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Ambient PM_1 air pollution and cardiovascular disease prevalence: Insights from the 33 Communities Chinese Health Study

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ABSTRACT

Backgrounds: Evidence on the association between long-term exposure to particulate matter with aerodynamic diameter ≤2.5 μm ($PM_{2.5}$) and cardiovascular disease (CVD) is scarce in developing countries. Moreover, few studies assessed the role of the PM_1 (≤1.0 μm) size fraction and CVD. We investigated the associations between PM_1 and $PM_{2.5}$ and CVD prevalence in Chinese adults.

Methods: In 2009, we randomly recruited 24,845 adults at the age of 18–74 years from 33 communities in Northeastern China. CVD status was determined by self-report of doctor-diagnosed CVD. Three-year (2006–08) average concentrations of PM_1 and $PM_{2.5}$ were assigned using a satellite-based exposure. We used spatial Generalized Linear Mixed Models to evaluate the associations between air pollutants and CVD prevalence, adjusting for multiple covariates. Stratified and interaction analyses and sensitivity analyses were also performed.

Results: A 10 μg/m^3 increase in long-term exposure to ambient PM_1 levels was associated a 12% higher odds for having CVD (OR = 1.12; 95% CI = 1.05–1.20). Compared to PM_1, association between $PM_{2.5}$ and CVD was lower (OR = 1.06; 95% CI = 1.01–1.11). No significant association was observed for $PM_{1-2.5}$ (1–2.5 μm) size fraction (OR = 0.98; 95% CI = 0.85–1.13). Stratified analyses showed greater effect estimates in men and the elder.

Conclusions: Long-term PM_1 exposure was positively related to CVD, especially in men and the elder. In addition, PM_1 may play a greater role than $PM_{2.5}$ in associations with CVD. Further longitudinal studies are warranted to confirm our findings.

Abbreviations: AOD, aerosol optical depth; AP, attributable proportion; BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; DAG, directed acyclic graph; GAM, generalized additive model; GLMMs, Generalized Linear Mixed Models; MODIS, Moderate Resolution Imaging Spectroradiometer; OR, odds ratio; PM, particulate matter; PM_{10}, PM with an aerodynamic diameter ≤10 μm; $PM_{2.5}$, PM with an aerodynamic diameter ≤2.5 μm; PM_1, PM with an aerodynamic diameter ≤1.0 μm; R^2, coefficient of determination; RERI, relative excess risk due to interaction; RMSE, Root Mean Squared Error; S, synergy index; WHO, World Health Organization; 33CCHS, the 33 Communities Chinese Health Study

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1. Introduction

Cardiovascular disease (CVD) contributes to about one third of deaths worldwide (World Health Organization (WHO), 2017), which has also been ranked as the leading cause of death and disability in China (Wang et al., 2016). Numerous previous studies have linked particulate matter (PM) to CVD (Cohen et al., 2017; Shah et al., 2013; Shah et al., 2015). However, those previous studies have mainly investigated the mass concentration of PM with an aerodynamic diameter $\leq 10\,\mu m$ (PM_{10}) or $\leq 2.5\,\mu m$ ($PM_{2.5}$); evidence on the cardiovascular effects of smaller PM with an aerodynamic diameter $\leq 1.0\,\mu m$ (PM_1) is very limited.

PM_1 is a major component of $PM_{2.5}$ (Koulouri et al., 2008; Vecchi et al., 2004). However, PM_1 may be different from $PM_{2.5}$ in terms of physicochemical properties (e.g. higher surface area to mass ratio and more toxic chemical composition) (Ravindra et al., 2008; Valavanidis et al., 2008). PM_1 could have more deleterious health effects than $PM_{2.5}$ (Brown et al., 2001; Chuang et al., 2005). Despite this, to our best knowledge, only two epidemiological studies have estimated the relationship between short-term exposure to PM_1 and CVD mortality (Lin et al., 2016; Perez et al., 2009), and no study has investigated the association for long-term PM_1 exposure and CVD morbidity to date.

In addition, most previous studies investigating the association for long-term $PM_{2.5}$ exposure and CVD were conducted in developed countries (Cesaroni et al., 2014; Johnson et al., 2010; Kim et al., 2017; Kloog et al., 2012; Lipsett et al., 2011; Miller et al., 2007; Puett et al., 2009; Stafoggia et al., 2014; To et al., 2015), where background $PM_{2.5}$ levels were relatively low. Studies performed in developing nations mainly focused on short-term cardiovascular effects of $PM_{2.5}$ or PM_{10} exposure, and only a handful of studies explored long-term effects of PM_{10} on CVD mortality (Newell et al., 2017). This means that concentration-response functions for $PM_{2.5}$ and CVD morbidity were largely based on evidence from North America and European countries. Considering the non-linear relationship between air pollutants concentrations and health impacts (Burnett et al., 2014), and the heterogeneity in specific sources of particles with those in developed nations, assessing the impact of $PM_{2.5}$ on CVD in developing countries where typically have higher $PM_{2.5}$ levels is necessary.

