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Association of short-term exposure to ambient PM_1 with total and cause-specific cardiovascular disease mortality

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ABSTRACT

Background: The acute effects of exposure to ambient particulate matter with an aerodynamic diameter ≤1 μm (PM_1) on cardiovascular disease (CVD) mortality remain unclear.
Objectives: To investigate whether short-term exposure to ambient PM_1 was associated with mortality from total and/or cause-specific CVDs, and estimate the excess mortality.
Methods: A time-stratified case-crossover study was conducted among 1,081,507 CVD deaths in Jiangsu province, China from 2015 to 2020. We assessed daily residential ambient PM_1 exposures using a validated grid dataset for each subject. Conditional logistic regression models and distributed lag linear or nonlinear models were employed to quantify the association of PM_1 exposure with mortality during the same day of CVD death and 1 day prior.
Results: Each 10 $\mu g/m^3$ increase of PM_1 exposure was significantly associated with a 1.46 % (95 % confidence interval: 1.28 %, 1.65 %), 1.95 % (1.28 %, 2.63 %), 1.16 % (0.86 %, 1.47 %), 1.41 % (1.13 %, 1.69 %), and 1.83 % (1.37 %, 2.30 %) increased odds of mortality from total CVDs, hypertensive diseases (HDs), ischemic heart diseases (IHDs), stroke, and sequelae of stroke, respectively (all p <0.05). No significant association was identified with mortality from pulmonary heart disease or chronic rheumatic heart diseases. The excess fraction of total CVD mortality attributable to PM_1 exposure was 5.71 %, while the cause-specific excess fractions ranged from 4.98 % for IHDs to 7.46 % for HDs. Significantly higher excess fractions were observed for total and certain cause-specific CVD mortality in adults 80 years or older.
Conclusions: We found that short-term exposure to ambient PM_1 was significantly associated with an increased odds of mortality from total and specific CVDs and may lead to considerable excess mortality especially among older adults. Our findings highlight a potential approach to prevent premature CVD deaths by reducing PM_1 exposures and provide essential quantitative data for the development of future air quality standards for ambient PM_1.

Abbreviations: CI, condifence interval; CIHD, chronic ischemic heart disease; CO, carbon monoxide; CRHD, chronic rheumatic heart disease; CVD, cardiovascular disease; *df*, degree of freedom; DLM, distributed lag model; DLNM, distributed lag non-linear model; HD, hypertensive disease; HHD, hypertensive heart disease; HRD, hypertensive renal disease; HS, hemorrhagic stroke; ICD-10, International Statistical Classification of Diseases and Related Health Problems 10th Revision; IHD, ischemic heart disease; IS, ischemic stroke; MI, myocardial infarction; NO_2, nitrogen dioxide; O_3, ozone; PHD, pulmonary heart disease; PM_1, particulate matter with an aerodynamic diameter ≤1 μm; $PM_{2.5}$, particulate matter with an aerodynamic diameter ≤2.5 μm; SO_2, sulfur dioxide.

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1. Introduction

Cardiovascular diseases (CVDs) continue to be the leading cause of death and remain a critical disease burden worldwide (Virani et al., 2021). As ambient particulate pollution is recognized as a major environmental health issue in both developing and developed countries, extensive epidemiological evidence has linked exposure to particulate matter (PM), especially PM with an aerodynamic diameter $\leq$2.5 μm ($PM_{2.5}$), to a higher risk of CVD mortality (Lelieveld et al., 2019; Rajagopalan et al., 2018). Recently, with increasing interest in health effects of PM with smaller sizes, growing evidence suggests that the observed cardiovascular effects of $PM_{2.5}$ are mainly from PM with an aerodynamic diameter $\leq$1 μm (PM_1), which has drawn much concern globally (Hu et al., 2018; Kan, 2017; Lin et al., 2016a). However, the potential adverse effects of PM_1 exposure on mortality from CVDs remain poorly understood.

To date, only two time-series studies in Guangzhou, China, one time-series study in Zhejiang province, China, and one case-crossover study in Barcelona, Spain have evaluated the acute effects of PM_1 exposure on CVD mortality (Hu et al., 2018; Lin et al., 2016a; Lin et al., 2016b; Perez et al., 2009). While all these studies have provided evidence of positive associations between short-term exposure to ambient PM_1 and risks of mortality from total CVDs and/or stroke, the effect estimates varied materially due to methodological differences in study design, exposure assessment, PM_1 exposure level, and analytical strategy. In addition, it remains unknown if and how PM_1 exposure is associated with an increased risk of mortality from specific types of CVD including hypertensive diseases (HDs), ischemic heart diseases (IHDs), pulmonary heart disease (PHD), and sequelae of stroke, which can be of great importance and interest to frail individuals, clinical practitioners, and public health policymakers in reducing premature deaths from specific CVDs.

Therefore, we conducted a case-crossover study among 1.1 million CVD deaths in Jiangsu province, China during 2015–2020 to comprehensively investigate the association of short-term exposure to ambient PM_1 with total and cause-specific CVD mortality, and estimate the corresponding excess mortality. We also performed stratified analyses to explore potential susceptible populations.

