



The contribution of PM_{2.5} to cardiovascular disease in China

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Abstract

China is experiencing rapid urbanization and industrialization with correspondingly high levels of air pollution. Although the harm of PM_{2.5} has been long reported, it is only quite recently that there is increasing concern in China for its possible adverse health effects on cardiovascular disease. We reviewed the epidemiologic evidence of potential health effects of PM_{2.5} on cardiovascular disease reported from recent studies in China (2013 onwards). There is clear evidence for the contribution of PM_{2.5} to cardiovascular outcomes, including mortality, ischemic heart disease, and stroke from studies based in various regions in China. This evidence adds to the global evidence that PM_{2.5} contributes to adverse cardiovascular health risk and highlights the need for improved air quality in China.

Keywords PM_{2.5} · Air pollution · Cardiovascular mortality · Ischemic heart disease · Stroke · China

Introduction

Cardiovascular disease (CVD) is a group of diseases of multifactorial origin that involve damage to the heart and/or vascular system. Contributing factors include hypertension, dyslipidemia, diabetes, and obesity (GBD 2017 Risk Factor Collaborators 2018; Cercato and Fonseca 2019). Cigarette smoking is another major contributor, as a result of damage to the vasculature that results from the regular inhalation of a cocktail of noxious chemicals, including those in gaseous form and those carried on particulate matter (Conklin et al. 2019). It is not surprising, therefore, that inhaled particulates from other sources, including industrial emissions, heating fuels, and traffic exhaust emissions, can also contribute to risk. There is growing evidence for an association between long-term exposure to fine particulate matter and cardiovascular

mortality (Requia et al. 2018; Rajagopalan et al. 2018; Yuan et al. 2019). In addition, people with existing cardiovascular disease, from whatever origin, are at risk of acute and potentially fatal cardiovascular events such as heart attack and stroke. A common factor in such events is the formation or rupture of a blood clot that can block blood vessels leading to the death of heart muscle or neural cells (Robertson and Miller 2018). Consequently, it is important to understand the role of air borne particulates in both the long-term and short-term effects on populations undergoing high levels of exposure as well as considering that some people are particularly susceptible to short-term peaks in exposure. The aging population and acceleration of urbanization augment the prevalence of cardiovascular disease in China. According to statistics from the China CDC, cardiovascular diseases were the top cause of death in 2016, which was 45.50% in rural areas and 43.16% in urban areas with a continuous increasing trend (National Center for Cardiovascular Diseases 2017).

China is a large and rapidly developing country with great variations in socioeconomic status among its population. Rapid economic growth has led to increased industrial pollution, and huge urban development and urban wealth has been accompanied by increases in traffic emissions. Consequently, many types of particulate matter, from industrial processes and traffic emissions, co-exist, with variation in distribution of specific types of particulates in different regions. Understandably, many studies have been carried out in the mega cities such as Beijing, Shanghai, and Guangzhou but there have been an increasing number of studies in recent

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years around China. In this review, we focus on the impact of $PM_{2.5}$ on cardiovascular health, especially as reported in studies published since 2013, a period of rapidly increasing research in this area.

Search strategy

We searched the databases PubMed and Web of Science for epidemiological literature on the cardiovascular effect of $PM_{2.5}$ published between 2013 and 2019. Combinations of the following keywords were used: (1) particulate, particulate matter, PM, air pollution; (2) cardiovascular disease, heart attack, stroke, cerebrovascular disease, cardiovascular mortality, CVD; (3) China. The search strategies identified the studies conducted in China that examined the adverse effects of exposure to $PM_{2.5}$ on cardiovascular health. The inclusion criteria we used for selection were as follows: (1) The subjects of epidemiological studies were all Chinese population. (2) Original studies expressed quantitative relationships between $PM_{2.5}$ and health outcomes, e.g., relative risk, odds ratios, excess risk (ER), or hazard ratio. (3) The health outcomes involved CVD mortality, IHD, or cerebrovascular disease. For the selected studies, the title, authors, location, publication year, study period, study design, number of events/controls, measure of $PM_{2.5}$ increase, health outcomes, statistical methods, and specific risk estimates were extracted and entered into Microsoft Excel database. The search results were grouped into 3 sections according to health outcomes including cardiovascular end points, IHD end points, and cerebrovascular end points.