Due to rapid urbanization and industrialization, ambient air pollution has become China's leading environmental problem (Guan et al., 2016). In particular, evidence has shown that PM_1 contributed over 80% of $PM_{2.5}$ in most parts of China (Chen et al., 2018a; Wang et al., 2015). In this study, we examined the association between PM_1 and $PM_{2.5}$ and CVD (including both heart disease and stroke) prevalence, and explored if PM_1 had different associations with CVD from $PM_{2.5}$, by analyzing data from the 33 Communities Chinese Health Study (33CCHS).

2. Methods

2.1. Study population

Study participants were enrolled in the 33CCHS, a large, population-based cross-sectional investigation that was conducted in Liaoning province, previously described in detail (Yang et al., 2017; Yang et al., 2018b). Briefly, we implemented a four-stage stratified cluster sampling strategy to randomly recruit study participants using a random number generator (SAS 9.2 (SAS Institute, Inc. Cary, NC)). In 2009, we selected three large cities (Shenyang, Anshan, and Jinzhou) from the 14 cities in Liaoning province in northeastern China. We next randomly selected three study communities from each of five districts in Shenyang, three districts in Anshan, and three districts in Jinzhou (Fig. 1). In China, due to high population density in urban areas, people mainly live in high-rise and high-end residential buildings. Thus, the area of these studied communities was small, with a range of 0.25 to 0.64 km^2. Later, we randomly selected 700–1000 households from each study community. Finally, we randomly selected an adult from each household, who was: (1) aged 18–74 years; (2) living in the study area for more than five years; (3) without significant existing illness (such as cancer); and (4) not pregnant.

The above sampling strategy generated 28,830 eligible participants, of whom 24,845 participants completed the study questionnaire and were included in the current analysis (response rate = 86.2%). Written informed consent was obtained from all participants prior to data collection. The Human Studies Committee of Sun Yat-sen University approved the study protocols.

2.2. CVD definition

Study outcomes were based on the questionnaire data (Dong et al., 2013; Qin et al., 2015). A heart disease case ($n = 477$) was defined as an affirmative response to “has a doctor ever diagnosed heart failure, coronary heart disease, or myocardial infarction to you”. A stroke case ($n = 589$) was defined as an affirmative response to “has a doctor ever diagnosed stroke including cerebral hemorrhage, cerebral embolism, cerebral thrombosis, or subarachnoid hemorrhage to you”. We combined heart disease and stroke cases as a single larger group and defined as “CVD” ($n = 1006$).

2.3. Exposure assessment

Daily 2006–2008 PM_1 and $PM_{2.5}$ concentrations for the 33 study communities were predicted at a $0.1^o \times 0.1^\circ$ spatial resolution using a combination of ground monitoring data (supplemental methods: explanation for ground-monitored data on PM_1 and $PM_{2.5}$), satellite remote sensing, meteorology, and land use information, which we previously described in detail (Chen et al., 2018b; Yang et al., 2018b). Briefly, we abstracted aerosol optical depth (AOD) from Moderate Resolution Imaging Spectroradiometer (MODIS) data, using the Dark Target and Deep Blue data processing algorithms, combined with an inverse variance weighting method strategy, after filling data gaps. Daily meteorological data were retrieved from the China meteorological data sharing service system (http://data.cma.gov.cn), including temperature, barometric pressure, relative humidity, and wind speed. We obtained annual land cover data, including urban cover, forest cover, and water cover at a 500 m spatial resolution from Global Mosaics of the standard MODIS land cover type data Collection 5.1 product of Global Land Cover Facility (http://glcf.umd.edu/). Monthly average Normalized Difference Vegetation Index data (MODIS Level 3) were downloaded from the NASA Earth Observatory (http://neo.sci.gsfc.nasa.gov), and spatial predictors including Aqua and Terra active fires (http://earthdata.nasa.gov/data/near-real-time-data/firms) and elevation (http://srtm.csi.cgiar.org/) were also collected.

We constructed a generalized additive model (GAM) to link ground-monitored PM_1 and $PM_{2.5}$ data with AOD data, meteorological data, land use information and vegetation data, and other spatial predictors. We first included AOD and then incorporated other predictors one-by-one to achieve a parsimonious model that maximized the explained variability in air pollutant concentrations. Later, we used a 10-fold cross-validation process to assess the validity of the predictors by calculating the adjusted coefficient of determination (R^2) and root mean squared error (RMSE). Finally, the adjusted R^2 and RMSE were 71% and 13.0 $\mu g/m^3$, respectively, for monthly average PM_1 concentration, and were 75% and 15.1 $\mu g/m^3$, respectively, for monthly average $PM_{2.5}$. We estimated $PM_{1-2.5}$ (1–2.5 μm) concentration as $PM_{2.5}$ minus PM_1 concentrations. We assigned the three-year average PM_1, $PM_{2.5}$, and $PM_{1-2.5}$concentrations to the 33 study community centroids, as estimates of long-term exposure to air pollution.