2. Methods

2.1. Study population

We included 1,081,507 individuals who died from CVDs in Jiangsu province, China during 2015–2020 from the Jiangsu provincial mortality surveillance system, which was administrated by the Chinese Center for Disease Control and Prevention. This mortality surveillance system achieved provincial coverage in Jiangsu province since 2011 (Liu et al., 2016). For each death, we collected individual information including date of birth, sex, race, residential address, and date of death. This study was approved by the Ethical Committee of School of Public Health, Sun Yat-sen University with an exemption of informed consent.

2.2. Outcomes

Based on the underlying cause of death, the study outcomes included mortality from CVDs coded by the International Statistical Classification of Diseases and Related Health Problems 10th revision (ICD-10). We focused on mortality from total CVDs (ICD-10 codes: I00–I99) and 6 main types of CVD including chronic rheumatic heart diseases (CRHDs; I05–I09), HDs (I10–I15), IHDs (I20–I25), PHD (I26–I28), stroke (I60–I64), and sequelae of stroke (I69.0–I69.4). HDs were subdivided into hypertensive heart disease (HHD; I11, I13) and hypertensive renal disease (HRD; I12–I13); IHDs were subdivided into myocardial infarction (MI; I21–I22) and chronic ischemic heart disease (CIHD; I25); stroke was subdivided into hemorrhagic stroke (HS; I60–I62) and ischemic stroke (IS; I63); and sequelae of stroke was subdivided into sequelae of HS (I69.0–I69.2) and sequelae of IS (I69.3).

2.3. Study design

A time-stratified case-crossover design was used to estimate the association of short-term exposure to ambient PM_1 and CVD mortality (Liu et al., 2019b; Liu et al., 2021). In this design, each subject served as his or her own control by assessing referent exposures before and/or after the day of death within a given time stratum (i.e., a month). For each subject, we defined the date of death as the case day, and chose its corresponding control days as those days sharing the same year, month (the time stratum) and day of week with the case day. For example, if a subject died on February 20, 2019 (Thursday), the February 20, 2019 was defined as the case day and all other Thursdays in February 2019 (i.e., February 6, 13, and 27) were defined as the corresponding control days. The association between PM_1 exposure and CVD mortality was then assessed by comparing the exposure on the case days with that on the control days, which could control the effects of time trend, seasonal pattern, and day of week (Bateson and Schwartz, 1999). We finally matched 3,670,295 control days for 1,081,507 case days and included them in the analysis.

2.4. Exposure assessment

We retrieved daily grid data (spatial resolution: 10 km × 10 km) on ambient PM_1, sulfur dioxide (SO_2), nitrogen dioxide (NO_2), carbon monoxide (CO) and ozone (O_3) in Jiangsu province during 2015–2020 from the ChinaHighAirPollutant (CHAP) dataset (available at https://weijing-rs.github.io/product.html) (Wei et al., 2019, 2021a, 2021b, 2022a, 2022b). This dataset was generated from our proposed artificial intelligence models combining with big data including ground measurements, satellite remote sensing products, atmospheric reanalysis, which had a full spatiotemporal coverage in China during 2015–2020 and good agreements with measured air pollutant concentrations in China. The cross-validated coefficient of determination (R^2) was 0.83, 0.84, 0.84, 0.80, and 0.87 for PM_1, SO_2, NO_2, CO, and O_3, respectively. For each subject, we extracted 24-hour average PM_1, SO_2, NO_2, CO and maximum 8-hour moving average O_3 concentrations from the CHAP dataset at his or her residential address on both the case and control days. As proposed in previous studies, we used a cumulative exposure during the same day of death and 1 day prior (lag 0–1 day) to quantify the effects of PM_1 on CVD mortality (Vicedo-Cabrera et al., 2020).

2.5. Covariates

Using the China Meteorological Administration Land Data Assimilation System (CLDAS version 2.0), we obtained daily grid data (spatial resolution: 0.0625° × 0.0625°) on weather conditions in Jiangsu province during 2015–2020, and assessed exposure to 24-hour average temperature (°C) and relative humidity (%) by extracting daily values at each subject's residential address on both the case and control days (Liu et al., 2020; Zhou et al., 2020). As individual-level covariates (e.g., age, sex, race, genetics, and lifestyle) generally remained constant within a short time (i.e., the time stratum), they were not considered as potential confounding factors in this analysis (Carracedo-Martínez et al., 2010).

2.6. Statistical analysis

2.6.1. Exposure-response analysis

We performed conditional logistic regression models and distributed lag models (DLMs) to evaluate the exposure–response association of exposure to ambient PM_1 with total and cause-specific CVD mortality by cumulating the risks during the same day of death and 1 day prior (Vicedo-Cabrera et al., 2020). We estimated the percent change in odds ([odds ratio − 1] × 100%) of CVD deaths and the 95 % confidence

interval (CI) per 10 μg/m^3 increase of PM_1 exposure. In main models, we included natural cubic spline functions with 6 degrees of freedom (*df*) for temperature and 3 *df* for relative humidity (Liu et al., 2019a), and a cross-basis function of PM_1 exposure built by the DLM (Gasparrini et al., 2010). The cross-basis function was composed of a linear function for the space of PM_1 exposures and the space of 2 days lag (Gasparrini et al., 2010; Vicedo-Cabrera et al., 2020). In addition, we further employed distributed lag non-linear models (DLNMs) by including a cross-basis function with a natural cubic spline function ($df = 3$) for the space of PM_1 exposures and a linear function for the space of 2 days lag. Likelihood ratio tests were used to examine if the associations were nonlinear. The lowest PM_1 exposure level was used as the reference in estimating the association of exposure to PM_1 with mortality from total and cause-specific CVDs.