$PM_{2.5}$ and cardiovascular mortality in China

$PM_{2.5}$ are particles of mean aerodynamic diameter below $2.5\ \mu\text{m}$ and consist of a carbon core associated with various inorganic pollutants (e.g., sulfates, nitrates, metals) and organic combustion products (Newby et al. 2014). Particles of this size, especially those below $0.1\ \mu\text{m}$, can reach deep into the respiratory system, and some may be able to enter the bloodstream (Mills et al. 2009; Pan et al. 2016). Thus, the toxic metals and organic chemicals they carry may potentially be delivered to the circulatory system or trigger an inflammatory response in the lungs that impacts on the cardiovascular system.

As seen in other countries, high $PM_{2.5}$ concentrations are associated with cardiovascular mortality in China (Yin et al. 2017; Table 1). In a prospective study, average $PM_{2.5}$ concentrations between 2000 and 2005 were estimated from a variety of data across 45 disease surveillance points in China, from which nearly 222,000 men were enrolled in a National Cohort of 40-year-old men in 1990–1991. This study covered a wide

geographical distribution of the population, with a range of health and lifestyle data and follow-up from death certificates. $PM_{2.5}$ exposures were estimated using a combination of satellite-derived and chemical transport model estimates, calibrated to surface measurements. It was found that for every $10\ \mu\text{g}/\text{m}^3$ increase in $PM_{2.5}$, the hazard ratio (HR) was 1.09 (95% CI 1.08–1.10) and dose response curves were calculated showing increased risk of cardiovascular death at average $PM_{2.5}$ concentrations above about $20\ \mu\text{g}/\text{m}^3$.

In Guangzhou, southern China, Lin et al. (2016a) reported a significant impact of PM_{10} , $PM_{2.5}$, and PM_1 concentrations in the previous 1–3 days on cardiovascular mortality for the period 2009–2011. The excess risk was 6.1% (95% CI 1.76–10.64%) for PM_{10} , 6.11% (95% CI 1.76–10.64%) for $PM_{2.5}$, and 6.48% (95% CI 2.10–11.06%) for PM_1 per IQR increase in the particulates. Importantly, the analysis controlled for numerous potential confounders, including the weather and influenza epidemics. For $PM_{2.5}$, further breakdown of results by chemical constituents showed that organic carbon, elemental carbon, sulfate, nitrate, and ammonium were significantly associated with cardiovascular mortality. Focusing on short time increases in pollution, the same group (Lin et al. 2017) found significant associations between hourly peak concentrations of $PM_{2.5}$ and cardiovascular mortality, particularly from ischemic heart diseases (IHD) and cerebrovascular diseases (CBD). This highlights the potential for acute peak levels of pollution to impact on cardiovascular mortality, although no significant association was observed for acute myocardial infarction (AMI). Hourly peak concentration of $PM_{2.5}$ was defined in this study as the maximum concentration of 24-h $PM_{2.5}$ values within a given day.

More recently, Chen et al. (2018) have reported an increased risk in cardiovascular mortality with short-term increased $PM_{2.5}$ concentrations from a large multicenter study including data covering the period 2013–2015, collected from 30 counties across northern, eastern, and southwestern China. Controlling for 24-h temperature and relative humidity, this study found that for a $10\text{-}\mu\text{g}/\text{m}^3$ increase in $PM_{2.5}$, there was a 0.12% (95% CI 0.001–0.25%) increase in CVD mortality and a 0.42% (95% CI 0.03–0.81%) increase in AMI on the same day. The authors noted that while this confirms the impact of short-term exposure to $PM_{2.5}$, the magnitude of the effect was lower than that seen in similar multicenter studies in the USA and Europe. They also reported a higher susceptibility of effects among people aged 65–74.