2.4. Potential confounders

We collected individual-level data from study participants using

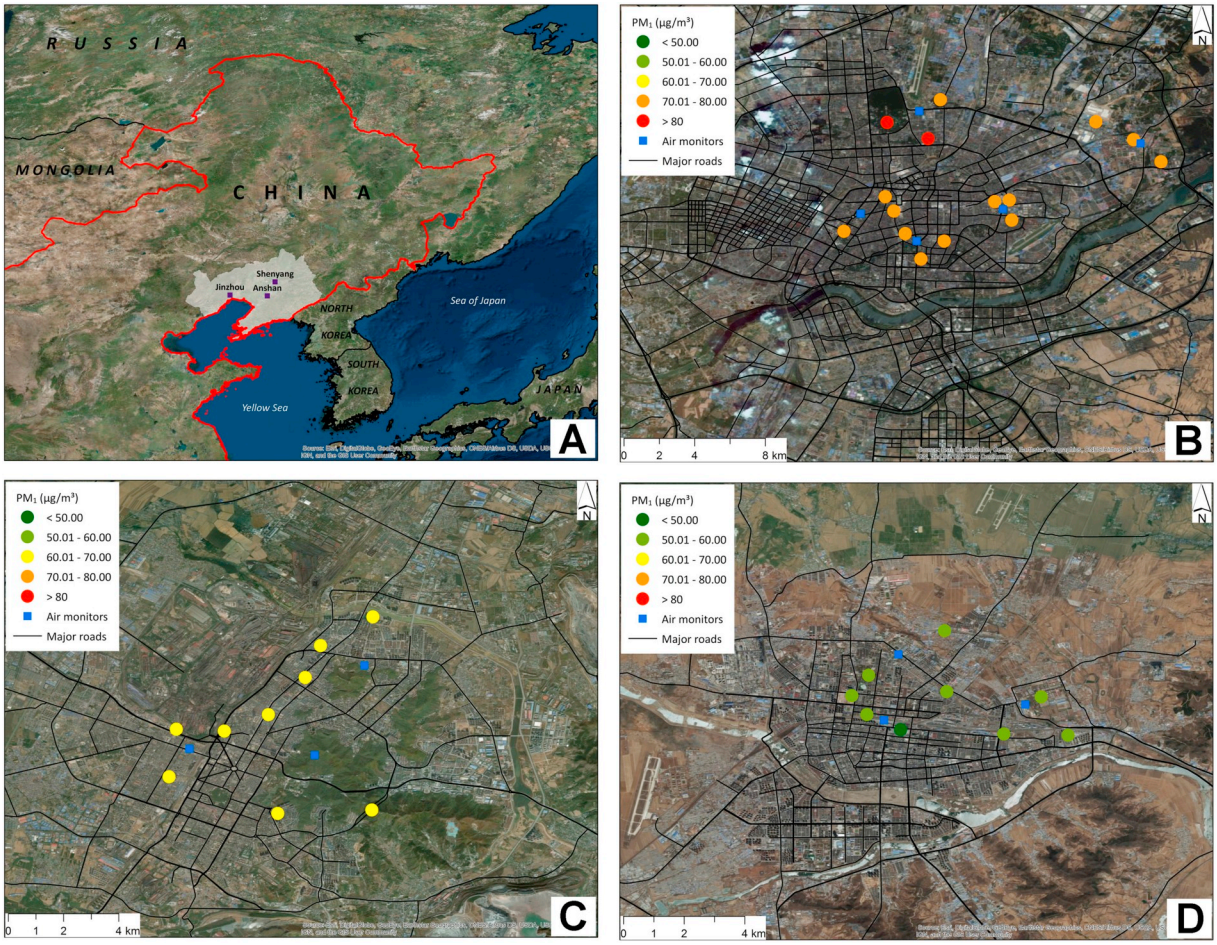

Fig. 1. Annual average PM_1 concentrations in 33 communities in three cities of Liaoning province (A: Liaoning province; B: Shenyang; C: Anshan; D: Jinzhou).

self-reported questionnaires: age in years; sex as man or woman; ethnicity as Han or "others"; highest level of formal education as none, primary school, middle school, or > junior college; household income as ≤5000 Yuan, 5001–10,000 Yuan, 10,001–30,000 Yuan, and ≥30,000 Yuan; cigarette smoking status as non-smoker and smoker; and exercise regularly as yes (≥180 min/week) or no (< 180 min/week). We also captured self-reported family history of CVD as a grandparent, parent, sibling, or child who had been diagnosed. Hypertension (yes or no), diabetes (yes or no), and dyslipidemia (yes or no) were defined based on examined blood pressures, blood glucoses, and blood lipids levels. Body mass index (BMI) was calculated based on measured height and body weight. District-level per-capita gross domestic product was obtained from Shenyang, Jinzhou, and Anshan cities' Statistical Yearbooks.