2.6.2. Excess mortality

We used the exposure–response estimates to further assess the excess mortality by calculating excess fraction and number of excess deaths according to a previously proposed approach (Gasparrini and Leone, 2014), using the following formula:

$$\text{Excess fraction}_{x,t} = 1 - e^{\left(-\sum_{l=l_0}^{L}\beta_{x_{t-l},l}\right)}$$

$$\text{Number of excess deaths}_{x,t} = N_t \times \text{excess fraction}_{x,t}$$

where $\sum\beta_{x_t,l}$ corresponds to the logarithm of cumulative odds ratio associated with exposure to x (i.e., PM_1) at time t from the DLMs or DLNMs; N_t is the number of total or cause-specific CVD deaths at time t; $\text{excess fraction}_{x,t}$ and $\text{number of excess deaths}_{x,t}$ represent the excess fractions and number of deaths at time t attributable to exposures to x in the period $t-l_0,\cdots,t-L$, compared to the referent x exposure level (i.e., the lowest PM_1 exposure level). Monte Carlo simulations were performed to calculate the empirical confidence interval (eCI) for each estimated excess fraction and number of excess deaths (Gasparrini and Leone, 2014). The difference of excess fractions between given two specific types of CVD was tested by a 2-sample *z* test (Altman and Bland, 2003).

2.6.3. Stratified analysis

In stratified analyses, we estimated the associations and excess fractions by sex (male, female) and age (≤80 years, >80 years), and further examined the difference across each stratification by the 2-sample *z* test (Altman and Bland, 2003).

2.6.4. Sensitivity analysis

We conducted several sensitivity analyses to evaluate the robustness of our results: 1) fitting 2-pollutant models by separately adding each of the gaseous air pollutants (i.e., SO_2, NO_2, CO and O_3) as a cross-basis function with DLNM in the same model and compared the estimates using likelihood ratio tests; 2) using single-day lag exposures and moving average day exposures for PM_1 (lag 0 day to lag 3 day, lag 01 day to lag 03 day), and calculating the excess fraction based on the exposure–response estimates in lag 01 day; 3) calculating the excess mortality according to results from nonlinear associations. In this study, R (version 4.1.2) with the *data.table*, *dlnm* and *survival* packages was used to perform all analyses, and a 2-sided p value <0.05 was considered statistically significant.

3. Results

3.1. Study subjects and characteristics

During 2015–2020, we identified 1,081,507 deaths from CVDs in Jiangsu province, China. Among these deaths, 57.1 % died above 80 years, 49.5 % were male, and most of them (99.8 %) were Han race. Overall, the study population included 8865 (0.8 %) CRHD deaths, 79,955 (7.4 %) HD deaths, 321,668 (29.7 %) IHD deaths, 7757 (0.7 %) PHD deaths, 442,000 (40.9 %) stroke deaths, and 172,076 (15.9 %) deaths from sequelae of stroke (Table 1).

3.2. Ambient PM_1 exposure

Table 2 shows the distribution of air pollutants and weather conditions on case days during 2015–2020. Mean exposure to ambient PM_1, temperature, and relative humidity was 33.7 μg/m^3, 14.6 °C, and 73.5 %, respectively. The spatial and temporal distributions of ambient PM_1 and daily number of CVD deaths during the study period in Jiangsu province, China are presented in Fig. 1. Overall, the annual average PM_1 concentration decreased from 2015 to 2020 in most of the study area. The daily PM_1 concentration was higher from December to February (winter) and lower from June to August (summer), while the distribution of daily number of CVD deaths yielded a similar trend. Exposures to ambient PM_1, SO_2, NO_2 and CO were positively correlated, whereas the O_3 exposure was negatively correlated with exposures to PM_1, SO_2, NO_2 and CO (all p <0.0001; Table S1).

3.3. Exposure-response analysis

A 10 μg/m^3 increase in PM_1 exposure was significantly associated with an increased odds of 1.46 % (95 % CI: 1.28 %, 1.65 %), 1.95 % (1.28 %, 2.63 %), 1.16 % (0.86 %, 1.47 %), 1.41 % (1.13 %, 1.69 %), and 1.83 % (1.37 %, 2.30 %) for mortality from total CVDs, HDs, IHDs, stroke and sequelae of stroke, respectively (all p <0.05); no statistically significant association was identified with mortality from CRHDs or PHD (Table 3). The associations of PM_1 exposure with mortality from CRHDs, HDs (including HHD and HRD), MI, HS, and sequelae of HS were linear, while the odds of mortality from total CVDs, IHDs (including CIHD), stroke (including IS), and sequelae of stroke (including sequelae of IS) increased monotonically at lower PM_1 exposures but attenuated at higher exposures (p for nonlinear <0.05; Fig. 2). In 2-pollutant models, the associations remained or slightly decreased with adjustment for exposure to SO_2, NO_2, CO, and O_3 (Table S2).

