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Effect of Ambient Fine Particulate Matter Air Pollution and Colder Outdoor Temperatures on High-Density Lipoprotein Function

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Abstract

Fine particulate matter (PM_{2.5}) air pollution and environmental temperatures influence cardiovascular morbidity and mortality. Recent evidence suggests that several air pollutants can promote dyslipidemia; however, the impact of ambient PM_{2.5} and temperature on high-density lipoprotein (HDL) function remains unclear. We hypothesized that daily exposures to higher levels of ambient PM_{2.5} and colder outdoor temperatures would impair HDL functionality. Lipoproteins, serum cholesterol efflux capacity (CEC) and HDL oxidation markers were measured twice in 50 healthy adults (age: 32.1 ± 9.6 years) living in southeast Michigan and associated with ambient and personal-level exposures using mixed models. Although prior 7-day mean outdoor temperature (4.4 ± 9.8 °C) and PM_{2.5} levels (9.1 ± 1.8 µg/m³) were low, higher ambient PM_{2.5}

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exposures (per 10 $\mu\text{g}/\text{m}^3$) were associated with significant increases in the total cholesterol-to-HDL-C ratio (rolling average lag days 1 and 2) as well as reductions in CEC by -1.93% (lag day 5, $p=0.022$) and -1.62% (lag day 6, $p=0.032$). Colder outdoor temperatures (per 10°C) were also associated with decreases in CEC from -0.62 to -0.63% (rolling average lag days 5 and 7, $p=0.027$ and 0.028). Prior 24-hour personal-level $\text{PM}_{2.5}$ and temperature exposures did not impact outcomes, nor were any exposures associated with changes in HDL-oxidation metrics. In conclusion, we provide the first evidence that ambient $\text{PM}_{2.5}$ (even at low levels) and outdoor temperatures may influence serum CEC, a critical anti-atherosclerotic HDL function.

Keywords

Cholesterol Efflux Capacity; 3-Chlorotyrosine; 3-Nitrotyrosine; Myeloperoxidase

Introduction

Fine particulate matter ($<2.5\ \mu\text{m}$ diameter, $\text{PM}_{2.5}$) air pollution is a leading cause of global morbidity and mortality and this is primarily attributable to the increased cardiovascular (CV) disease burden ^{1,2}. Mounting evidence suggests that the long-term $\text{PM}_{2.5}$ exposure may play a crucial role in the development and progression of atherosclerosis ³⁻⁵. Extreme swings in outdoor temperatures are also linked to CV morbidity and mortality ⁶⁻⁸. Epidemiologic studies suggest that $\text{PM}_{2.5}$ -mediated increases in low-density lipoproteins (LDL) and reductions in high-density lipoproteins (HDL) cause the CV burden ^{5,9-13}. While low HDL levels are linked to CV risk, specific anti-atherosclerotic functions of HDL, namely the ability of HDL to off-load cholesterol from macrophages (measured as cholesterol efflux capacity, CEC) predict both prevalent and incident CV events ¹⁴⁻¹⁹. Myeloperoxidase (MPO), a heme-enzyme, together with a host of other systemic inflammatory responses are elevated with $\text{PM}_{2.5}$ exposure ^{3,20,21}. One pathway whereby $\text{PM}_{2.5}$ might thus impair HDL function is via heightened MPO-induced oxidation of HDL ²². In this context, we evaluated the effects of ambient $\text{PM}_{2.5}$, along with environmental temperatures on CEC, a critical facet of anti-atherosclerotic HDL function and the role of MPO-induced HDL-oxidation on HDL function.