2.5. Statistical analysis

We evaluated and characterized the distributions for all covariates, and outlying values were identified and examined. Spearman rank correlation coefficients were performed to explore correlations among PM concentrations.

We used spatial Generalized Linear Mixed Models (GLMMs) to examine the relationships between air pollutants and CVD prevalence (expressed as odds ratio (OR) and 95% confidence interval (CI) per 10 μg/m^3 increase in air pollutants), in which participants and communities were considered as the first- and second-level units, respectively. A detailed description can be found in the supplemental materials (detailed information on Generalized Linear Mixed Models). We established a crude, unadjusted model and an adjusted model. In the adjusted model, we controlled for covariates selected using a directed acyclic graph (DAG) (Textor et al., 2011), constructed with Dagittty 1.0 software (http://www.dagitty.net/development/dags.html) and retained age, sex, ethnicity, education level, household income, physical activity, and gross domestic product as confounders in the models (Fig. S1). We incorporated community as a random effect and the remaining covariates as fixed effects.

To assess the robustness of our effect estimates, we performed two sensitivity analyses. First, we applied multi-annual average air pollutant concentrations (i.e. one year average (2008), two years average (2007–08), and three years average (2006–08)) to evaluate the impact of shorter-term exposure fluctuations. Second, we estimated the associations for air pollutants with heart disease and stroke in separate models.

To test the potential effect modification, we first examined interactions between PM_1 and age (≥65 years vs. < 65 years), sex (men vs. women), smoking status (nonsmoker vs. smoker), regular exercise (yes vs. no), and household income (< 10,000 Yuan vs. ≥10,000 Yuan). We used the relative excess risk due to interaction (RERI), attributable proportion (AP), and synergy index (S) with corresponding 95% confidence intervals (CI) to characterize interaction on the additive scale (Andersson et al., 2005). An additive interaction was defined as RERI and AP are unequal to 0 and S unequal to 1. Then, we conducted a stratified analysis to further characterize statistically significant interactions.

Data were analyzed using GLIMMIX procedure in SAS 9.2 (SAS Institute, Inc. Cary, NC). We defined statistical significance as $p < 0.05$ for a two-tailed test.

3. Results

3.1. Baseline characteristics

The average age of the study participants was 45.6 years, and nearly half of them were men (51%) (Table 1). Most participants were of Han ethnicity (95%) and had a middle school or higher educational level (82%). Twenty-nine percent of the participants were current smokers, 23% were current alcohol consumers, and 31% had a regular exercise. The prevalence of CVD was 4%, which is in line with the general Chinese population (Wang et al., 2014). CVD patients were significantly different from non-CVD participants in being men, older, Han ethnicity, smokers, and having lower educational level and lower income levels. Unexpectedly, CVD patients exercised more frequently than non-CVD participants, which might be caused by higher proportion of men in CVD patients than non-CVD individuals (73.9% versus 50.0%), as men are found to have more exercise than women in our study (data not shown). In addition, people with CVD might have changed their lifestyles (e.g., exercise more regularly) as part of the treatment strategy.

Air pollutants levels varied markedly across the study communities, with ranges of 50–82 $\mu g/m^3$ for PM_1, 64–104 $\mu g/m^3$ for $PM_{2.5}$, and 10–22 $\mu g/m^3$ for $PM_{1-2.5}$ (Table 2; Fig. 1). The studied air pollutants were correlated highly with each other (Spearman correlation coefficients ranged from 0.63 to 0.99). Based on the WHO guideline, all the 33 study communities exceeded the recommended level for $PM_{2.5}$ (10 $\mu g/m^3$). The $PM_1/PM_{2.5}$ ratios in the study communities ranged from 77.0% to 87.0%, with an average ratio of 80.7% (data not shown).

3.2. Associations between air pollutants and CVD prevalence

Table 3 shows the ORs (95% CIs) from crude and adjusted models for air pollutants and CVD prevalence. In the adjusted model, a 10 $\mu g/m^3$ increase in PM_1 was significantly associated with a 12% higher odds for CVD prevalence (OR = 1.12; 95% CI = 1.05–1.20; P = .0007). Compared to PM_1, the association between $PM_{2.5}$ and prevalent CVD was lower (OR = 1.06; 95% CI = 1.01–1.11; P = .0208). No significant association was detected for $PM_{1-2.5}$ and CVD. In addition, our results were consistent in sensitivity analyses where multi-annual average air pollutants concentrations were used (Table S1), where the relationships of air pollutants with heart diseases and stroke were explored separately (Table 4).