3.4. Excess mortality

The excess fraction of total CVD deaths was 5.71 % (95 % eCI: 4.99 %, 6.43 %), corresponding to 61,708 (95 % eCI: 53,994, 69,547) excess deaths (Table 3). The excess fraction was 7.46 % (95 % eCI: 4.91 %, 10.00 %), 4.98 % (3.67 %, 6.30 %), 5.63 % (4.50 %, 6.77 %), and 6.77 % (5.07 %, 8.47 %) for mortality from HDs, IHDs, stroke, and sequelae of stroke, respectively (all p <0.05), while no significant excess fraction was observed for mortality from CRHDs or PHD (p >0.05). The excess fraction of IS deaths attributable to PM_1 exposure was significantly higher than that of HS deaths (6.88 % vs 3.97 %; p for difference = 0.018); no significant difference of excess fractions in two subtypes was observed for mortality from HDs, IHDs or sequelae of stroke (all p for difference >0.05). The excess fraction calculated using estimates from the DLNMs was 6.80 %, 4.78 %, 7.52 %, 7.28 %, 10.02 %, 7.82 %, and 10.54 % for mortality from total CVDs, IHDs, CIHD, stroke, IS, sequelae of stroke, and sequelae of IS, respectively, which were similar with or slightly higher than the corresponding excess fractions calculated using estimates from the DLMs (Table S3).

3.5. Stratified and sensitivity analyses

In stratified analyses, significantly higher excess fractions of mortality from total CVDs, HHD, and stroke (including HS) were observed in adults over the age of 80 (p for difference <0.05; Fig. 3 and Tables S4–S6). Using moving average day exposures (lag 01 day) of PM_1 yielded slightly higher estimates (Tables S7–S8).

Table 1
Characteristic of study subjects in Jiangsu province, China, 2015–2020.

Characteristic	Cardiovascular diseases	Chronic rheumatic heart diseases	Hypertensive diseases	Ischemic heart diseases	Pulmonary heart disease	Stroke	Sequelae of stroke
No. of deaths (case days)	1,081,507	8865	79,955	321,668	7757	442,000	172,076
No. of control days	3,670,295	30,086	271,294	1,090,925	26,281	1,500,619	584,051
Age, year							
Mean ± SD	79.3 (11.9)	75.4 (13.2)	82.6 (10.6)	79.7 (12.4)	78.9 (12.9)	78.2 (11.6)	81.4 (8.9)
Median ± IQR	81.8 (13.5)	77.9 (17.6)	84.8 (11.2)	82.6 (14.4)	81.7 (13.0)	80.6 (13.8)	82.7 (10.8)
≤80	464,088 (42.9)	5040 (56.9)	23,778 (29.7)	130,221 (40.5)	3324 (42.9)	211,780 (47.9)	64,083 (37.2)
>80	617,419 (57.1)	3825 (43.1)	56,177 (70.3)	191,447 (59.5)	4433 (57.1)	230,220 (52.1)	107,993 (62.8)
Sex							
Male	535,346 (49.5)	3514 (39.6)	34,928 (43.7)	156,412 (48.6)	4231 (54.5)	224,594 (50.8)	85,157 (49.5)
Female	546,161 (50.5)	5351 (60.4)	45,027 (56.3)	165,256 (51.4)	3526 (45.5)	217,406 (49.2)	86,919 (50.5)
Race							
Han	1,078,976 (99.8)	8846 (99.8)	79,797 (99.8)	320,882 (99.8)	7739 (99.8)	441,080 (99.8)	171,594 (99.7)
Other	2531 (0.2)	19 (0.2)	158 (0.2)	786 (0.2)	18 (0.2)	920 (0.2)	482 (0.3)

SD: standardized deviation; IQR: interquartile range.

Table 2
Distribution of air pollutants and weather conditions on the date of CVD deaths in Jiangsu province, China, 2015–2020.

	Mean (SD)	Min	P_{25}	P_{50}	P_{75}	Max
Air pollutant						
PM_1, μg/m^3	33.7 (13.9)	2.4	24.1	30.7	40.4	133.6
SO_2, μg/m^3	17.2 (10.1)	1.8	10.4	14.7	21.2	152.9
NO_2, μg/m^3	36.4 (15.3)	3.6	25.3	33.3	44.6	168.0
CO, mg/m^3	0.90 (0.30)	0.18	0.71	0.85	1.06	3.84
O_3, μg/m^3	101.3 (42.7)	3.8	68.5	93.4	128.6	323.6
Weather condition						
Temperature, °C	14.6 (9.4)	−10.7	6.3	14.2	22.8	36.3
Relative humidity, %	73.5 (13.7)	16.6	64.4	75.1	84.5	100.0

CO: carbon monoxide; CVD: cardiovascular disease; NO_2: nitrogen dioxide; O_3: ozone; PM_1: particulate matter with an aerodynamic diameter ≤1 μm; SD: standardized deviation; SO_2: sulfur dioxide.

