CK-MB when the exposure duration was short. For example, the association was $\beta = -0.04$ (95% CI: −0.07, −0.02) for 1-month exposure duration and $\beta = -0.05$ (95% CI: −0.09, −0.01) for 2-month exposure duration. However, the direction of the association switched from negative to positive as the exposure duration increased. Positive associations was observed from a duration of 12 months onwards. The magnitude of the positive association reached the peak with 23-month exposure duration ($\beta = 0.14$, 95% CI: 0.04, 0.23), and remained roughly stable after that.

Similar to resistin and leptin, MCP-1 was positively associated with $PM_{2.5}$ exposure and this association exhibited an inverted-U-shaped trend over the exposure durations. Beginning from $\beta = 0.13$ (95% CI: 0.01, 0.25) for 1-month duration, the association was strengthened as duration increased and had the strongest magnitude with 12-month exposure duration ($\beta = 1.05$, 95% CI: 0.69, 1.41). The association was eventually attenuated to non-significant from a duration of 30 months ($\beta = 0.35$, 95% CI: −0.03, 0.73).

3.2. Binary cardiometabolic biomarkers

We also observed positive associations with all four binary cardiometabolic biomarker variables in this study (Fig. 3; original values in Supplemental Table S4). The magnitudes of associations exhibited an inverted-U-shaped trend across different exposure durations for TNF-alpha and troponin, while the trends were vague for NT-proBNP and IL-6.

$PM_{2.5}$ exposure was associated with higher odds for the high-level

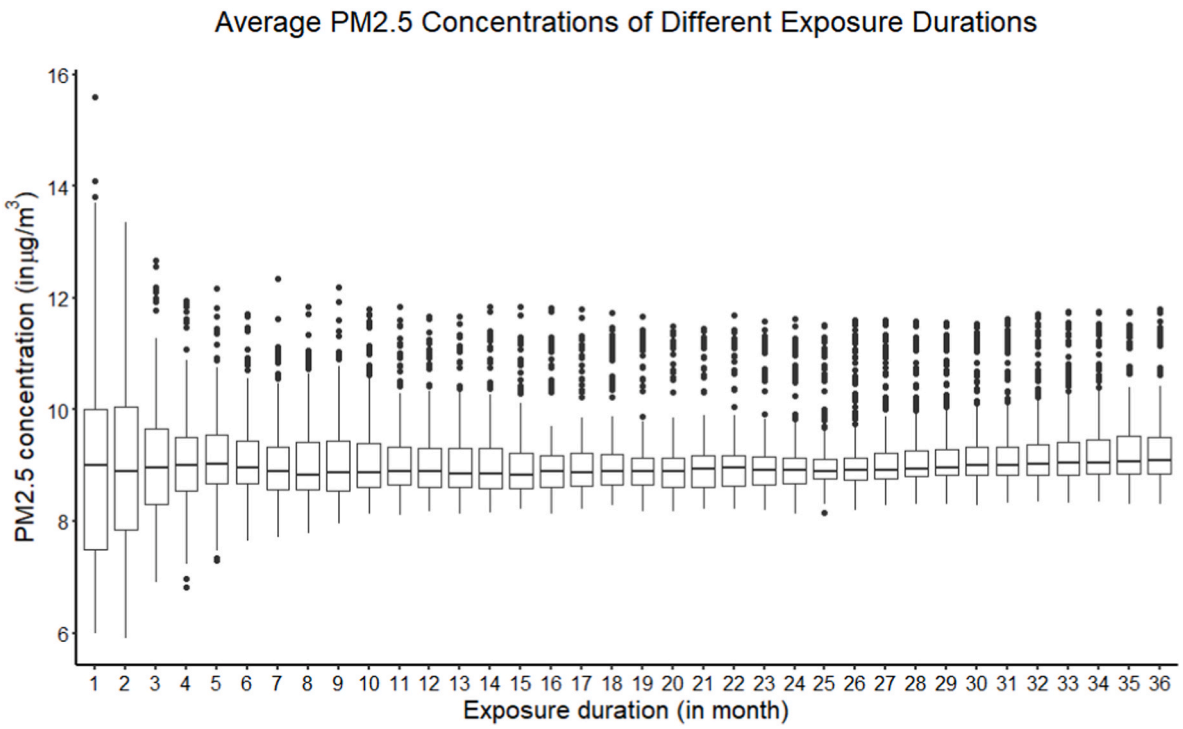

Fig. 1. Boxplots of average $PM_{2.5}$ concentrations of different exposure durations in the study.