3.3. Stratified analyses for PM_1 and CVD

Table 5 summarizes the associations between PM_1 and CVD stratified by modifiers. Sex and age showed significant additive interactions with PM_1 on CVD prevalence. RERI, AP, and S estimates for sex and PM_1 were 1.01 (95% CI = 0.47, 1.55), 0.28 (95% CI = 0.14, 0.42), and 1.65 (95% CI = 1.19, 2.27), respectively, and for age and PM_1, they were 2.02 (95% CI = 0.89, 3.14), 0.37 (95% CI = 0.21, 0.53), and 1.83 (95% CI = 1.31, 2.56), respectively. Stratified analyses showed higher associations in men and the elder. There was no significant effect modification of PM_1 and CVD association by exercise, smoking, and household income.

4. Discussion

4.1. Key findings

In the large population-based study of 24,845 Chinese urban-dwelling adults, we observed that long-term exposure to higher levels of PM_1 and $PM_{2.5}$ was associated with greater odds for having had CVD. In addition, the associations with PM_1 were stronger than with $PM_{2.5}$, and no significant association was observed for $PM_{1-2.5}$. These findings suggest that smaller particles (PM_1) may play a greater role than larger particles ($PM_{2.5}$) in the associations with CVD. Furthermore, men and the elderly may be more vulnerable to the cardiovascular effects of PM_1.

4.2. Comparison with other studies and interpretations

To the best of our knowledge, this was the first study to investigate the association between long-term exposure to ambient PM_1 pollution and CVD prevalence. Thus, it is hard to directly compare our findings with those from other studies. We are aware of only two similar studies, but both explored short-term effects of PM_1 on CVD mortality. Specifically, a case-crossover study in Spain reported that a 10 $\mu g/m^3$ increase in 1-day average PM_1 concentrations was significantly associated with a 2.8% and 6.3% elevated risk of cardiovascular mortality and cerebrovascular mortality, respectively (Perez et al., 2009). A time-series study in China reported that a 28.8 $\mu g/m^3$ increase in 4-day moving average PM_1 concentrations was significantly associated with a 7% increased risk of cardiovascular mortality (Lin et al., 2016). Although the two previous studies were different from our study in terms of air pollution exposure duration (short-term vs long-term) and health outcomes (CVD mortality vs CVD morbidity), findings of those studies, combined with our findings, provide consistent support for the cardiovascular effects of PM_1.

In contrast to the limited evidence on PM_1, many studies in

Table 1
Main characteristics of study participants (n = 24,845).

Variables	CVD (n = 1006)[a]	Non-CVD (n = 23,839)	P value
Age, n (%)			< 0.0001
< 65 years	720 (71.6)	21,891 (91.8)	
≥65 years	286 (28.4)	1948 (8.2)	
Sex, n (%)			< 0.0001
Men	743 (73.9)	11,918 (50.0)	
Women	263 (26.1)	11,921 (50.0)	
Ethnicity, n (%)			< 0.0001
Han	980 (97.4)	22,490 (94.3)	
Others	26 (2.6)	1349 (5.7)	
Education, n (%)			< 0.0001
Junior college or higher	170 (16.9)	5305 (22.3)	
Middle school	556 (55.3)	14,377 (60.3)	
Primary school	232 (23.1)	3214 (13.5)	
No school	48 (4.8)	943 (4.0)	
Family income/year, n (%)			< 0.0001
≤5000 Yuan	216 (21.5)	2008 (8.4)	
5001–10,000 Yuan	150 (14.9)	3387 (14.2)	
10,001–30,000 Yuan	390 (38.8)	11,958 (50.2)	
≥30,000 Yuan	250 (24.9)	6486 (27.2)	
Smoking status, n (%)			< 0.0001
Non-smoker	577 (57.4)	16,966 (71.2)	
Smoker	429 (42.6)	6873 (28.8)	
Alcohol consumption, n (%)			0.1207
Non-drinker	793 (78.8)	18,289 (76.7)	
Drinker	213 (21.2)	5550 (23.3)	
Regular exercise, n (%)			< 0.0001
Yes	402 (40.0)	7245 (30.4)	
No	604 (60.0)	16,594 (69.6)	
Controlled diet of low calories and low fat, n (%)			0.1282
Yes	271 (26.9)	5917 (24.8)	
No	735 (73.1)	17,922 (75.2)	
Sugar-sweetened soft drink intake, n (%)			< 0.0001
≥5 day per week	90 (9.0)	842 (3.5)	
2–4 days per week	21 (2.1)	1953 (8.2)	
≤1 days per week	895 (89.0)	21,044 (88.3)	
Family history of CVD			0.0157
Yes	282 (28.0)	5882 (24.7)	
No	724 (72.0)	17,957 (75.3)	

Abbreviations: CVD, cardiovascular disease.
[a] CVD patients included 417 participants with heart disease; 529 with stroke, and 60 with both.

Table 2
Three-year (2006–08) average concentrations and pairwise correlations of air pollutants.