4. Discussion

4.1. Key findings

In this large case-crossover study on 1.1 million CVD deaths, we found significantly positive associations of short-term exposure to ambient PM_1 with mortality from total and specific CVDs in Jiangsu province, China. Each 10 μg/m^3 increase in PM_1 exposure was significantly associated with a 1.46 %, 1.95 %, 1.16 %, 1.41 %, and 1.83 % increase in odds of mortality from total CVDs, HDs, IHDs, stroke, and sequelae of stroke, respectively. The excess fraction of total CVD deaths was 5.71 %, and ranged from 4.98 % for IHD deaths to 7.46 % for HD deaths. Significantly higher excess fractions for mortality from total CVDs, HHD, and stroke (including HS) were detected in older adults. No significant associations or excess mortality were identified for mortality from CRHDs or PHD.

4.2. Comparison with other studies

This is the first study to systematically assess the adverse effects of exposure to ambinet PM_1 on mortality from a wide range of specific CVDs. A few previous studies have evaluated the acute effects of

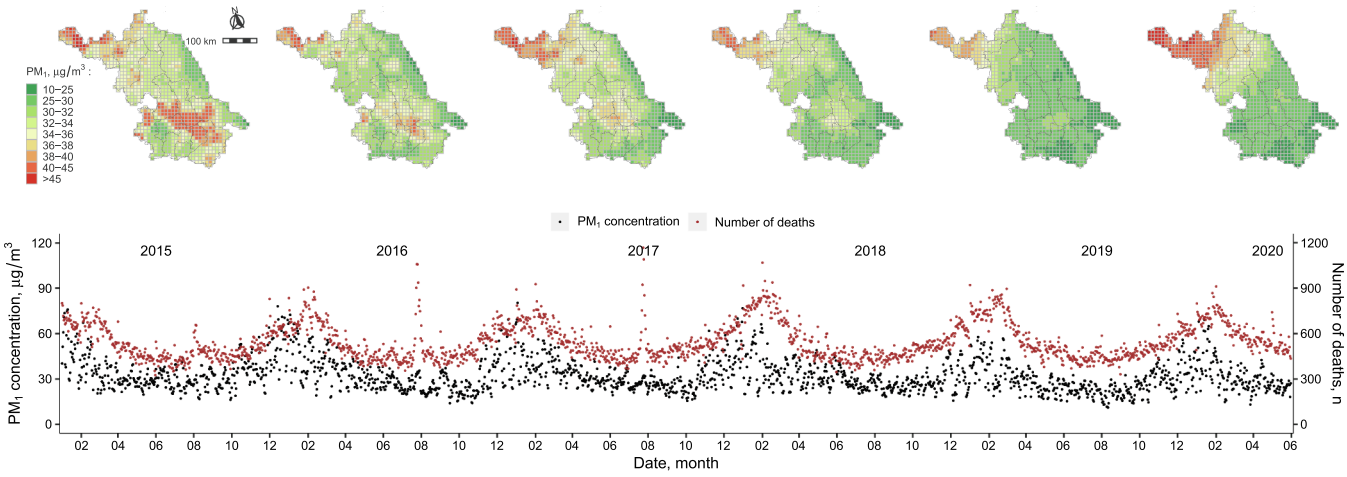

Fig. 1. Distribution of annual average PM_1 concentrations and daily number of CVD deaths in Jiangsu province, China, 2015–2020. The grids (spatial resolution: 10 km × 10 km) with different colors indicate the PM_1 concentrations. CVD: cardiovascular disease; PM_1: particulate matter with an aerodynamic diameter ≤1 μm.

Table 3
Percent change in odds, excess fraction and number of excess deaths from CVDs associated with lag 0-1 day exposure to ambient PM_1.