Methods

The study was approved by the Institutional Review Board of the University of Michigan, and all participants signed a written informed consent. Potential participants were recruited from the local community in the southeast Michigan area by advertisements. Inclusion criteria were healthy nonsmoking adults living in nonsmoking households (by self-report) aged 18–50 years old, without a history of CV disease or risk factors (screening blood pressure $<140/90\ \text{mm Hg}$ and fasting glucose $<126\ \text{mg/dL}$). Subjects were excluded if they reported taking any antihypertensive, cholesterol, diabetes medication or any drug that could alter HDL function metrics (e.g., antioxidants, fish oil, folate). Qualifying participants ($n=50$) were enrolled into a repeated measures panel study conducted from August 2014 to February 2016 in Michigan (Figure S1). For a 24-hour period before the blood draws (fasting 8 hours), participants wore a personal environmental monitor while following

usual daily activities (no travel or exercise). Participants were then discharged home and underwent a 6-day (minimum) to 3-week (maximum) washout period before repeating the same process. Full details for protocols and statistical methods can be found in the online supplement.

Each patient had their own unique seven distinct 24-hour ambient outdoor temperature and PM_{2.5} data exposure (24-hour average) calculated starting retrospectively from the time in the morning of each blood draw. In addition, the rolling average of exposures from 1 to 7 days in duration was calculated. Personal-level exposures and temperatures were recorded as averages for the 24-hour period before the blood draw visit in each study block ²³.

Total Cholesterol, triglycerides, and HDL were measured by the enzymatic, GPO-PAP and a 2-step direct method on a Randox RX Daytona Chemistry analyzer (West Virginia, USA). HDL was prepared from plasma by sequential ultracentrifugation. HDL proteins were precipitated and delipidated, and oxidized amino acids were isolated by solid-phase extraction from an acid hydrolysate of HDL proteins. Oxidized amino acids were quantified using isotopically labeled internal standards- ¹³C₆ tyrosine, ¹³C₆ 3-chlorotyrosine, and ¹³C₆ 3-nitrotyrosine by liquid chromatography-electrospray ionization tandem mass spectrometry (LC-ESI-MS/MS) with multiple reaction monitoring (MRM) and positive ion acquisition mode²².

CEC was assessed was using J774 murine macrophages that were labeled with 2 µCi/mL ³H cholesterol (Perkin Elmer, Waltham, MA) for 24 hours in the presence of an acyl-CoA: cholesterol acyltransferase (ACAT) inhibitor (Sandoz 58-035, Santa Cruz Biotechnology, CA, USA) and equilibrated overnight with 0.3mM 8-(4-chlorophenylthio)-cyclic AMP to induce ATP-binding cassette A1 (ABCA1) expression. ApoB-depleted serum was obtained from polyethylene glycol (PEG) precipitation and used as an efflux acceptor (2.8% v/v) for 4 hours. Efflux was quantified by liquid scintillation and expressed as a percentage of total cell ³H-cholesterol content. All assays were performed in duplicate, and average values were used in calculations¹⁵.

Summary statistics were computed for continuous measures as the mean ± standard deviation (SD), as well as median (interquartile range, IQR), and for categorical variables as frequency and proportion (%). We analyzed the associations of repetitive measurements with 24-hour average outdoor ambient and personal-level PM_{2.5} and temperature using mixed-effect models. All analyses were performed using the statistical software package R (version 3.2.5).

Results

The 50 study participants (34 women) were young and overall healthy (Table 1). Prior 24-hour personal-level and 7-day outdoor-ambient exposures for temperatures and PM_{2.5} concentrations are provided in Table 2. PM_{2.5} levels were low and on-average within annual National Ambient Air Quality Standards < 12 µg/m³. There were few correlations between HDL function metrics and participant demographics (Table S1). Moreover, PM_{2.5} and temperatures were weakly or not-at-all correlated supporting their potential as independent

factors on study endpoints (Table S2). There were trends toward higher concentrations of ambient PM_{2.5} over the previous week being related to increases in the total cholesterol-to-HDL ratio (Figure 1). An increase of 10 µg/m³ was associated with a mean 0.18 (p=0.022) and 0.20 (p=0.032) elevation on rolling average lag days 1 and 2, respectively. This change was not due to a lowering of HDL but rather driven by a tendency for increases in LDL-C (Figure S2). Lipoprotein changes had no significant relationships with prior 24-hour personal-level PM_{2.5} or any temperature exposures.

