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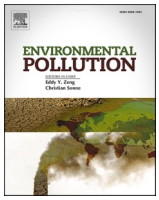

Particle surface area, ultrafine particle number concentration, and cardiovascular hospitalizations☆

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ABSTRACT

While the health impacts of larger particulate matter, such as PM_{10} and $PM_{2.5}$, have been studied extensively, research regarding ultrafine particles (UFPs or $PM_{0.1}$) and particle surface area concentration (PSC) is lacking. This case-crossover study assessed the associations between exposure to PSC and UFP number concentration (UFPnc) and hospital admissions for cardiovascular diseases (CVDs) in New York State (NYS), 2013–2018. We used a time-stratified case-crossover design to compare the PSC and UFPnc levels between hospitalization days and control days (similar days without admissions) for each CVD case. We utilized NYS hospital discharge data to identify all CVD cases who resided in NYS. UFP simulation data from GEOS-Chem-APM, a state-of-the-art chemical transport model, was used to define PSC and UFPnc. Using a multi-pollutant model and conditional logistic regression, we assessed excess risk (ER)% per inter-quartile change of PSC and UFPnc after controlling for meteorological factors, co-pollutants, and time-varying variables. We found immediate and lasting associations between PSC and overall CVDs (lag0–lag0-6: ERs% (95% CI%) ranges: 0.4 (0.1,0.7) - 0.9 (0.7–1.2), and delayed and prolonged ERs%: 0.1–0.3 (95% CIs: 0.1–0.5) between UFPnc and CVDs (lag0-3–lag0-6). Exposure to larger PSC was associated with immediate ER increases in stroke, hypertension, and ischemic heart diseases (1.1%, 0.7%, 0.8%, respectively, all $p < 0.05$). The adverse effects of PSC on CVDs were highest among children (5–17 years old), in the fall and winter, and during cold temperatures. In conclusion, we found an immediate, lasting effects of PSC on overall CVDs and a delayed, prolonged impact of UFPnc. PSC was a more sensitive indicator than UFPnc. The PSC effects were higher among certain CVD subtypes, in children, in certain seasons, and during cold days. Further studies are needed to validate our findings and evaluate the long-term effects.

1. Introduction

While relatively large particulate matter, such as PM_{10} (those smaller than 10 μm) and $PM_{2.5}$ (those smaller than 2.5 μm), have been associated with adverse health outcomes in many prior studies (Li et al., 2017; Schraufnagel, 2020), few know that ultrafine particles (UFPs) may threaten human health even more so. Classically, PM has been classified by size, an important factor in determining its health impacts. Airborne particulates smaller than 100 nm or ≤0.1 μm in diameter are called UFPs or $PM_{0.1}$ (these two terms are used interchangeably in this paper). Sources of UFPs include engine combustion, cooking, indoor heating, wood-burning, new particle formation and growth, and, more recently, products generated through nanotechnology (HEI Review Panel on Ultrafine Particles, 2013; Lippmann et al., 2013). Studies have shown that

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exposure to ambient UFPs has detrimental effects on respiratory and cardiovascular systems (Ostro et al., 2015; US EPA, 2019; Schraufnagel, 2020). Compared to larger particles, UFPs are of greater public health concern due to their 1) small size, which allows them to move into the lung interstitium and periphery easily, 2) large surface area to mass ratio, allowing them to effectively absorb trace metals/chemicals, and 3) ability to penetrate the alveoli and translocate to other organs via systemic circulation quickly (HEI Review Panel on Ultrafine Particles, 2013; Chen et al., 2020; Schraufnagel, 2020).

There is mounting evidence connecting the adverse health effects of $PM_{2.5}$ to cardiovascular diseases (CVDs). However, fewer studies have examined the CVD effects of UFPs (Brook et al., 2010; Franck et al., 2011; Liu et al., 2013; Du et al., 2016; Schraufnagel, 2020). In addition, among the few UFP studies, UFP number concentration (UFPnc) was found to be associated with multiple CVDs, such as ischemic heart diseases (IHDs), stroke, hypertension, myocardial infarction (MI), and heart failure, but not found in $PM_{2.5}$ or PM_{10} (Andersen et al., 2010; Li et al., 2017; Downward et al., 2018; Chen et al., 2020). However, despite the rapid growth of published studies on UFPs over the past decade, the evidence for the associations between UFP exposure and cardiovascular effects remains inconclusive due to the paucity of epidemiologic studies in this area, exposure misclassification, and lack of standard metrics.

Most previous studies assessed the effect of UFPs on mortality (Janssen et al., 2013; Lanzinger et al., 2016) or respiratory diseases rather than on CVD, although CVD is the leading cause of death in the US, leading to 659,000 deaths (1 in 4) each year (Centers for Disease Control and Prevention, 2020). In addition, heart disease costs the US approximately $363 billion per year (Aparicio et al., 2021), and CVD is the top cause of hospital admissions in New York State (NYS). Unfortunately, there is currently no network of UFP monitors in any country. As a result, almost all published papers in this area used UFP measurement data from one or very few monitoring sites, usually located in urban areas. Since UFPs have high spatial variability, the limited number of special monitoring sites introduces significant exposure misclassification problems and limited generalizability for studies utilizing them.

Furthermore, fine particle metrics other than particle number concentration (PNC) have rarely been used to assess their health effects in prior research. For instance, Chen et al. (2020) found that particle surface area concentration (PSC) was associated with a higher risk of MI than UFPnc, and PSC may be a more sensitive and biologically relevant metric. Finally, previous studies have not considered the interaction of meteorological and seasonal factors with UFPs on CVD, although these factors are considered important effect modifiers (Sioutas et al., 2005).

This study helps fill the knowledge gaps described above by assessing the association between PSC and UFPnc on hospital admissions for overall CVDs and several major CVD subtypes in NYS using simulated data generated by the innovative GEOS-Chem-APM model. Finally, we estimated the effects of PSC on CVD across lag days, socio-demographics, seasons, and meteorological factors.