groups of TNF-alpha and troponin. These associations were significant from a duration of 1 month, and then became stronger when duration increased. The associations reached the peak with 12-month duration for both TNF-alpha (OR = 2.70, 95% CI: 1.77, 4.11) and troponin (OR = 2.33, 95% CI: 1.49, 3.65). After a duration of 12 months, the associations weakened as the exposure duration increased. The association of troponin became non-significant from a duration 31 months (OR = 1.55, 95% CI: 0.98, 2.46), while the association of TNF-alpha was still significant for a duration of 36 months (OR = 1.57, 95% CI: 1.03, 2.40).

NT-proBNP was significantly associated with $PM_{2.5}$ exposure only for short durations of 1 month (OR = 1.73, 95% CI: 1.19, 2.51) and 2 months (OR = 1.73, 95% CI: 1.09, 2.73). The association then became non-significant when the exposure duration increased. The trend of association magnitudes was neither increasing nor declining.

IL-6 was associated with $PM_{2.5}$ exposure at the early stage as well. The significant association was observed between 1- and 5-month durations (e.g., for 4-month, the strongest association, OR = 1.57, 95% CI: 1.13, 2.18). After these durations, the association generally exhibited a declining trend, and no significant association was observed.

In sensitivity analysis, we restricted to non-Hispanic Black people and additionally adjusted for hypertension medication intake. The results remained almost unchanged compared to those from our main analysis (supplemental figures S3 and S4).

4. Discussion

In this predominantly African American population of low SES that was historically under-represented in biomedical research, exposure to ambient $PM_{2.5}$ was associated with a spectrum of changes in all ten cardiometabolic biomarkers investigated in this study. Specifically, $PM_{2.5}$ exposure was positively associated resistin, leptin, C-peptide, MCP-1, TNF-alpha, NT-proBNP, troponin, and IL-6, and inversely associated with ghrelin; a mix of inverse and positive associations were observed for CK-MB. The magnitudes of these associations were dependent on exposure durations, suggesting that the sensitive exposure durations differ across these biomarkers. Findings from this study provide insights regarding the latency period of the adverse effect of $PM_{2.5}$, which offers opportunities for potential interventions.

Ghrelin, resistin, leptin, and C-peptide are mainly related to energy metabolism, while they also play roles in inflammation (Meier and Gressner, 2004). Ghrelin stimulates food intake, and a low ghrelin level can be an indicator for obesity and type 2 diabetes. Resistin acquired its name because of its role in insulin sensitivity. The resistin level was elevated in individuals with insulin resistance, obesity, and type 2 diabetes. Leptin regulates energy balance, and its level is generally proportional to body fat mass. C-peptide is used as a marker of insulin secretion as it is secreted in equimolar amounts to insulin. The inverse association of ghrelin and positive associations of resistin, leptin, and C-peptide observed in this study suggests higher risks for insulin resistance, obesity, and type 2 diabetes, as supported by prior studies (Bowe et al., 2018; Chen et al., 2016). The significant associations for ghrelin, resistin, and leptin was observed in a short duration of only 1 or 2 months, further corroborating the conclusion about the adverse effects of short-term $PM_{2.5}$ exposure on insulin resistance (Bowe et al., 2018; Chen et al., 2016). Notably, the effect magnitude changed across different exposure durations, but were most pronounced for a duration of around 12 months for resistin and leptin, 18 months for ghrelin, and 24 months for C-peptide. The changing magnitude implies that on one hand the adverse effect of $PM_{2.5}$ exposure can be chronic and accumulative, and on the other hand these biomarkers are unable to completely reflect the very long-term effect $PM_{2.5}$ exposure. Findings from this study also suggest that the sensitive exposure duration for different cardiometabolic biomarkers vary.