Higher ambient PM_{2.5} levels over the preceding week tended to be associated with impairments in serum CEC (Figure 2). The associations reached statistical significance in a delayed fashion with reductions ranging from -1.93% (p= 0.022) to -1.62% (p=0.032) for a single day increase in ambient PM_{2.5} of 10 µg/m³ on lag days 5 and 6, respectively. However, personal-level PM_{2.5} exposures during the previous 24-hours were not associated with CEC. Neither ambient nor personal-level PM_{2.5} exposures were associated with MPO-induced or other HDL oxidation markers (Figure S3).

Exposures to colder outdoor temperatures over the previous week were also associated with impairments in serum CEC (Figure 3). Significant decreases ranged from -0.62% (p= 0.027) to -0.63% (p=0.028) for rolling average colder temperatures (per -10°C) over lag days 6 and 7. However, personal-level temperature exposure during the previous 24-hours was not associated with CEC. Neither outdoor nor personal-level temperature exposures were significantly associated with levels of MPO-induced or other HDL oxidation markers (Figure S4).

Finally, there was no effect modification (no significant interaction in the statistical models) between temperature levels and PM_{2.5} exposures for CEC. Therefore, we evaluated the combined effect of a colder temperature (-10°C rolling average level) and higher PM_{2.5} (10 µg/m³ single day level) on lag day 5. In this potential real-life situation, the adverse impact of both co-exposures led to a more substantial decrease in CEC by -2.17% (p=0.011).

Discussion

We herein demonstrated that ambient PM_{2.5} and outdoor temperatures each influence CEC. PM_{2.5} also acutely shifted lipoproteins toward a more pro-atherogenic pattern. While both environmental factors are known to affect lipids^{5,9-13,24,25}, this is the first report providing evidence that ambient levels of PM_{2.5} and colder outdoor temperatures might each independently impair HDL function. Given the critical role that CEC plays in mitigating the atherosclerotic process^{14,15}, our results elucidated a novel mechanistic linkage between PM_{2.5} and heightened CV risk¹⁻⁵. These findings may also help to explain the increase in CV events during colder seasons^{6,7}.

Prior studies have shown that air pollutants can promote dyslipidemia^{5,9-13}. Long-term PM_{2.5} exposures were linked to lower HDL particle numbers in Multi-Ethnic Study of Atherosclerosis-MESA¹³. We also observed that PM_{2.5} prompted an acute increase in the total cholesterol-to-HDL ratio, primarily due to increasing trends in LDL. While important, we posited that a PM_{2.5}-mediated impairment in HDL function would be a stronger

mechanistic explanation for pro-atherosclerotic actions. Converging epidemiological and experimental evidence highlights that CEC, rather than HDL levels per se, is the critical HDL-facilitated process responsible for protecting against CV events^{14,15}. However, few studies have evaluated the impact of air pollutants on HDL function^{16–19}. Animals exposed to high PM levels developed a blunted HDL anti-oxidant capacity^{16,17}. In our prior study, acute exposure to concentrated PM_{2.5} prompted a similar response in a subset of adults¹⁸. As far as we are aware, the lack of impact on CEC following a 2-hour exposure to coarse PM is the only previous study to evaluate the effect of any air pollutant on this endpoint¹⁹. This makes our current findings - that ambient PM_{2.5} levels and not 24-hour personal PM_{2.5} were independently associated with a reduction in CEC over subacute time periods - both novel and clinically relevant. Our results could help further explain epidemiological studies linking PM_{2.5} with heightened atherosclerosis and increased CV events^{3–5}. Billions of people (particularly across Asia) continue to face markedly-poor air quality, with daily PM_{2.5} levels commonly 2 to 50-fold above those in Michigan¹. The fact that even low levels of PM_{2.5} are linked to an impaired facet of anti-atherosclerotic HDL function supports the imperative to reduce this ubiquitous air pollutant as much as possible to protect global CV health².