2. Methods

2.1. Study design and health outcomes

We used a time-stratified case-crossover design where days of admission are defined as case days while identical day of the week in the same calendar month are defined as control days (Zhang et al., 2018; Rich et al., 2019). The exposure level is compared between the case and control days for the same person, thereby controlling for personal confounders such as sex, age, family history of heart disease, and genetic variations. In addition, holidays, seasons, and long-term secular trends are important confounders in short-term air pollution studies as they can affect hospital visits. For example, hospital admissions are more frequent on Mondays. This time-stratified design will control for various time-varying variables, including the effects of weekdays, weekends, holidays, seasons, and long-term trends. We obtained CVD-related hospital admissions data (2013–2018) from the New York State (NYS) Statewide Planning and Research Cooperative System (SPARCS), a legislatively mandated database that requires all hospitals in NYS to report every hospital admission and covers over 95% of NYS hospital records (SPARCS, 2022). We defined CVDs using principal diagnosis and the International Classification of Diseases (ICD) 9: 390–459 and ICD-10: I00–I99. In addition, we included the following major CVD subtypes for stratified analysis: 1) cerebrovascular diseases (ICD-9: 430–438, ICD-10: I60–I69), 2) hypertensive diseases (ICD-9: 401–405, ICD-10: I10–I16), 3) IHDs (ICD-9: 410–414 and ICD-10: I20–I25), 4) acute rheumatic fevers (ICD-9: 390–392 and ICD-10: I00–I02), 5) chronic rheumatic heart diseases (ICD-9: 393–398 and ICD-10: I05–I09), and 6) diseases of pulmonary circulation (ICD-9: 415–417 and ICD-10: I26–I28). All hospital admissions were geocoded to the residential street level, assigned to one of the GEOS-Chem simulation grids, and matched to the exposure variables.

2.2. PSC and UFP Simulation Model and Data

Due to the absence of a statewide network of PSC and UFP monitors, this study relied on particle size distribution simulations generated by GEOS-Chem-APM, a state-of-the-art global chemical transport model equipped with a size-resolved advanced particle microphysics (APM) module (Yu and Luo, 2009). Similar to an emissions-based model with a 4-km spatial scale used by Ostro et al. (2015), our GEOS-Chem-APM model is a global 3-D model of atmospheric composition (Bey et al., 2001) and is continuously being improved (Martin et al., 2003; Evans and Jacob, 2005; Pye and Seinfeld, 2010; Murray et al., 2012; Keller et al., 2014; Holmes et al., 2019; Luo et al., 2020). The APM model has the following relevant features to accurately simulate particle size distributions: (1) 40 bins to represent secondary particles with high size resolution for the size range important for the growth of nucleated particles to CCN sizes (Yu and Luo, 2009); (2) a state-of-the-art Ternary Ion mediated Nucleation (TIMN) mechanism (Yu et al., 2018) and temperature-dependent organics-mediated nucleation (Yu et al., 2017); (3) explicit kinetic condensation of both H_2SO_4 and low volatile organic gases onto particles (Yu, 2011); and (4) explicit resolution of the coating of secondary species on primary particles. GEOS-Chem-APM has been used in several studies, and modeling results have been evaluated against a large set of land-, ship-, aircraft-, and satellite-based measurements (Yu and Luo, 2009; Yu et al., 2010; Yu, 2011; Yu et al., 2015; Luo and Yu, 2011; Ma et al., 2012; Ma and Yu. 2014; Williamson et al., 2019).

In the present study, we ran GEOS-Chem-APM over a nested domain in the northeastern US with a $0.3125^\circ \times 0.25^\circ$ horizontal resolution (approximately 17 miles × 17 miles). PSC and UFPnc were calculated based on simulated particle size distribution (see Fig. 1 in Results for an example). With this resolution, the model can detect regional "blooms" of UFPs and UFP pollution associated with traffic emissions in major urban areas (such as New York City, Buffalo, and Rochester). While the model cannot resolve near roadway UFP, it can consider the mean elevated UFP exposure in major urban areas.

2.3. Statistical analysis

We used conditional logistic regression to compare the exposure levels between the case and control days for each case and calculated the exposure ratio for all the cases while controlling for three major categories of covariates (meteorological factors, air pollutants, and time-varying variables). Specifically, these categories of the covariates include ambient temperature, relative humidity, $PM_{2.5}$, O_3, NH_3, and time-varying variables (days of the week, holidays, season, and long-time trend). As each case is compared with themselves on control days in the case-crossover design, all inherited personal confounders such as sex, age, family history of heart disease, and genetic variations are

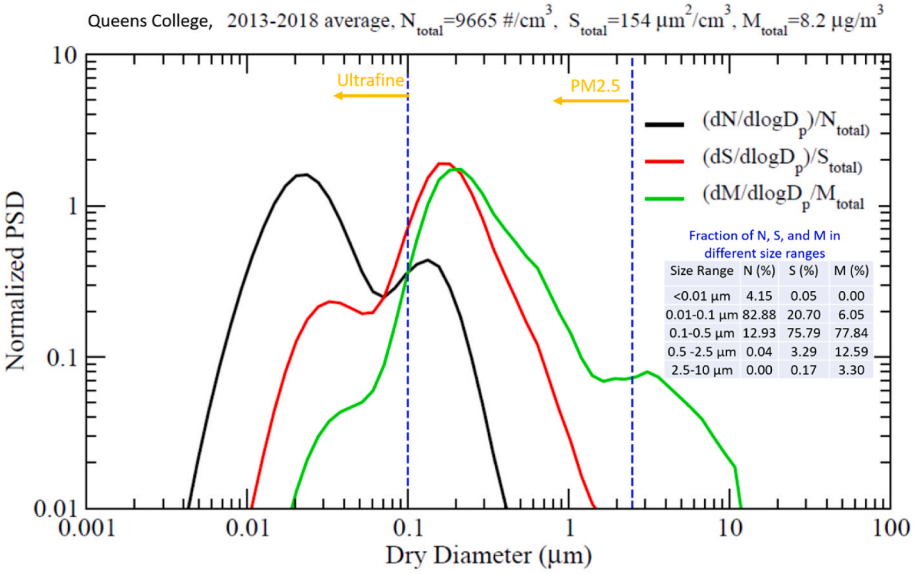

Fig. 1. 2013–2018 mean normalized particle size distributions (PSD) in terms of number (N, in #/cm^3), surface area (S, in μm^2/cm^3), and mass (M, in μg/m^3) concentrations in an urban site (Queen College, New York City). The total N, S, and M are 9665 #/cm^3, 154 μm^2/cm^3, and 8.2 μg/m^3, respectively. The fractions of N, S, and M in the different size ranges (<0.01, 0.01–0.1, 0.1–0.5, 0.5–2.5, and 2.5–10 μm) are given in the inserted table. UFPs (<0.1 μm) account for 87% of particle number concentration, 21% of particle surface area, and 6% of particle mass concentrations.