	Summary statistics				Spearman correlation coefficients			
	Mean	Median (IQR)	Minimum	Maximum	WHO guideline	PM_1	$PM_{2.5}$	$PM_{1–2.5}$
PM_1 (μg/m^3)	65.97	62 (61–76)	50	82	None	1.00	0.99 (< 0.0001)	0.63 (< 0.0001)
$PM_{2.5}$ (μg/m^3)	82.02	73 (71–97)	64	104	10		1.00	0.67 (< 0.0001)
$PM_{1–2.5}$ (μg/m^3)	16.04	14 (11 − 21)	10	22	None			1.00

Abbreviations: IQR, interquartile range; PM_1, particle with aerodynamic diameter ≤ 1.0 μm; $PM_{1–2.5}$, particle with aerodynamic diameter ranges from 1 to 2.5 μm; $PM_{2.5}$, particle with aerodynamic diameter ≤ 2.5 μm, WHO, World Health Organization.

Table 3
Associations of CVD with per 10-μg/m^3 increase in air pollutants (n = 24,845).

	OR (95% CI)			
Air pollutants	Crude model	*p*-value	Adjusted model[a]	*p*-value
PM_1	1.11 (1.05,1.18)	0.0002	1.12 (1.05, 1.20)	0.0007
$PM_{2.5}$	1.07 (1.02,1.11)	0.0023	1.06 (1.01, 1.11)	0.0208
$PM_{1–2.5}$	1.07 (0.94, 1.22)	0.3113	0.98 (0.85, 1.13)	0.8052

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; OR, odds ratio; PM_1, particle with aerodynamic diameter ≤1.0 μm; $PM_{1–2.5}$, particle with aerodynamic diameter ranges from 1 to 2.5 μm; $PM_{2.5}$, particle with aerodynamic diameter ≤2.5 μm.

[a] Adjusted for age, sex, ethnicity, income, education, smoking status, exercise, and district-level of gross domestic product.

developed countries have investigated the association between long-term exposure to $PM_{2.5}$ and major CVD (Cesaroni et al., 2014; Johnson et al., 2010; Kim et al., 2017; Kloog et al., 2012; Lipsett et al., 2011; Miller et al., 2007; Puett et al., 2009; Stafoggia et al., 2014; To et al., 2015) (these studies are listed in Table S2). Although the published studies differed in terms of geographical area, population characteristics, $PM_{2.5}$ physicochemical properties, and timing of exposure, they generally supported positive associations of long term $PM_{2.5}$ exposure with prevalent or incident CVD. Our study is among the first to provide evidence on the $PM_{2.5}$-CVD morbidity association in a developing country.

A novel finding of our study is that most of the observed cardiovascular effects of $PM_{2.5}$ may be attributed to PM_1. Our results were similar to the study by Lin and coworkers, in which CVD mortality was reported to be significantly associated with $PM_{2.5}$ and PM_1, but not with $PM_{1–2.5}$ in Southern Chinese (Lin et al., 2016). Mechanistically, PM_1 originates almost entirely from combustion processes and secondary particle formation (Jaiprakash Singhai et al., 2017), and PM_{10} mainly comes from mechanical processes, such as dust resuspension or mineral processing. $PM_{2.5}$ can be dominated by either combustion processes/particle formation (PM_1) or mechanical sources (PM_{10}), thus the relationships between these fractions differ regionally (Chen et al., 2018a; Morawska et al., 2008). Our current study was performed in three big cities in Northeastern China, which are highly urbanized and industrialized. As shown in our results, the $PM_1/PM_{2.5}$ ratios ranged from 77.0% to 87.0%. Thus, the findings observed in our study may be explained by the fact that the majority of $PM_{2.5}$ is PM_1 in the study sites. Many developed countries may also face the similar situation that PM_1 constitutes most $PM_{2.5}$. This means that in many other places (e.g. developed countries) the epidemiology of $PM_{2.5}$ may be in fact of PM_1. However, this was not confirmed due to the unavailability of PM_1 data. Our study therefore provides a new insight into exposure and risk assessment of ambient air pollutants. Despite this, future studies remain warranted to further explore the health effects of PM_1 and to confirm our findings, especially considering that we only measured PM exposures between 2006 and 2008 and since then air quality in China has improved greatly (Chen et al., 2018b, 2018c), but the incidence of CVD continues to increase (Chen et al., 2017). One possible explanation may be that although air quality has improved, the air pollutants levels remain much higher than the WHO standard (Chen et al., 2018c). Therefore, more precise risk assessment of air pollution is still needed, and more strict controls and standards should be developed in China. Another explanation may be that although PM has been closely related to CVD, its effects were relatively modest. The increased CVD incidence may be caused by other contributors, such as obesity, physical inactivity, and unhealthy dietary habits (World Bank, 2011).