	N (%)	Percent change, % (95 % CI)	Excess fraction, % (95 % eCI)	Number of excess deaths, N (95 % eCI)
Cardiovascular diseases	1,081,507 (100)	1.46 (1.28, 1.65)	5.71 (4.99, 6.43)	61,708 (53,994, 69,547)
Chronic rheumatic heart diseases	8865 (0.8)	1.19 (-0.05, 2.45)	6.82 (-0.58, 13.71)	604 (-52, 1215)
Hypertensive diseases	79,955 (7.4)	1.95 (1.28, 2.63)	7.46 (4.91, 10.00)	5965 (3927, 7992)
Hypertensive heart disease	70,593 (6.5)	2.01 (1.30, 2.73)	7.69 (4.98, 10.38)	5427 (3514, 7326)
Hypertensive renal disease	7916 (0.7)	1.88 (0.45, 3.33)	9.69 (2.21, 16.66)	767 (175, 1319)
Ischemic heart diseases	321,668 (29.7)	1.16 (0.86, 1.47)	4.98 (3.67, 6.30)	16,019 (11,801, 20,271)
Myocardial infarction	184,060 (17.0)	0.95 (0.60, 1.30)	4.62 (2.89, 6.35)	8497 (5313, 11,689)
Chronic ischemic heart disease	132,631 (12.3)	1.28 (0.80, 1.77)	5.24 (3.24, 7.25)	6956 (4300, 9611)
Pulmonary heart disease	7757 (0.7)	0.33 (-1.26, 1.94)	1.67 (-7.16, 9.76)	129 (-555, 757)
Stroke	442,000 (40.9)	1.41 (1.13, 1.69)	5.63 (4.50, 6.77)	24,863 (19,869, 29,902)
Hemorrhagic stroke	167,747 (15.5)	1.00 (0.53, 1.46)	3.97 (2.08, 5.86)	6656 (3488, 9824)
Ischemic stroke	228,593 (21.1)	1.58 (1.23, 1.94)	6.88 (5.35, 8.41)	15,725 (12,235, 19,227)
Sequelae of stroke	172,076 (15.9)	1.83 (1.37, 2.30)	6.77 (5.07, 8.47)	11,645 (8723, 14,578)
Sequelae of hemorrhagic stroke	14,950 (1.4)	2.26 (1.03, 3.51)	10.00 (4.58, 15.15)	1494 (685, 2264)
Sequelae of ischemic stroke	126,175 (11.7)	1.81 (1.27, 2.35)	6.70 (4.70, 8.69)	8449 (5936, 10,961)

CI: confidence interval; CVD: cardiovascular disease; eCI: empirical confidence interval; PM_1: particulate matter with an aerodynamic diameter $\leq$1 μm.

exposure to PM_1 on CVD mortality; however, all of them focused on the PM_1-related associations for mortality from total CVDs and/or stroke (Hu et al., 2018; Lin et al., 2016a; Lin et al., 2016b; Perez et al., 2009). An early case-crossover study in Barcelona, Spain reported that each 10 $\mu g/m^3$ increase of PM_1 exposure (lag 0 day) was associated with a 2.9 % increased odds of mortality from total CVDs, which was slightly higher than our estimates (1.53 %) (Perez et al., 2009). Despite of the differences in study design, similar significantly adverse effects of PM_1 exposure on mortality from total CVDs and stroke have been demonstrated in three time-series studies in China (Hu et al., 2018; Lin et al., 2016a, 2016b).

4.3. Interpretations and future perspectives

In addition to significant associations with total CVD and stroke mortality, we found new evidence of significant associations between short-term exposure to ambient PM_1 and an increased odds of mortality from HDs (including HHD), IHDs (including MI and CIHD), and sequelae of stroke (including sequelae of IS and sequelae of HS). These findings indicate that ambient PM_1 is a modifiable risk factor for mortality from a variety of specific CVDs. In addition, given that PM_1 exposure may lead to a considerable excess mortality from specific CVDs, reducing PM_1 exposure level can be a potential measure to prevent premature cause-specific CVD deaths and may bring health benefits for both individuals and the society. However, due to insufficient knowledge on the PM_1-related health effects, there are no air quality standards for ambient PM_1 to date. Our findings on the association between PM_1 exposure and CVD mortality provide important quantitative data for the formulation of future air quality standards for ambient PM_1.

In this study, we did not identify significant differences in the adverse effects of PM_1 exposure on mortality from different types of specific CVDs, indicating that the underlying pathological mechanisms of the CVD death associated with PM_1 may be similar. However, the pathological mechanisms have not been fully elucidated to date. As proposed in previous studies, the small particle size enables PM_1 to be inhaled and deposited in the respiratory system, and passed into the circulation system directly, which may induce blood coagulation and vasoconstriction, promote oxidative stress and trigger systematic inflammation (Chen et al., 2015). Because of the large surface area to mass ratio, PM_1 can carry large concentrations of toxic components (such as redox-active components, carbonaceous elements and hazardous metals), some of which may reach cardiovascular target sites and disrupt biological functions (Delfino et al., 2005; Zou et al., 2017). In addition, previous epidemiological and animal studies have linked PM exposure to autonomic nervous system imbalance, including change in heart rate variability, elevation of blood pressure and glucose levels, and lipid metabolism disturbances. These pathophysiological changes have been demonstrated to trigger CVD events (Bartoli et al., 2009; Bhatnagar, 2022; Rajagopalan et al., 2018). Further investigations are warranted to elucidate the specific biological mechanisms. In addition, our study showed that ambient PM_1 exposure might pose more considerable adverse effects on mortality from CVDs among older adults. Older adults tend to comorbid with relatively poor health conditions, which can damage bodily functions and therefore increase the risk of CVD events when exposed to ambient air pollutants (Kelly et al., 2003). Nonetheless, the stronger association between PM_1 and CVD mortality among older adults needs to be further investigated.