automatically adjusted. In addition, since each case's exposure days and control days were compared within the same month of the same year, various time-varying variables, including long-term trends, have been controlled in this time-stratified case-crossover design. We did not control for other air pollutants in the model, such as NO_2 or SO_2, because they are highly correlated with UFPs (correlation coefficients >75%). We also conducted several stratified analyses for PSC by disease subtype, season, temperature, relative humidity (RH), age, ethnicity, and race. As multi-day lag is a more sensitive and robust indicator than single-day lag according to prior literature (US EPA, 2019) and our data, we presented the results from multi-day lags as the primary tables/figures. Multi-day lag was calculated using the moving average of PSC and UFPnc, i.e., the sum concentrations of the daily means of these exposures on multiple days (0–6) divided by total days (US EPA, 2019). Single-day lag analysis results are provided in the supplemental materials as the sensitivity analyses. The excess risk (ER%) per each interquartile range (IQR) increase was calculated as (exp (β*IQR)-1)*100%, where beta was the regression coefficient. All analyses were conducted using R 4.1.2.

3. Results

Particles in the atmosphere have different sizes, and particles of different sizes are dominated by different particle numbers, surface areas, and mass concentrations. The size distributions of particles in NYS are explicitly simulated using the GEOS-Chem-APM model described earlier. Fig. 1 gives an example of normalized particle number, surface area, and mass size distributions at Queens College in New York City. Fig. 1 describes the fractions of number, surface area, and mass in the different size ranges of particles (<0.01, 0.01–0.1, 0.1–0.5, 0.5–2.5, and 2.5–10 μm). UFPs (<0.1 μm) account for 87% of PNC, 21% of PSC, and 6% of particle mass concentrations. Both PSC and mass concentrations are dominated by particles smaller than 0.5 μm in diameter. Unfortunately, no direct measurements of PSC are available for us to compare with model simulations. For PNC, continuous measurements are available at a monitoring site in Pinnacle State Park (PSP) (77.21° W, 42.10° N) in New York State. The PSP is in a remote area with minor influence from local sources and thus is suitable for comparison with the modeled value representing the average concentration over the 17 miles × 17 miles area containing the measurement site. Supplement 1 compares simulated total PNC with those observed at the PSP site. The model reasonably captures the observed absolute values and daily variations at the site, with a normalized mean bias (NMB) of −7.2% and a correlation coefficient of 0.65.

Table 1 describes the demographic profile of the study population, i.e., all the CVD cases included in this study (n = 1,773,474). A majority (55.2%) of cases were older adults (65+ years old, mean = 65.56 years), 11.4% were Hispanic, and 22.4% were African American. In addition, 4.2% of cases had no insurance, and 9.9% had Medicaid insurance.

The associations between each IQR increase in PSC or UFPnc, and the ER for overall CVDs by multi-day and single-day lags are presented in Table 2. Overall, we found that the corresponding risks of PSC and UFPnc on overall CVDs were higher on multi-day lag than on single-day lag. For example, the highest CVD risks (ERs (95%CI)) occurred immediately after PSC exposure (lag 0 and 0–1) were 0.9% (0.7%–1.2%) and 0.9% (0.6%–1.2%), respectively. The significantly positive associations occurred in all multi-day lags (Table 2). For UFPnc, the delayed highest

Table 1
Demographic profile of hospital admissions of all cardiovascular diseases in NYS, 2013–2018.

	Population (N)	% of Total
Sex		
Female	847,450	49.5
Male	864,728	50.5
Unknown	29	0.0
Age (years)		
0-4	4,975	0.3
5-17	16,862	1.0
18-64	782,068	45.7
>64	908,302	53.0
Race		
White	988,037	57.7
Black/African American	386,306	22.6
Native American/Alaskan Native	4,762	0.3
Asian	42,937	2.5
Native Hawaiian/Other Pacific Islander	1,295	0.1
Unknown	288,870	16.9
Ethnicity		
Spanish/Hispanic Origin	188,737	11.0
Not of Spanish/Hispanic Origin	1,459,742	85.3
Unknown	63,728	3.7
Insurance		
Self-Pay	81,075	4.7
Workers' Compensation	4,443	0.3
Medicare	846,151	49.4
Medicaid	177,436	10.4
Insurance Company	399,094	23.3
Blue Cross	176,798	10.3
Unknown	13,612	0.8
Other Insurance	13,598	0.8

Table 2
Association between each IQR increase in particle surface area or number concentrations of ultrafine particles and the excess risk (%) for hospital admissions due to cardiovascular diseases, NYS, 2013–2018.

	Case(N)	Multi-day lags			Single-day lags		
		Lag	IQR	Excess Risk (%)	Lag	IQR	Excess Risk (%)
Surface Area	1,712,207	0	213	0.9 (0.7, 1.2)*	0	213	0.9 (0.7, 1.2)*
	1,711,284	0–1	193	0.9 (0.6, 1.2)*	1	212	0.5 (0.2, 0.7)*
	1,710,171	0–2	173	0.8 (0.5, 1.1)*	2	213	0.1 (−0.1, 0.4)
	1,709,003	0–3	159	0.7 (0.4, 1.0)*	3	213	−0.1 (−0.3, 0.2)
	1,707,810	0–4	151	0.6 (0.3, 0.9)*	4	213	−0.1 (−0.3, 0.2)
	1,706,895	0–5	144	0.4 (0.1, 0.7)*	5	213	−0.4 (−0.6, −0.2)
	1,706,015	0–6	139	0.4 (0.1, 0.7)*	6	213	0.0 (−0.3, 0.2)
Ultrafine Particle	1,712,207	0	1950	−0.1 (−0.2, 0.1)	0	1950	−0.1 (−0.2, 0.1)
	1,711,284	0–1	1798	0.0 (−0.2, 0.1)	1	1950	0.1 (−0.1, 0.2)
	1,710,171	0–2	1680	0.1 (0.0, 0.3)*	2	1950	0.2 (0.1, 0.4)*
	1,709,003	0–3	1601	0.3 (0.1, 0.4)*	3	1950	0.2 (0.1, 0.4)*
	1,707,810	0–4	1543	0.3 (0.1, 0.5)*	4	1950	0.0 (−0.1, 0.2)
	1,706,895	0–5	1500	0.3 (0.1, 0.5)*	5	1950	0.1 (−0.1, 0.2)
	1,706,015	0–6	1466	0.3 (0.1, 0.5)*	6	1950	0.0 (−0.1, 0.2)

risks were observed from lag 0–3 to lag 0–6 days (ERs: 0.3%, 95% CIs ranged 0.1%–0.5%). For single-day lags, the highest risks for PSC were found on the same day (ER: 0.9%, 95% CI: 0.7%, 1.2%), but 2–3 days later (ER: 0.2%, 95% CI: 0.1%, 0.4%) for UFPnc.