4.3. Susceptible populations

We observed a stronger PM_1-CVD association in older population. This could be a reflection of that older people are exposed to air pollution over a longer period, which accumulated hazardous effects on the cardiovascular system (Yang et al., 2018a) and diminished toxicodynamic response/repair (Geller and Zenick, 2005). In addition, preexisting lung and cardiovascular conditions are usually more prevalent in the elderly (Kan et al., 2008), thus they may be more likely to develop CVD when exposed to air pollutants. The impact of PM_1 on CVD seemed to be stronger in men. One plausible explanation may be that men have higher chance to ambient air pollution exposure as they engage in more frequent outdoor activities than women. Another likely explanation is that men have larger lung capacity on average than women and they are different in pulmonary physiology (Carery et al., 2007).

4.4. Potential mechanisms

Several biologic mechanisms have been hypothesized to explain the

Table 4
Associations of air pollutants with heart diseases and stroke.

	OR (95% CI)[a]			
Air pollutants	Heart diseases (n = 477)	*p*-value	Stroke (n = 589)	*p*-value
PM_1	1.16 (1.05, 1.28)	0.0026	1.11 (1.01, 1.22)	0.0240
$PM_{2.5}$	1.07 (1.00, 1.15)	0.0661	1.06 (0.99, 1.13)	0.0739
$PM_{1–2.5}$	0.91 (0.73, 1.13)	0.3687	1.06 (0.88, 1.29)	0.5258

Abbreviations: CI, confidence interval; OR, odds ratio; PM_1, particle with aerodynamic diameter ≤ 1.0 μm; $PM_{1–2.5}$, particle with aerodynamic diameter ranges from 1 to 2.5 μm; $PM_{2.5}$, particle with aerodynamic diameter ≤ 2.5 μm.

[a] Adjusted for age, sex, ethnicity, income, education, smoking status, exercise, and district-level of gross domestic product.

Table 5
Association of CVD with per 10-μg/m^3 increase in PM_1, stratified by potential modifiers (n = 24,845).

	Effect estimate	Additive interaction		
Modifiers	OR (95% CI)[a]	RERI (95% CI)	AP (95% CI)	S (95%CI)
Sex		1.01 (0.47, 1.55)[f]	0.28 (0.14, 0.42)[f]	1.65 (1.19, 2.27)[f]
Men	1.16 (1.08, 1.24)[a]			
Women	1.02 (0.96, 1.10)[a]			
Age		2.02 (0.89, 3.14)[f]	0.37 (0.21, 0.53)[f]	1.83 (1.31, 2.56)[f]
< 65 years	1.08 (1.01, 1.16)[b]			
≥65 years	1.28 (1.20, 1.37)[b]			
Smoking status		0.32 (−0.10, 0.73)	0.14 (−0.04, 0.32)	1.35 (0.88, 2.07)
Non-smoker	1.10 (1.03, 1.18)[c]			
Smoker	1.15 (1.07, 1.23)[c]			
Regular exercise		0.27 (−0.09, 0.63)	0.14 (−0.04, 0.33)	1.45 (0.81, 2.58)
No	1.11 (1.04, 1.19)[d]			
Yes	1.14 (1.06, 1.22)[d]			
Household income		0.36 (−0.17, 0.89)	0.13 (−0.05, 0.32)	1.27 (0.89, 1.81)
< 10,000 Yuan	1.17 (1.09, 1.25)[e]			
≥10,000 Yuan	1.09 (1.02, 1.17)[e]			

Abbreviations: AP, attributable proportion; CI, confidence interval; OR, odds ratio; PM_1, particle with aerodynamic diameter ≤1.0 μm; $PM_{2.5}$, particle with aerodynamic diameter ≤2.5 μm; $PM_{1-2.5}$, particle with aerodynamic diameter from 1 to 2.5 μm; RERI, relative excess risk due to interaction; S, synergy index.
[a] Adjusted for age, ethnicity, income, education, smoking status, exercise, and district-level of gross domestic product.
[b] Adjusted for sex, ethnicity, income, education, smoking status, exercise, and district-level of gross domestic product.
[c] Adjusted for age, sex, ethnicity, income, education, exercise, and district-level of gross domestic product.
[d] Adjusted for age, sex, ethnicity, income, education, smoking status, and district-level of gross domestic product.
[e] Adjusted for age, sex, ethnicity, education, smoking status, exercise, and district-level of gross domestic product.
[f] Statistically significant interaction (p < .05).