The link between $PM_{2.5}$ exposure and metabolic disorders is accompanied with systemic inflammation, as indicated by positive associations of biomarkers including MCP-1, TNF-alpha, and IL-6 that are closely related and can influence each other's production and activity through complex signaling pathways (Jain et al., 2009). Systemic inflammation is a long-standing established pathway for the adverse effect of $PM_{2.5}$ exposure as supported by solid experimental evidence (Rajagopalan et al., 2018b). In population studies, investigations of MCP-1 and TNF-alpha generally focused on short-term $PM_{2.5}$ exposure and reported elevated MCP-1 and TNF-alpha levels associated with high $PM_{2.5}$ exposure levels (Chen et al., 2015; Dadvand et al., 2014; Zhang

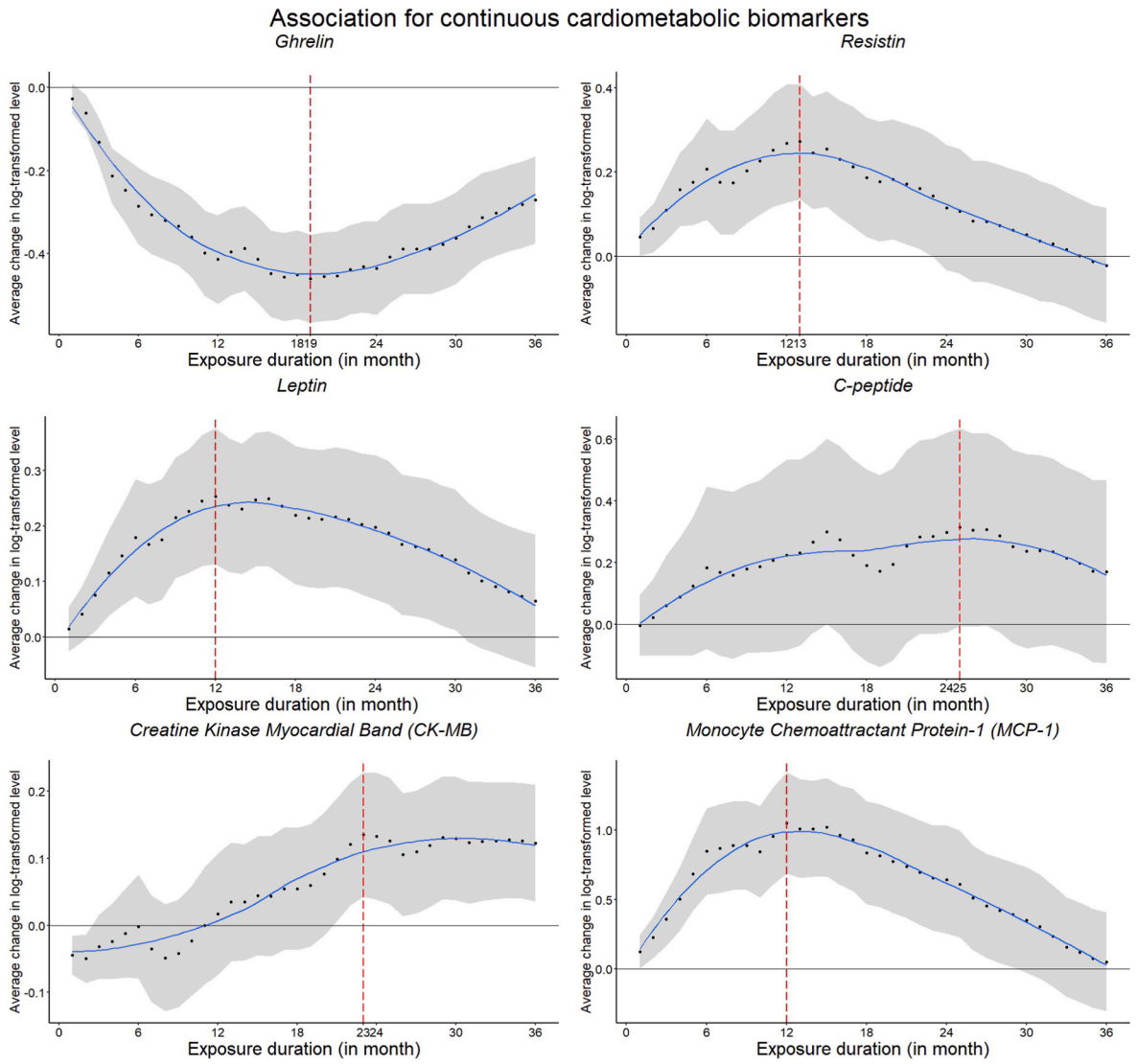

Fig. 2. Associations of average PM2.5 concentrations over different exposure durations with continuous cardiometabolic biomarkers in linear regression. The grey area indicates 95% confidence interval. The red vertical line indicates the strongest association over these exposure durations. The blue curve is the smoothing line generated from LOESS that describes the trend of effect estimates over these exposure durations. The mixed effect models were adjusted for age (35–39, 40–44, 45–49, 50–64, 65+), race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, other), gender (male, female), education (less than high school, high school, some college, college or more), household income (<$15,000, $15,000 - $24,999, $25,000 - $34,999 and >$34,999), body mass index (BMI; <25, 25–29.9, 30–39.9, >39.9), seasonality (January–March, April–June, July–September, October–December), smoking status (never, former, current), hypertension (yes, no), type 2 diabetes (yes, no), and heart attack history (yes, no), and neighborhood area deprivation index (ADI, in quartiles).

et al., 2022; Xia et al., 2019; Tseng et al., 2022). Our findings corroborated these conclusions and further demonstrate that the utilization of short exposure duration might underestimate the adverse effects of $PM_{2.5}$ exposure. Again, these findings suggest that the adverse effect of $PM_{2.5}$ exposure on systemic inflammation can be chronic and accumulative.