We compared six CVD subtypes in relation to PSC and UFPnc using multi-day lags, which were significantly associated with cerebrovascular (stroke), hypertensive disease, and IHDs, but not with acute rheumatic fever, chronic rheumatic heart disease, and disease of pulmonary circulation (Table 3). In general, surface area was associated with immediately elevated risk of stroke (ERs (lags: 0, 0–1, 0–2): 1.1%–1.4%, 95% CIs: 0.5%–2.2%), and IHD (ERs (lags: 0, 0–1): 0.7%–0.8%, 95%CIs: 0–1.6%). The adverse effects of PSC on hypertensive admissions lasted a week (ERs (lags: 0, - 0–6): 0.7%–0.8%, 95%CIs: 0.1%–1.5%). In addition, UFPnc was statistically associated with a week-long elevated risk of hypertensive diseases (ERs (lag 0 – 0-6): 0.4%–0.9%; 95% CIs: 0–1.4%) with the highest risk on lag 0–3 (0.9%) and lag 0–4 day (0.8%).

In Fig. 2, the ERs associated with each IQR increase in surface area (PSC) with the CVDs by socio-demographical characteristics are described across multi-day lags. Generally, the associations of PSC and CVDs among different demographical groups were strongest on lag 0 and not statistically significant (P for interaction >0.05). Interestingly, we found that children (5–17 years) were at the highest risk (ER: 2.4%, 95% CI: 0.6%, 4.2%). Compared to their counterparts, males (ER: 1.1%, 95% CI: 0.8%, 1.4%), non-black individuals (ER: 1.2%, 95% CI: 0.9%, 1.5%), and non-Hispanic individuals, (ER: 1.0%, 95% CI: 0.7%, 1.3%) had higher risks.

Fig. 3 and Supplement Table 2 shows the ERs of PSC-CVD associations for different seasons per IQR increase in multi-day lag exposure. The interaction effects were statistically significant for all multi-day lags over a week (P for interaction <0.05). Statistically significant elevated ERs were observed for all seasons on lag 0 day (ER% (95% CI%) ranged from 0.4 (0–0.8) to 1.6 (1.2–2). However, the effects of PSC on CVD in winter were the strongest (ERs (lag 0–1, 0–2): 1.7%, 95% CI: 1.2–2.2), followed by fall (ER%s (0, 0–1): 1.2–1.3, 95%CI%: 0.8–1.7). Winter and fall seasons had significantly lasting CVD effects for the entire week after exposure. The abrupt transition between summer and fall in Fig. 3 is an artifact of putting the seasons in this order. This happened to be the pattern across lag days in the different seasons and are not comparable, as different lag days between seasons (i.e., “0–6” lag in Summer vs. “0” lag in Fall) are not temporally connected.

The interaction effects between temperature or relative humidity and PSC on CVDs are presented in Fig. 4 and Supplement Table 3. The interaction effects were consistently significant for temperature and relative humidity across all lag days (P-value for interaction <0.001). Compared with temperature >90th, we found that PSC increased risks of CVDs when the temperature was <90th (ER%s range: 0.7–1.4, 95%CI%: 0.3–1.7), with the risks declining over lag days. Similarly, the CVD risks of PSC were higher when the relative humidity was <90th (ER% range: 0.4–0.7, 95%CI%:0.1–0.9).

Table 3
Multi-day excess risk (%) associated with each IQR increase in particle surface area or number concentrations of ultrafine particles by subtypes of CVD admissions in NYS, 2013–2018.

Lag	Cerebrovascular (N = 210,427)	Hypertensive Disease (N = 378,479)	Ischemic Heart Disease (N = 223,589)	Acute Rheumatic Fever (N = 415)	Chronic Rheumatic Heart Disease (N = 1,798)	Diseases of Pulmonary Circulation (N = 44,896)
Surface area						
0	1.1 (0.4, 1.8)*	0.7 (0.3, 1.2)*	0.7 (0.0, 1.3)*	−12.0 (−24.8, 3.2)	−0.1 (−6.9, 7.2)	0.0 (−1.6, 1.5)
0–1	1.1 (0.4, 1.9)*	0.7 (0.1, 1.2)*	0.8 (0.1, 1.6)*	−17.8 (−30.8, −2.3)	−0.6 (−8.3, 7.8)	0.4 (−1.3, 2.1)
0–2	1.4 (0.5, 2.2)*	0.7 (0.1, 1.3)*	0.6 (−0.2, 1.4)	−7.6 (−22.2, 9.9)	0.00 (−8.2, 8.9)	0.10 (−1.7, 2.0)
0–3	1.0 (0.1, 1.8)*	0.8 (0.1, 1.4)*	0.2 (−0.6, 1.0)	−3.8 (−19.5, 15.0)	0.3 (−8.2, 9.5)	0.12 (−1.8, 2.1)
0–4	0.8 (−0.1, 1.8)	0.8 (0.2, 1.5)*	−0.1 (−1.0, 0.8)	−4.7 (−21.1, 15.0)	1.8 (−7.1, 11.6)	−0.3 (−2.2, 1.7)
0–5	0.5 (−0.4, 1.5)	0.7 (0.0, 1.3)*	−0.2 (−1.1, 0.8)	−3.8 (−21.0, 17.1)	4.6 (−4.9, 15.1)	−0.6 (−2.7, 1.4)
0–6	0.0 (−1.0, 1.0)	0.8 (0.1, 1.5)*	0.0 (−0.9, 1.0)	−2.7 (−21.2, 20.3)	4.7 (−5.3, 15.6)	−0.4 (−2.5, 1.8)
Ultrafine Particle						
0	0.2 (−0.2, 0.6)	−0.3 (−0.6, 0.0)	0.4 (0.0, 0.8)*	−2.8 (−10.8, 5.9)	−1.7 (−5.6, 2.4)	−0.2 (−1.1, 0.6)
0–1	0.3 (−0.2, 0.7)	−0.4 (−0.8, −0.1)	0.5 (0.1, 1.0)*	−3.4 (−12.0, 6.0)	−0.9 (−5.4, 3.8)	−0.1 (−1.1, 0.8)
0–2	0.2 (−0.3, 0.6)	−0.3 (−0.7, 0.0)	0.7 (0.2, 1.2)*	−6.1 (−15.2, 3.9)	1.6 (−3.6, 7.0)	0.3 (−0.7, 1.4)
0–3	0.2 (−0.3, 0.7)	−0.2 (−0.5, 0.2)	0.9 (0.4, 1.4)*	−7.3 (−17.0, 3.5)	2.3 (−3.3, 8.2)	−0.1 (−1.2, 1.1)
0–4	0.3 (−0.2, 0.9)	−0.2 (−0.6, 0.2)	0.8 (0.3, 1.4)*	−7.3 (−17.7, 4.3)	3.0 (−2.9, 9.3)	−0.9 (−2.1, 0.4)
0–5	0.3 (−0.3, 0.9)	−0.2 (−0.6, 0.2)	0.7 (0.1, 1.3)*	−8.5 (−19.1, 3.6)	1.4 (−4.7, 7.9)	−0.8 (−2.0, 0.5)
0–6	0.5 (−0.1, 1.1)	−0.4 (−0.8, 0.1)	0.6 (0.0, 1.2)*	−8.5 (−19.6, 4.3)	2.0 (−4.5, 8.8)	−1.0 (−2.3, 0.3)