association between PM exposure and cardiovascular health (Bourdrel et al., 2017; Brook et al., 2010). Thrombosis and coagulation are important pathological events that could precede the development of CVD. Evidence has shown that exposure to $PM_{2.5}$ was associated with increased concentrations of circulating von Willebrand factor (Riediker, 2007). Studies have also documented that people exposed to PM had higher concentrations of fibrinogen and plasma viscosity, which are all indicators of thrombosis and coagulation (Peters et al., 1997; Pekkanen et al., 2000). Impaired vascular function contributes to the progression of atherosclerosis, which is the main cause of CVD. Inhalation of PM might impair vascular function and accelerate the progression of atherosclerosis. For example, both animal and human studies have reported that inhalation of PM could impair endothelium-dependent and -independent vasodilation, likely by inducing inflammation and oxidative stress (Nurkiewicz et al., 2006; O'Neill et al., 2005). Also, higher $PM_{2.5}$ levels were found to be significantly associated with an increase in common carotid intima-media thickness, a measure of atherosclerosis (Diez Roux et al., 2008). In addition, evidence also suggests that autonomic nervous system imbalance, inflammation, and epigenetic changes could be involved in the biological pathways between $PM_{2.5}$ and CVD (Bourdrel et al., 2017; Brook et al., 2010). Few mechanistic studies directly focused on PM_1. However, compared with $PM_{2.5}$, PM_1 has a higher surface area to mass ratio and could more easily penetrate the lung alveoli and the systemic circulation, and thus exert more deleterious health effects (Brown et al., 2001; Chuang et al., 2005; Valavanidis et al., 2008). Additionally, PM_1 often carries more toxic constituents than larger particulates, such as transition metals and organic compounds, which were able to cause pro-inflammatory response and alter epigenetic status (Ravindra et al., 2008). These proposed mechanisms may be consistent with the positive associations of PM_1 and $PM_{2.5}$ with CVD observed in our study and support our inference that smaller PM_1 may play a greater role than $PM_{2.5}$ in the associations with CVD in our study region and population.

4.5. Implication for policy makers and future researchers

In this study, we observed that a 10 μg/m^3 increase in PM_1 was associated with a 12% higher CVD risk, and for specific susceptible populations the risk was greater. These findings suggest that effective and prompt strategies to improve air quality by the government could yield public health benefits by averting some of the disease burden. Additionally, as shown in our current study and previous studies (Chen et al., 2018b; Wang et al., 2015), PM_1 contributed > 80% of $PM_{2.5}$ in big parts of China. Thus, for control measures and standards to be most efficient, government and policy makers should pay more attention to sources of PM_1 (combustion) than those of $PM_{2.5}$.

4.6. Strengths and limitations

A major strength of our study is its large sample size and high response rate. An additional point of merit is that a rich set of covariates were available for confounder adjustment. This study, however, also has limitations. First, the cross-sectional design prevented us from inferring temporality of the exposures and the outcomes. Second, exposure levels were assigned to the community centroids rather than to personal addresses, which means that only 33 unique air pollution values were available for the study population and might have led to some exposure misclassification. However, previous work indicates that this kind of non-differential misclassification usually biases the effect estimates towards null (Hutcheon et al., 2010), implying that the effect estimates for air pollutants would have been higher than our current estimates, if we had individual level exposure data. We also found limited heterogeneity in PM exposures, which might have undermined statistical power to detect modest associations. Still, the range of $PM_{2.5}$ exposure in our study (40 μg/m^3) exceeded those reported by several previously published epidemiologic investigations of PM and adverse human health outcomes (Dockery et al., 1993; Hwang and Lee, 2010; Johnson et al., 2010; Lepeule et al., 2012) (please also see Table S3), and was sufficient for detecting statistically significant higher risks for CVD in association with higher $PM_{2.5}$ and PM_1. Third, we calculated a three-year average exposure window for all participants based on calendar year, but not for each participant based on the date of her/his interview, which could also have caused exposure misclassification. However, effects of possible misclassification were likely modest as annual average levels of air pollutants for each community were stable during 2006 through 2009 (data not shown), and the effect estimates

for multi-annual average concentrations of air pollutants were consistent. Fourth, information on covariates were collected by a questionnaire, thus recall bias is possible. Fifth, CVD outcomes were self-reported, thus recall bias is possible, especially by considering the possibility that people from low socio-economic status might have less informed about the exact diagnosis of their CVD. In addition, due to the limited detail and number of CVD outcomes, we could not explore the associations of air pollutants with individual CVD conditions, which would have different pathogenesis. However, our results were similar from sensitivity analyses in which we analyzed associations with heart diseases and stroke separately. Sixth, although we have incorporated a rich set of covariates into the models to adjust for confounding, residual confounding caused by unmeasured covariates across the studies communities (such as noise, walkability, and built environment) or misclassification of measured covariates (such as smoking and exercise) might have affected the effect estimates. Finally, weather factors may confound the air pollution-CVD association. However, we used meteorological data including air temperature, barometric pressure, relative humidity, and wind speed to model PM_1 and $PM_{2.5}$ concentrations. Thus, we could not control these variables in our models, in order to avoid over-adjustment.

5. Conclusions

Our study results suggest that long-term exposure to PM_1 may play a greater role than $PM_{2.5}$ in the associations with CVD, especially among men and the elderly. Efforts to improve air quality in China are warranted, and PM_1 should be prioritized in future air quality standards and guidelines. However, given the limitations of our study, more well-designed longitudinal studies are needed to confirm its findings.

Declaration of interests

None.

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Appendix A. Supplementary data

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