The mechanisms responsible for our findings must remain speculative. Animal models suggest that enhanced atherosclerosis progression may have risen from HDL dysfunction due to the heightened generation of reactive oxygen and nitrative species^{5,18}. We posited that PM_{2.5} might increase MPO-induced oxidation of HDL and thereby blunt CEC²². However, we found no evidence for increased MPO-specific (3-chlorotyrosine) or other oxidative changes (3-nitrotyrosine and *o,o'*-dityrosine) on HDL protein despite using a highly-sensitive assay (LC-ESI-MS/MS). It is possible that HDL oxidation/modification could have arisen from other sources that went undetected – free metal ions and radicals, various enzymes, glucose, and acute phase reactants^{26–29}. In the current study, blunted CEC occurred in a delayed fashion – 5 to 6 days following higher ambient PM_{2.5} levels but not acutely to 24-hour personal PM_{2.5} levels. This suggests that the underlying mechanism is a relatively slower (subacute) process, or that any acute PM_{2.5}-mediated damage to HDL takes several days to become manifest through reduced CEC. However, the personal exposures were monitored only for the 24-hour period leading up to the blood sampling and hence failed to capture this sub-acute process. It is interesting to note that in a recent study from Shanghai, subacute (9-days) of ambient PM_{2.5} exposure (albeit at much higher levels) induced a wide array of adverse metabolic-stress responses (e.g., altered corticosteroids, catecholamines, amino acids, lipids, and fatty acids)³⁰. We, therefore, plan to evaluate if any of these mediators, or other HDL factors such as an altered proteome, are responsible for the reduction in CEC observed in our current study. It will also be important in future analyses to explore the impact on other potentially-important facets of HDL function (e.g., anti-oxidant and anti-inflammatory indices).

We have previously shown that increasing levels of PM_{2.5} and outdoor temperatures are associated with opposing effects on blood pressure⁸. Given that people are often concomitantly exposed to multiple environmental factors, we felt it necessary to test whether there were individual effects of PM_{2.5} and temperatures on HDL function. We show here for the first time that colder outdoor temperatures were also independently associated with

reduced CEC. The response appeared in a delayed subacute time-period (lag days 5–7), similar to that induced by PM_{2.5}. This suggests that shared or overlapping mechanisms may be responsible; however, future studies are required in this regard. We speculate that cold-induced HDL dysfunction may help further explain the increase in CV events related to winter^{6,7}.

Our study was relatively small and conducted at a single location with low air pollution levels. The CEC changes observed were modest and of uncertain clinical relevance for a single individual; however, it is possible that much higher exposures to PM_{2.5} (such as across Asia) may be associated with more robust alterations. Moreover, PM_{2.5} causes serious public health problems not because of the small adverse health effects at the individual-level but because of the enormous number of people impacted worldwide on a continual involuntary basis¹. We cannot exclude the possibility that other unmeasured pollutants also affected CEC. However, our prior studies demonstrate that while other co-pollutants (e.g., ozone) may have had an independent effect, they are unlikely to explain or confound the associations with PM_{2.5}. The influence of other pollutants, the specific sources of exposure (e.g., traffic-related pollution), and particle components (e.g., metals) responsible for impairing HDL function warrant future investigation. Finally, as with all observational studies, any causation cannot be directly inferred from our findings. Nevertheless, our trial was a priori designed with the aim of evaluating the impact of PM_{2.5} on CEC and HDL function metrics, and there are biologically plausible explanations for our results. Follow-up larger trials in several locations with more varied PM_{2.5} levels would be essential to corroborate our findings as well as enhance our understanding of these novel observations. In conclusion, our study shows for the first time that subacute exposures to low levels of ambient PM_{2.5} as well as colder outdoor temperatures are each independently associated with near-term reductions in CEC – a vital aspect of HDL function. Future studies are needed to test whether interventions to reduce exposures to both environmental risk factors can improve HDL function and decrease CV events.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1. Associations of higher ambient PM_{2.5} concentrations with changes in total cholesterol to high density lipoprotein cholesterol ratio

Results provided per 10 µg/m³ increase in ambient PM_{2.5}. Average, rolling mean ambient PM_{2.5} concentrations averaged over all exposure days up through lag day(s) 1–7; Single day lag, individual lag day ambient PM_{2.5} concentrations; Linear mixed effect model adjusted for same-day ambient temperature, sex and study block. Significant associations highlighted in red. PM_{2.5}, Fine particulate matter; TC/HDL, total cholesterol to high density lipoprotein cholesterol ratio.