Analyzing data from 2013 to 2016 from the heavily polluted city of Shenyang, the city with the largest population in northeast China, Liu et al. (2019) reported an increase in daily CVD mortality of 0.4% (95% CI 0.22–0.59%) for each $10\ \mu\text{g}/\text{m}^3$ increase in $PM_{2.5}$ on the same day. They found that CVD mortality was 2–8 times higher during the warmer months, even though pollution increases during the cold winters when there was more heating used. The authors suggested that a

Table 1 Cardiovascular mortality with increased risk associated with PM_{2.5} exposure

Location, etc.	Time period	Outcome	Measure of PM _{2.5} increase	Excess risk or hazard ratio (HR) (95% CI)	Reference
Short-term exposure					
Guangzhou 104,756 cases	2009–2011	CVD mortality	Previous 1–3 days, IQR	6.11% (1.76–10.64%)	Lin et al. (2016a)
Guangzhou 46,850 cases	2013–2015	a) CVD mortality b) CBD (cerebrovascular)	Hourly peak at lag03 day	a) 1.15% (0.67–1.63%) b) 1.09% (0.27–1.91%)	Lin et al. (2017)
30 counties 379,133 cases	2013–2015	a) CVD mortality b) AMI	Same-day exposure, average increase per 10 µg/m ³	a) 0.12% (0.001–0.25%) b) 0.42% (0.03–0.81%)	Chen et al. (2018)
Shenyang 62,159 cases	2013–2016	CVD mortality	Same-day exposure, average increase per 10 µg/m ³	0.4% (0.22–0.59%)	Liu et al. (2019)
Beijing Outdoor workers 136,922 cases	2010–2012	CVD mortality	a) 7 days > 75 µg/m ³ b) 9 days > 105 µg/m ³	a) 30% (13–50%) b) 53% (29–52%)	Wang et al. (2017)
Yanbian Korean Autonomous Prefecture 16,365 cases (9029 ethnic Hans, 7336 ethnic Koreans)	2015–2016	CVD mortality	Lag1, average increase per 10 µg/m ³	2.6% (2.5–2.8%)	Zhang et al. (2018a)
Shenzhen 14,537 cases	2013–2015	a) CVD mortality b) CBD (cerebrovascular)	a) Lag5 and lag02, rose by 10 µg/m ³ b) Lag4 and lag04, rose by 10 µg/m ³	a) 1.50% (0.51–2.50%); 2.09% (0.79–3.41%) b) 2.09% (2.28–3.92%); 3.08% (0.68–5.53%)	Cai et al. (2018)
7 cities	2013–2015	CVD mortality	Lag01, average increase per 10 µg/m ³	0.315% (0.133–0.497%)	Liang et al. (2017)
Guangdong 131,765 cases	2013–2015	a) CVD mortality b) AMI	Daily exceedance concentration hours (DECH); average increase of 500 µg/m ³ h at lag03	a) 4.55% (3.59–5.52%) b) 3% (1.13–4.9%)	Lin et al. (2018)
Average annual exposure 45 locations, 222,000 40-year-old men	2000–2005	CVD mortality	Average increase per 10 µg/m ³	HR = 1.09 (95% CI 1.08–1.10)	Yin et al. (2017)

possible reason for this may be that people go out less often in the winter or that higher temperatures outdoors exacerbate the effects of the particulates.