Systemic inflammation elicited by $PM_{2.5}$ exposure is widely considered as a major contributor to a higher risk for cardiovascular diseases. In this study, results for CK-MB and troponin, two biomarkers closely related to heart injury, provides evidence for this hypothesis at the population level. Few studies have investigated the association between cardiac troponin levels and air pollution, and they have focused on short-term exposures (Wyatt et al., 2022). Troponin is a more specific marker of heart damage than CK-MB, as it is only found in the heart muscle and not in other parts of the body. Elevated levels of troponin in the blood indicate that there has been damage to the heart muscle. The stronger association between long-term $PM_{2.5}$ exposure and troponin suggests that this effect is accumulative. CK-MB, on the other hand, is also found in other muscles, such as skeletal muscle, and can be elevated in cases of muscle damage or injury, in addition to heart damage. However, in the context of suspected heart diseases, elevated levels of CK-MB could indicate cardiac damage. It is very interesting to observe an inverse association between CK-MB and short-term $PM_{2.5}$ exposure. This inverse association could be due to protective mechanisms such as anti-oxidant defense, or a chance findings. But when the $PM_{2.5}$ exposure was prolonged, the association for CK-MB switched to positive and became stable. Compared to troponin, the association for CK-MB better reflects the long-term and accumulative damages caused by $PM_{2.5}$ exposure.

NT-proBNP is a hormone that is released by the heart in response to increased pressure or volume in the heart's chambers, thus usually used as an indicator of cardiac health. We observed a significant association of NT-proBNP and 1-month exposure duration. However, this does not necessarily mean that long-term $PM_{2.5}$ would not influence NT-proBNP