Figure 2. Associations of higher ambient PM_{2.5} concentrations with serum cholesterol efflux capacity

Results provided per 10 $\mu\text{g}/\text{m}^3$ increase in ambient PM_{2.5}. Average, rolling mean ambient PM_{2.5} concentrations averaged over all exposure days up through lag day(s) 1–7; Single day lag, individual lag day ambient PM_{2.5} concentrations. Linear mixed effect model adjusted for same-day ambient temperature, sex and study block. Significant associations highlighted in red. CEC, cholesterol efflux capacity (% change); PM_{2.5}, Fine particulate matter.

Figure 3. Association of colder ambient temperatures with serum cholesterol efflux capacity
Results provided per 10°C decrease in ambient temperature. Average, rolling mean temperature averaged over all exposure days up through lag day(s) 1–7; Single day lag, individual lag day temperature. Linear mixed models adjusted for same-day ambient PM_{2.5} level, sex, study block. Significant correlations highlighted in red. CEC, cholesterol efflux capacity (% change).

Table 1

Clinical Characteristics of the Study Participants (n=50, 34 women)

Variable	Obs	Mean $\pm$ SD	Min	25 th percentile	Median	75 th percentile	Max
Age (years)	50	32.1 $\pm$ 9.6	19	24.0	28.5	41.0	50
BMI (kg/m ²)	50	26.1 $\pm$ 5.7	19.0	21.7	24.9	29.1	43.5
Systolic BP (mm Hg)	200	107.8 $\pm$ 13.3	86	99	105	112	161
Diastolic BP (mm Hg)	200	70.2 $\pm$ 9.4	50	65	69	75	107
Heart rate (beats/min)	200	70.6 $\pm$ 11.3	44	63	71	78	111
Total cholesterol (mg/dL)	100	149.4 $\pm$ 32.3	72	129.5	149	168	229
Triglycerides (mg/dL)	100	75.3 $\pm$ 52.7	21	44	57	95	345
LDL cholesterol (mg/dL)	100	86.8 $\pm$ 25.3	30	69.2	82.2	100.4	158
HDL cholesterol (mg/dL)	100	47.6 $\pm$ 13.5	23	38	46	54.5	100
CEC (%)	100	16.16 $\pm$ 3.57	9.29	12.94	15.93	18.90	26.32
3-chlorotyrosine*	100	7.84 $\pm$ 17.22	<0.01	0.04	1.16	4.51	87.82
3-nitrotyrosine*	100	4.68 $\pm$ 8.1	<0.01	0.78	2.09	5.36	67.39
<i>o,o'</i> -dityrosine*	100	0.65 $\pm$ 3.34	<0.01	<0.01	<0.01	0.18	31.97

BP, blood pressure; BMI, body mass index; CEC, cholesterol efflux capacity; HDL, high density lipoprotein; LDL, low-density lipoprotein; max, maximal value; min, minimal value; Obs, number of observations; SD, standard deviation;

* mmol/mol tyrosine.

Table 2**Ambient and Personal-Level Environmental Exposures**

Variable	Obs	Mean $\pm$ SD	Min	25 th percentile	Median	75 th percentile	Max
PM _{2.5} ($\mu\text{g}/\text{m}^3$)	95	12.2 $\pm$ 16.9	0.2	4.0	6.9	13.3	94.0
7-day average	94	9.1 $\pm$ 1.8	5.5	7.7	9.1	10.7	12.4
Personal Outdoor	98	22.0 $\pm$ 3.0	13.8	20.4	22.2	24.2	28.7
7-day average	97	4.4 $\pm$ 9.8	-13.4	-3.9	2.9	12.7	23.2

Personal PM_{2.5} and temperature levels were averaged from all available 24-hour long period measurements performed on lag day 1 prior to blood draw during both study blocks. Outdoor PM_{2.5} and temperature levels were averaged over 7-day long lag periods prior to all study visits. max, maximal value; min, minimal value; Obs, number of observations; SD, standard deviation.