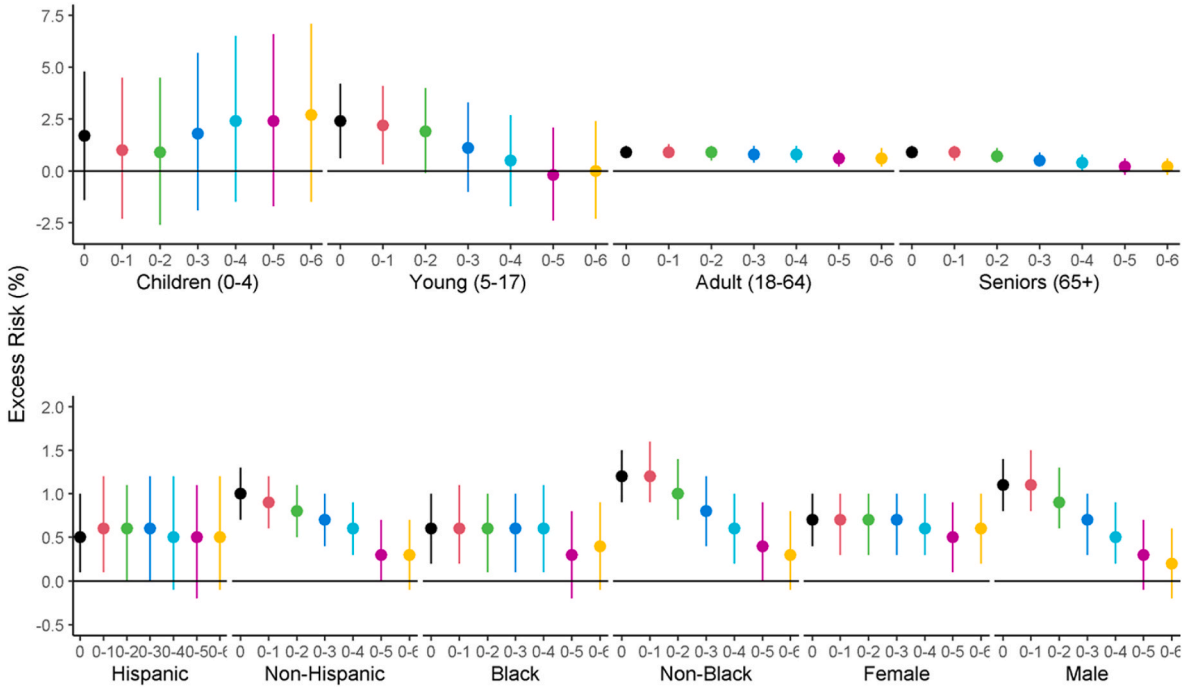

Fig. 2. Multi-day excess risks (%) of cardiovascular admissions associated with each IQR increase in particle surface area by different social demographics (age, ethnicity, race, and sex), NYS 2013–2018.

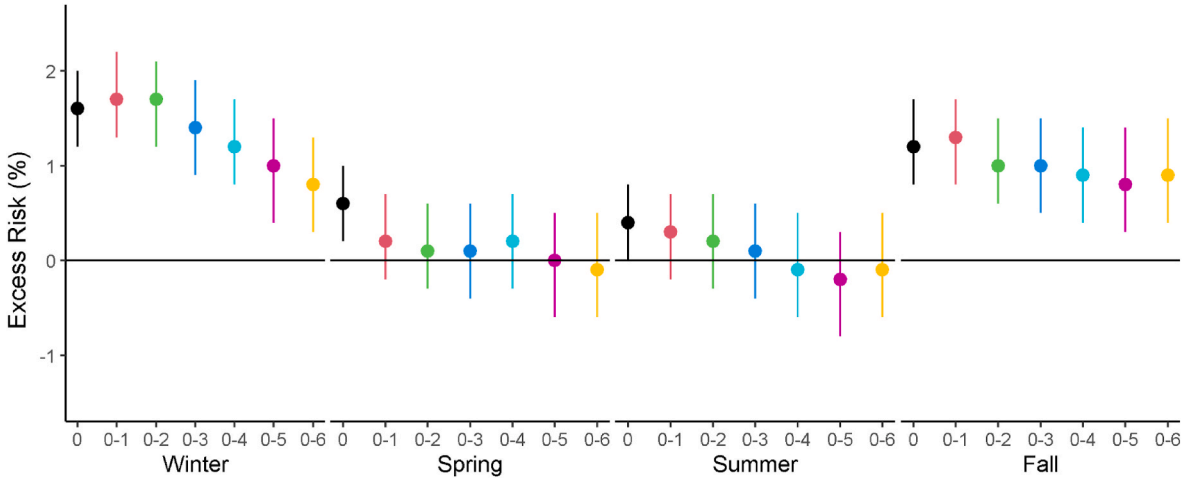

Fig. 3. Multi-day excess risk (%) of overall cardiovascular admissions associated with each IQR increase in particle surface area by season, NYS 2013–2018.