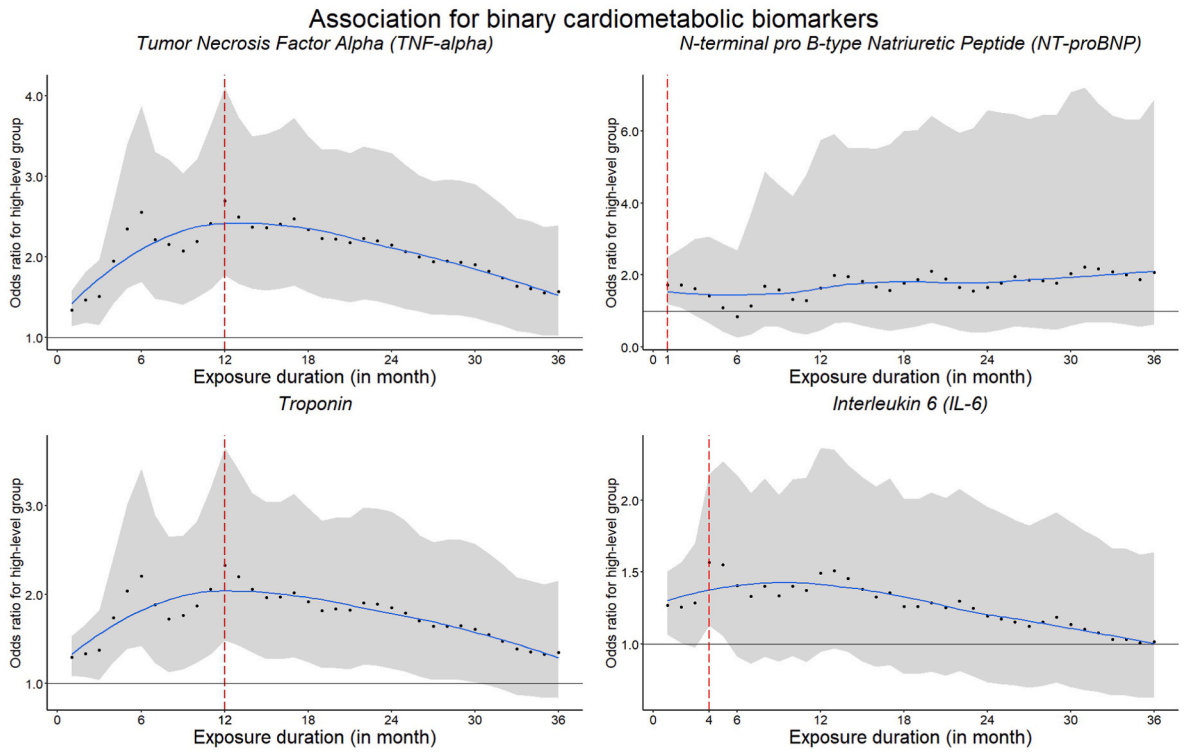

Fig. 3. Associations of average PM2.5 concentrations over different exposure durations with binary cardiometabolic biomarkers in logistic regression. The grey area indicates 95% confidence interval. The red vertical line indicates the strongest association over these exposure durations. The blue curve is the smoothing line generated from LOESS that describes the trend of effect estimates over these exposure durations. The mixed effect models were adjusted for age (35–39, 40–44, 45–49, 50–64, 65+), race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, other), gender (male, female), education (less than high school, high school, some college, college or more), household income (<$15,000, $15,000 - $24,999, $25,000 - $34,999 and >$34,999), body mass index (BMI; <25, 25–29.9, 30–39.9, >39.9), seasonality (January–March, April–June, July–September, October–December), smoking status (never, former, current), hypertension (yes, no), type 2 diabetes (yes, no), and heart attack history (yes, no), and neighborhood area deprivation index (ADI, in quartiles).

levels. It should be noted that only 10 participants were categorized as high NT-proBNP group. The limited sample size might prevent us drawing reasonable conclusion about NT-proBNP.

This study underscores the clinical significance of $PM_{2.5}$ exposure, providing evidence for its associations with crucial cardiometabolic biomarkers over time. Given the systemic nature of inflammation and its central role in many chronic diseases, the positive associations of $PM_{2.5}$ with inflammatory markers like MCP-1, TNF-alpha, and IL-6 are particularly alarming. On the other hand, the most sensitive time window for these associations identified in this study provides insights for potential interventions to mitigate the adverse health effects of $PM_{2.5}$ exposure, reinforcing the need for comprehensive public health strategies. These strategies should encompass stringent air quality control policies, community health monitoring, targeted healthcare services, and population-specific research to unravel the nuanced health impacts of air pollution in diverse communities. The unique findings concerning biomarkers like CK-MB and NT-proBNP, coupled with the limited sample size for the high NT-proBNP group, underscore the necessity for further research. The future research should be aimed at understanding the underlying biological mechanisms, refining predictive models for health outcomes, and developing preemptive interventions to safeguard cardiovascular health in susceptible populations exposed to $PM_{2.5}$.