4.4. Strengths and limitations

This study has several strengths. The key strength is that we included over 1 million CVD deaths in the analyses. The large sample size provided a unique opportunity for us to investigate the health impacts of ambient PM_1 exposure on mortality from various rarely studied cause-specific CVDs (including CVDs with relatively small number of deaths) with sufficient statistical power and representative estimates. Second, we firstly assessed PM_1 exposures based on the residential address with a validated and high-resolution grid air pollution dataset for each subject, which provided more accurate individual-level exposure assessment than that in previous studies which used the air pollution data from one single or several monitoring stations in a city as a proxy for individual-level exposure. Third, the time-stratified case-crossover method allows us to explore individual-based association and account for potential confounders including long-term trends, time-invariant individual covariates or relatively constant characteristics, and time-varying meteorological conditions.

There were also several limitations in this study. First, the individual-level PM_1 exposure in our study was not the actual individual exposure due to the unavailability of information on personal factors (e.g., personal indoor air pollution, time-activity pattern). This may introduce nondifferential exposure misclassification and possibly underestimate the true measure of effects (Zeger et al., 2000). Second, we made full use of the unique advantages of time-stratified case-crossover approach to control time-invariant factors (e.g., sex, race, genetics, lifestyle) and time-varying weather conditions in the model; however, there might still be certain residual confounders (e.g., medication use) which could not be controlled in our analyses and might introduce inaccurate estimates. Third, our study area is one single province in China, which may limit the generalizability of our results, although the total population of Jiangsu province was up to 84.7 million in 2020.

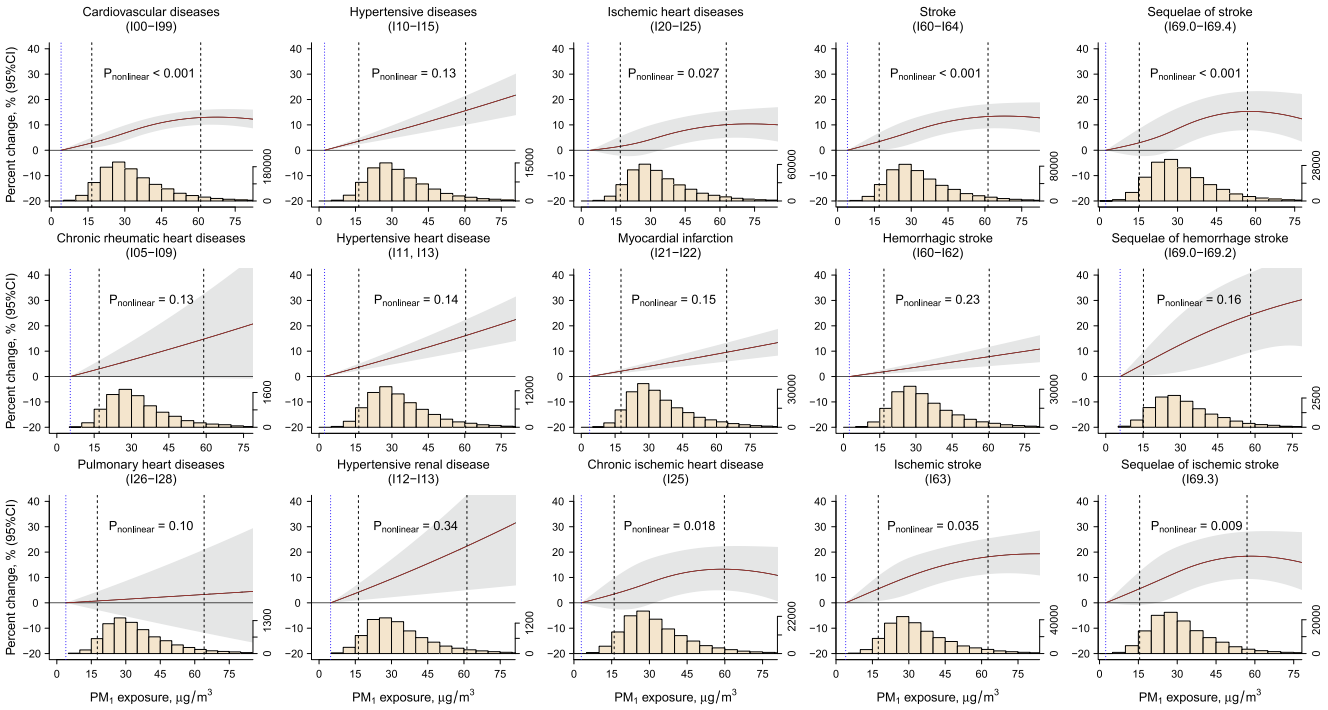

Fig. 2. Cumulative exposure–response curves for associations of lag 0-1 day exposure to ambient PM_1 with mortality from total and cause-specific CVDs. The vertical blue lines represent the referent PM_1 concentrations, while the two vertical black lines represent the 2.5th (left) and the 97.5th (right) percentile of ambient PM_1 concentrations, respectively. CI: confidence interval; other abbreviations as in Fig. 1.