4. Discussion

4.1. Effects of PSC or UFPnc on CVDs by lag days

Our study found an immediate and strongest positive association between PSC and overall CVDs on the day of exposure and one day after. We also found a delayed adverse effect of UFP on CVD. Both PSC and UFP's effects lasted for a week after exposure. Consistent with our findings, the only study regarding PSC on CVD by Chen et al. (2020) found that exposure to PSC was significantly associated with increased risks of myocardial infarction (MI) from lag 2–6, and lasted for two weeks, in Augsburg, Germany during 2005–2015. Compared to PSC, the authors also found that UFPs (10–100 nm) showed a significantly delayed effect on lag 6. In addition, Abrams et al. (2017) reported that exposure to ambient fine particulate matter increased emergency department visits for multiple cardiorespiratory outcomes during 0–2 moving average of lag days after exposure in Georgia, US. In summary, recent multicity studies that examined the lag structure of fine particles-CVD associations generally support the immediate effect of $PM_{2.5}$ on cardiovascular mortality (Janssen et al., 2013; Lippmann et al., 2013; Samoli et al., 2013; Lanzinger et al., 2016; Stafoggia et al., 2017), but also provide some evidence that associations may exist for exposures averaged over longer durations (Hertel et al., 2010; Samoli et al., 2013).

Aligning with the lasting effects of fine particles we found, Andersen et al. (2010) examined the relationship between UFP exposure measured at two urban monitoring sites and 7,485 incident hospital admissions for stroke in Copenhagen, Denmark (1995–2003). They found significant increases in the odds of hospital admissions for ischemic and mild stroke following UFP exposures over the previous five days (lag 0–4). In addition, Franck et al. (2011) observed positive associations between short-term UFPnc exposure (measured by a single fixed-site monitor) and emergency calls for hypertensive crises in Leipzig, Germany. The

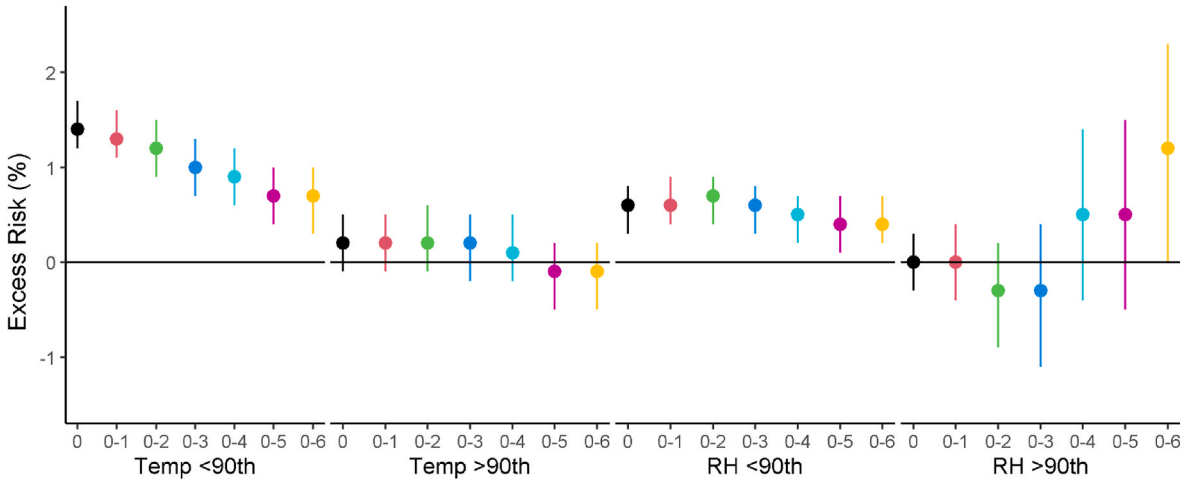

Fig. 4. Multi-day excess risk (%) of cardiovascular admissions associated with each IQR increase in particle surface area by temperature and relative humidity (RH), NYS 2013–2018.

authors observed positive associations at lag 2–9 days out of 0–10 days. Another interesting finding from this study is that multi-day lags moving average may be a more endpoint-sensitive indicator representing longer time or cumulative exposure. Studies that compared single-day and multi-day lag periods observed stronger associations using multi-day, aggregate CVD hospital admissions, and ED visits (Qiu et al., 2013; Talbott et al., 2014). Similarly, Liu et al. (2013) in Beijing, China reported a 7.2% (95% CI: 1.1, 13.7) increase in CVD ED visits per 9,040-particle/cm^3 increase using an 11-day moving average of UFPnc concentrations. In contrast to multi-day lags, single-day lags demonstrate the short-term or independent effect of each day's exposure. Our findings may highlight the importance of using both single-day and multi-day lags to demonstrate the short-/longer-term effects of UFP and identify the days with the highest effect on clinical facility (beds and care) preparation and public health preparedness. Additionally, there is always a lag period between the disease onset (for which we don't have data) and admission date. Therefore, up to a week may be needed to observe an admission episode. Unfortunately, no studies used both lag indicators to compare to our findings.

It is biologically plausible that exposure to UFP may trigger the onset of CVD in the short term, as demonstrated by multiple studies. The potential biological mechanisms include that UFP exposure may activate neural reflexes in the respiratory tract, provoke an imbalance of the autonomic nervous system, and initiate cardiac arrhythmias or MI (Brook et al., 2010). Several panel studies have also reported the associations between UFP and decreased heart rate variability within hours (Rich et al., 2012; Peters et al., 2015; Breitner et al., 2019) or even minutes (Pieters et al., 2015) of increased exposure. In addition, short-term exposure to UFPs may cause systemic oxidative stress and inflammation, leading to impaired vascular function and thrombosis (Brook et al., 2010). A panel study of cardiac patients in Rochester, New York, observed positive associations between UFP exposure in the previous 12 h and increased fibrinogen levels (Croft et al., 2017).