The most sensitive exposure duration varied for different biomarkers investigated in this study. A duration of 12 months can be a critical time window, because we observed the strongest association with this duration for resistin (13 months), leptin, TNF-alpha, and troponin. For CK-MB, we observed a positive association beginning from 12 months exposure. These findings are unlikely to occur by chance. We posit that the adverse effects of $PM_{2.5}$ exposure on different aspects of human bodies are synchronous. In contrast, ghrelin and C-peptide had longer sensitive exposure duration, while NT-proBNP and IL-6 had shorter sensitive exposure durations. The varying exposure durations also suggests that we can use different biomarkers to measure the impact of $PM_{2.5}$, though more studies are needed to examine these durations in other cohorts.

Several large-scale studies on the relationship between $PM_{2.5}$ exposure and clinical diagnosis of cardiovascular diseases usually focus on long-term exposures, for example, 8 years (Bowe et al., 2018) and even 10 years (Di et al., 2017). Leveraging on cardiometabolic biomarkers, we found that the adverse effects of $PM_{2.5}$ can be evident in short exposure durations, with the most pronounced effect in a duration of nearly 12 months, even when the exposure level is as low as 9 $\mu g/m^3$ in this study. The findings support more interventions to further reduce air pollution and improve population health.

There are several limitations to consider in this study. First, the study population may not be nationally representative, nor was it designed to be geographically representative. The oversampling of disadvantaged groups can be a strength, but also leads this study to suffer from generalizability problems. Since African Americans are more vulnerable to the adverse effect of $PM_{2.5}$ exposure as suggested by prior studies, the strong effects observed in this study may not apply to other cohorts. Second, the air pollution variation is low in study, as most exposure levels fell between 8 and 12 $\mu g/m^3$. Therefore, results in this study may not be applied to more polluted areas, for example, the $PM_{2.5}$ exposure level in China is usually reported to be around 50 $\mu g/m^3$, almost five times that of the concentration levels in the US (Liu et al., 2019). However, the strong effect associated with low concentration level further corroborate the adverse effect of air pollution. Third, the current study does not link changes in cardiometabolic biomarkers with specific clinical diagnoses, though measured hypertension and heart attack

history were adjusted for in the analysis. While our observations suggest a latency period for the $PM_{2.5}$ exposure effect, there are sufficient data in the literature demonstrating that acute $PM_{2.5}$ exposure can triggers a pro-thrombotic state and cause ischemic damage to organs with blood flow through end arteries such as the heart, brain and other vital organs (Wylie et al., 2017; Li et al., 2022; Dutta et al., 2018). How these changes eventually lead to clinical diagnosis and whether any intervention on these biomarkers would benefit the population should be investigated in future studies. Fourth, we only included one air pollutant, $PM_{2.5}$, in this study. It is unknown how other pollutants (e.g., NO_2 and O_3) interact with $PM_{2.5}$ jointly affecting cardiometabolic profiles. To our knowledge, there is no data on monthly exposure to other pollutants that covers our study period. Therefore, we are unable to conduct a similar analysis for other pollutants at this moment. Future studies may evaluate if other air pollutants also demonstrated duration-sensitive associations as observed for $PM_{2.5}$ in this study. Last, this study is cross-sectional in nature, even though we were able to assign the air pollution level retrospectively. Therefore, caution is needed when we established a relationship between $PM_{2.5}$ exposure and one-time biomarker measures.

In conclusion, this study investigated the association between $PM_{2.5}$ exposure and changes in cardiometabolic biomarkers across exposure durations ranging from 1 to 36 months. $PM_{2.5}$ exposure was significantly associated with elevated levels in resistin, leptin, C-peptide, CK-MB, MCP-1, TNF-alpha, NT-proBNP, troponin, and IL-6, and a reduced level in ghrelin. The results suggest that the magnitudes of these associations may be dependent on exposure duration. The strongest association was observed with a duration of nearly 12 months for resistin, leptin, TNF-alpha, and troponin, a duration of more than 18 months for ghrelin and C-peptide, and a duration of 1–4 months for NT-proBNP and IL-6.

Credit atuhor statement

J.L. conceptualized the study, performed the analysis, and drafted the manuscript. M.G.K., F.J., and A.S. collected the samples and conducted the lab analysis. Z.J. performed the analysis. R.S. provided clinical support and drafted the manuscript. K.K., C.O.O., and J.P. provided clinical and administration support. H.A. acquired the research funding and supervised the study. B.A. conceptualized the study and supervised all process. All authors read and critically reviewed the manuscript.

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Declaration of competing interest

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

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2023.117496.

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