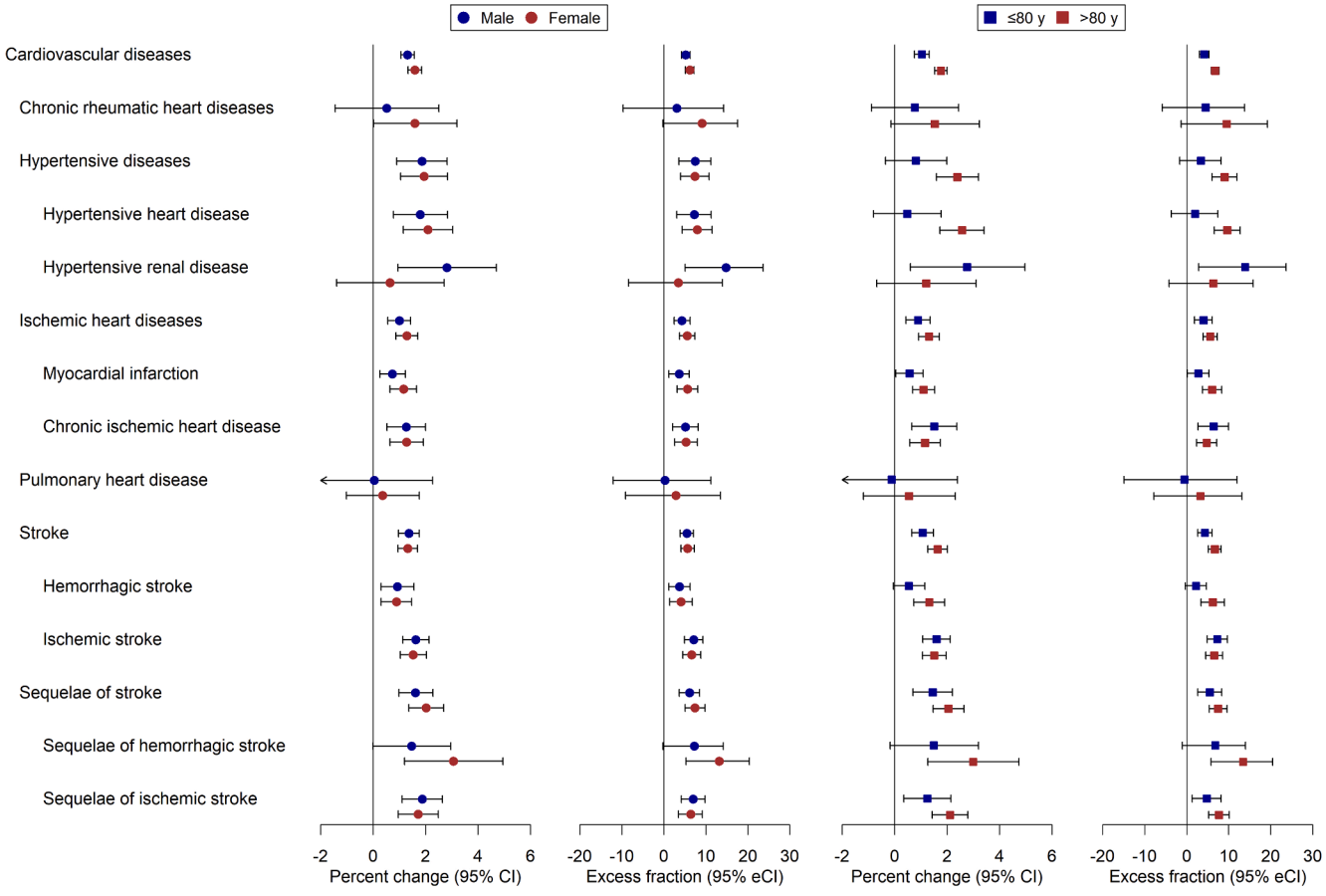

Fig. 3. Percent change in odds and excess fraction of mortality from CVDs associated with lag 0-1 day exposure to ambient PM_1, stratified by sex and age. The vertical black lines indicate the estimates of 0. *p values for difference were <0.05. Abbreviations as in Fig. 1.

5. Conclusions

Short-term exposure to ambient PM_1 was significantly associated with an increased odds of total and cause-specific CVD mortality and may lead to substantial excess mortality especially among older adults. Our findings highlight that lowering ambient PM_1 exposure may be an effective approach in reducing premature deaths from a wide range of CVDs. In addition, the quantified exposure–response relationship between PM_1 exposure and CVD mortality can aid to formulate future air quality standards for ambient PM_1.

CRediT authorship contribution statement

Ruijun Xu: Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Jing Wei:** Data curation, Methodology. **Tingting Liu:** Writing – review & editing. **Yingxin Li:** Writing – review & editing. **Chunyu Yang:** Writing – review & editing. **Chunxiang Shi:** Data curation. **Gongbo Chen:** Writing – review & editing. **Yun Zhou:** Writing – review & editing. **Hong Sun:** Conceptualization, Data curation, Funding acquisition, Supervision, Project administration, Writing – review & editing. **Yuewei Liu:** Conceptualization, Data curation, Funding acquisition, Supervision, Project administration, Writing – review & editing.

Declaration of Competing Interest

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

Data availability

The air pollution data are available at https://weijing-rs.github.io/product.html. The data on meteorological conditions and CVD mortality are confidential.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2022.107519.

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