4.2. Comparing particle surface area with UFP number concentration on CVD

Our study also found that PSC was a more sensitive indicator (with consistently higher excess CVD risks across all multi-day lags) than UFPnc. Although UFPs accounted for 87% of UFPnc and 21% of PSC in our study, the broad range of PSC for all particles may increase the sensitivity to identify the health risks than UFPnc in our study. Consistently, Chen et al. (2020) also found that the effects of PSC and particle length concentration (PLC) were stronger and more precise than the UFPnc and remained similar after adjustment for PM or gaseous pollutants. A prior study in Augsburg, also in line with our findings, found stronger positive associations of inflammatory biomarkers in the blood with PSC and PLC than for UFPnc (Rückerl et al., 2016). Additionally, Hennig et al. (2018) reported that UFPnc (50–500 nm) and lung-deposited PSC were positively associated with overall cardiovascular mortality in Germany.

Several toxicological studies also suggested that PSC might be the most biologically relevant and effective dose metric for acute nanoparticle toxicology in the lung (Sager and Castranova, 2009; Schmid and Stoeger, 2017). This may be explained because the particle surface is where components of UFP interact directly with bodily fluids and tissue (Schmid and Stoeger, 2017). Greater PSC may increase the surface reactivity and thus the oxidative stress and pro-inflammatory effects (Hussain et al., 2009). Furthermore, Henning et al. (2018) stated that PSC distributions could be directly linked to emission sources and thus may be used for planning potential public health interventions. In other words, compared to particle mass and number, PSC could be used as an alternative metric that constitutes an integrated marker of reactive particle surface and deposition efficiency, which likely serves as a better indicator of understanding the biological mechanisms by which the inhalation of particles leads to health outcomes.

4.3. PSC/UFPnc – CVD associations by CVD subtype groups and SES

Our study found that exposure to large PSC was associated with immediate adverse effects and hospital admissions due to stroke, hypertension, and IHD. UFP's effect on IHD also occurred immediately but was higher in the later lags. Both PSC-hypertension and UFP-IHD associations persisted for an entire week. However, there are no significant effects from PSC and UFPs on acute rheumatic fever, chronic rheumatic heart disease, and diseases of pulmonary circulation. In line with our findings, Abrams et al. (2017) reported that oxidative potential dithiothreitol exposure was associated with ED visits for multiple cardiorespiratory outcomes, including IHD, on the same day to two days after exposure in Atlanta, Georgia, US. In addition, an in-home survey in near-highway and urban background neighborhoods in and near Boston (MA, USA) found that time activity adjusted annual average UFPnc exposures were associated with stroke, IHD, and hypertension after controlling for BMI (Li et al., 2017). Multiple $PM_{2.5}$ studies summarized by the US EPA (2019) also indicated that the increased risk of cerebrovascular disease or stroke related to $PM_{2.5}$ exposure was rapid (on the same day) and had higher magnitudes than IHD (2 days after $PM_{2.5}$ exposures and lower risks). A consistent finding was that the cardiovascular effects of pollution were much stronger in the Northeast than in other regions. In addition, $PM_{0.1}$ exposure was associated with an

increased incidence of heart failure, acute MI, ischemic and thrombotic stroke, and increased blood pressure even after controlling for $PM_{2.5}$ and NO_2 (Andersen et al., 2010). Unexpectedly, we found a few protective associations between PSC or UFPs and CVD subtypes. These may be explained by CVD subtype differences in susceptibility (Brook et al., 2010; Ostro et al., 2015; US EPA, 2019), chance findings due to small sample sizes in certain groups, and different biological mechanisms (HEI Review Panel on Ultrafine Particles, 2013; US EPA, 2019).

We did not find significant differences in the PSC-CVD associations by different strata of various sociodemographic (SES) variables. One interesting finding is that young children aged 0–4 and 5–17 years old showed the highest CVD risk per each IQR change of PSC for all multi-day lags compared to adult groups. Unfortunately, we could not find any studies that evaluated the disparities of PSC-CVD associations by SES. Children are usually more vulnerable to air pollution's health effects, which may begin in utero and produce lifelong consequences (Schraufnagel et al., 2019). As CVD is quite rare among children, the highest CVD risk we found among them may be explained by a selected group of children with serious pre-existing health conditions. This finding demands further investigation.

4.4. UFP-CVD associations by seasonality and temperature

We found a significant seasonal difference in PSC-CVD relationships, i.e., the adverse effects of PSC on CVDs were approximately two-fold on most multi-day lags in the fall and winter as those in the spring or summer. Consistently, we also found that the PSC-CVD associations were stronger on the days with lower temperature and lower humidity than on hot days with high humidity. Another interesting finding is that an excess CVD risk occurred immediately (on the same day of PSC exposure) in summer and spring without delayed effects. This is consistent with elevated local UFP levels from traffic which are higher during colder temperatures, mainly due to lower boundary layer height and reduced mixing in the fall and winter (Guo et al., 2016). It should be noted that regional nucleation events (or "blooms"), which generally occur in warm weather, can also increase UFP concentrations in remote areas but only contribute to UFP abundance in urban areas with high population density and traffic emissions. The GEOS-Chem-APM model employed for this study considers regional "blooms" and local traffic contributions to daily variations of UFP in different parts of New York State.

Previous studies found that when cold weather or temperature increases, UFP and other gaseous pollutant emissions can increase, matching our findings (Mathis et al., 2005). Although UFPnc near busy roads may mainly depend on emissions patterns, the diurnal or seasonal temperature cycle can also strongly modify the UFPnc and their distributions (Charron and Harrison, 2003; Kuhn et al., 2005). Lower ambient temperatures favor the formation of higher numbers of the smallest particles (<50 nm) and favor the higher rates of new particle formation and slower atmospheric dispersion, which explains why UFP numbers or PSC are usually higher in the winter than in the summer (Sioutas et al., 2005). Interestingly, Herner et al. (2006) stated that lower temperatures near the ground at night might contribute to the formation of stable atmospheric layers that trap primary pollutants near their emissions source; and this effect can thus dominate UFP concentrations in regions that are not heavily influenced by photochemistry (Herner et al., 2005). Therefore, UFP concentration, composition, and volatility exhibit significant seasonal variability due to high spatial variability, indoor sources, variable infiltration of UFPs from various outside sources, and meteorological conditions (Sioutas et al., 2005).

4.5. Potential mechanisms of UFP and PSC on CVD

There are multiple reasons to believe that the health effects of UFPs or $PM_{0.1}$ are greater than those with larger particles. Toxicological studies found that UFPs are present in larger numbers, have a greater combined surface area, and adsorb larger concentrations of toxic air pollutants (oxidant gases, organic compounds, transition metals) per unit mass (Sioutas et al., 2005). After entering the body through the lungs, UFPs quickly translocate to other organs. Due to their small size, UFPs have different distribution characteristics in the respiratory tree and may alter cellular function in ways that circumvent normal signaling pathways (Li et al., 2016). Additionally, UFPs can penetrate intracellularly and potentially cause DNA damage.

Another potential mechanism by which UFPs cause adverse health outcomes is lung inflammation and its subsequent spread of inflammatory mediators to distal organs. UFPs may cause systemic inflammation, endothelial dysfunction, and coagulation changes through which individuals may further develop IHD or hypertension (Schraufnagel, 2020). These findings were supported by the elevated multiple biomarkers among these patients, including C-reactive protein (CRP), circulating polymorphonuclear leukocytes, platelets, fibrinogen, plasma viscosity, and other markers after UFP exposure. Fine particles also promote endothelial dysfunction, vascular inflammation, and atherosclerosis. Increasingly, literature reports that $PM_{0.1}$ plays a major role in most of these factors (Hildebrandt et al., 2009; Olsen et al., 2014). Most studies show a far greater effect for UFPs than larger particles. Furthermore, UFPs that enter alveoli can be retained in surfactant, thus sidestepping the mucociliary escalator clearance mechanisms (Möller et al., 2008). The retention half-lives of titanium dioxide particles in animal lungs are 170 days for 250-nm particles and 500 days for 20-nm particles, indicating that smaller particles cause more persistent inflammation than larger ones (Oberdorster et al., 1994).

4.6. Study strengths and limitations

To our knowledge, this is one of the few studies that have improved UFP exposure assessment by using high-resolution air pollution simulation data generated by GEOS-Chem-APM, a previously validated chemical transport model. Compared to the relatively limited number of EPA $PM_{2.5}$ monitors in NYS, this study utilized 286 simulation grids/points spread out evenly over NYS at a 17 × 17-mile resolution. This exposure assessment model controlled for many environmental factors, including several co-pollutants, meteorological conditions, major exposure sources (traffic, power plants, residential, agriculture, biomass burning, biogenic, ships, aviation, and others), and chemical reactions occurring in the atmosphere. In contrast to most prior UFP studies that utilized one or a few PM monitors, our exposure assessment can be applied to larger areas, thereby reducing the exposure misclassification bias in previous studies. In addition to UFPnc, we also evaluated the impacts of PSC on CVD, which helped us compare and identify the most sensitive exposure metrics. Furthermore, this may be the largest study evaluating the effects of UFPs and PSC on CVD in the US. We evaluated approximately 2 million CVD hospital admission records and several major CVD subtypes in NYS, one of the largest states in the US. Another advantage is the use of objective SPARCS health data to reduce reporting bias, a common limitation encountered by studies based on survey data. Finally, we used a multi-pollutant model to control for several co-pollutants in the analyses, which is a major strength compared to many prior studies that used single pollutant models.

On the other hand, several potential limitations should be considered. The first concern is how accurate the high-resolution air pollution simulations are. While GEOS-Chem-APM has been validated around the globe by several previous studies as described in a previous session (PSC and UFP Simulation Model and Data), detailed measurements of UFPs and PSC in NYS are very limited or unavailable and need further validation. For this concern, we have validated the model simulated UFP against those observed at a monitoring site in the Pinnacle State Park (PSP) in NYS (see Supplement 1). Additionally, we performed sensitivity analyses using the available UFP monitoring data in two small urban areas (Queens and Rochester sites) to link with the CVD hospitalization data within the 15 miles of the same regions. We found a similar range of

excess risks (0.3%–0.7%) of overall CVD admissions and immediate effect per IQR increase of UFP in this sensitivity analysis as we originally found in our statewide study. We also found that cardiac arrhythmias, stroke, and IHD increased in the sensitivity analysis. However, the increased risk of stroke and IHD were not statistically significant due to the small sample sizes.

Another limitation is that we only included CVD hospital admission cases, representing the most severe patients but missing the less severe cases. Therefore, the generalizability of this study may be limited. However, stroke, IHD, and most cardiovascular diseases typically require immediate and urgent medical attention. Therefore, it may be appropriate to use emergency department visits for these health outcomes. In addition, our result that one of the younger age groups (5–17 years old) showed the highest CVD risk associated with PSC is very interesting because CVDs are usually higher among adults or seniors. We evaluated the CVD subtypes among children and found that the most common CVDs among 5–17 years old children are lymphadenitis, followed by dysrhythmias, hypertension, and hypotension. These uncommon CVDs occurring in children deserve further research.

Finally, confounding effects are an important concern. Nevertheless, the case-crossover design has automatically controlled for some confounders and inherited factors, such as age, sex, race, ethnicity, family history of CVD or other diseases, lifestyle choices (smoking or alcohol drinking), occupation, and indoor exposures that usually do not change within one month, and the cases were compared with themselves. The potential bias resulting from intramonthly variability in indoor exposure or occupation is likely non-differential, and the real association may have been underestimated. We also controlled for all simulated co-pollutants (which have correlation coefficients <0.70 with UFPs), temperature, relative humidity, and time-varying variables (weekday or weekend, holidays, season, long-term trend) in the model. However, we could not adjust for some residual confounders, such as activity patterns.

This study provides a useful tool for environmental scientists or epidemiologists to predict UFPnc and PSC at a much finer resolution throughout NYS than ever before. As there are currently very few UFP monitors statewide, our GEOS-Chem-APM model would significantly improve the current exposure assessment in UFP and other criteria pollutants if more measurements become available and model resolution can be further refined. Our study also compared two particle metrics and their relationship with CVDs, contributing to new scientific knowledge. Furthermore, physicians and public health agencies should be aware of the transient and lasting effects of UFPs on CVDs, which could be used to prevent and intervene in those severe cases.

5. Conclusion

Our study found an immediate and strong positive association between PSC and overall CVDs, but a delayed, lasting effect of UFPnc on CVD. PSC was a more sensitive indicator than UFPnc. Exposure to large PSC was associated with an immediate increased risk of hospital admissions for a stroke, hypertension, and IHD. The adverse effects of PSC on CVDs were highest among children (5–17 years old), during the fall and winter seasons, and during cold temperature days. Further studies are needed to validate our findings and evaluate the long-term effects of PSC and UFPs on CVDs and other health outcomes.

Author statement

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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.envpol.2022.119795.

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