The studies described above provide further evidence from China that short-term peaks in PM_{2.5} exposure are associated with increased cardiovascular mortality. But in cities such as Beijing, there is often prolonged exposure to high levels of this and other pollutants. Wang et al. (2017) studied CVD mortality data throughout 2010, 2011 and 2012 in relation to extended periods of high PM_{2.5} (at least > 75 µg/m³) as recorded at the US Embassy monitoring station in central Beijing. They found that for periods of more than 7 days with levels continuously > 75 µg/m³, the excess risk of cardiovascular deaths increased. At 7 days continuous concentrations > 75 µg/m³, the excess risk for outdoor workers was estimated to be 30% (95% CI 13–50%), rising to 53% (95% CI 29–52%) for 9 days continuously > 105 µg/m³. At levels of PM_{2.5} > 115 µg/m³, for which prolonged continuous exposure events were rarer, the effect on CVD mortality was already seen at 6 days continuous exposure. In addition to the observed impact on outdoor workers, increased excess risk was observed for single and illiterate subgroups in the study.

China is a vast country with different climatic zones, and both local variations in pollution sources and meteorological conditions may influence the contribution of particulates to health burden. Lanzhou is an industrialized city on the banks of the Yellow River in the semi-arid Gansu Province in the northwest of China. Cardiovascular mortality peaks in the cold, dry winter. Using the data collected for daily pollution levels during 2014–2017, Wu et al. (2019) examined cardiovascular mortality in relation to airborne pollution and found an association between higher PM_{2.5} levels and cerebrovascular deaths, with high PM₁₀ being also associated with ischemic heart disease mortality. During this period, the average annual levels of PM_{2.5} were 60–70 µg/m³, which is two times the annual mean national air quality standard II (35 µg/m³). Overall, the health impacts of PM_{2.5} were found to be greater than PM₁₀. A study in Yanbian Korean Autonomous Prefecture, a region with lower average particulate levels, just below the 35 µg/m³ standard, also found that higher PM_{2.5} concentrations were associated with higher incidence of cardiovascular and cerebrovascular deaths (Zhang et al. 2018a). For each 10 µg/m³ increase in lag1 day concentration of PM_{2.5}, there was a 2.6% (95% CI 2.5–2.8%) increase in cardiovascular mortality in this population. The authors point out

that this effect is more severe than for some studies reported in more polluted areas of China such as Beijing or Shenyang, suggesting that the dose response curve may show higher responses at lower ends of the curve. Another city with a relatively low annual average PM_{2.5} level (at 35 µg/m³) is Shenzhen in southern Guangdong Province. Cai et al. (2018) found that for the years 2013–2015, there were also significant effects of increased PM_{2.5} concentrations on cardiovascular mortality, ischemic heart disease mortality, and cerebrovascular mortality. It is clear therefore that PM_{2.5} concentrations pose a cardiovascular health risk at levels below official air quality standards.

There are different approaches to measuring particulate concentrations, including mean daily concentration (used by Wu et al. 2019; Zhang et al. 2018a, b; Cai et al. 2018; Liang et al. 2017) and hourly peak concentration (used by Lin et al. 2017). A novel measure of measuring concentration of PM_{2.5} was proposed by Lin et al. (2018) to study the effects of high particulate concentrations on cardiovascular mortality. Daily exceedance concentration hour (DECH) is an indicator designed to focus on the length of time levels exceed a threshold, selected as 25 µg/m³, and calculated as the number of hours of exceedance multiplied by the level of exceedance in micrograms per cubic meter. Using this indicator in models studying the contribution of PM_{2.5} levels on cardiovascular deaths in six cities from the subtropical Pearl River Delta region, Lin et al. (2018) reported a greater effect of the particulates compared with other studies. An increase of 500 µg/m³ h at lag03 was associated with an increase of 4.55% (95% CI 3.59–5.52%) in cardiovascular mortality, a 4.45% (95% CI 2.81–6.12%) increase in ischemic heart disease deaths, and a 3% (95% CI 1.13–4.9%) increase in AMI related deaths. The authors suggest that the daily mean concentration could be underestimating the effects of high air pollution, possibly because the DECH takes into account the peak exceedances that may have a greater impact on triggering cardiovascular events in susceptible individuals. The authors argue for the need to ensure peak exceedances are reduced by interventions that target mean exposure levels.

The fact that multiple pollutants (including PM_{2.5}, PM₁₀, NO₂, SO₂) contribute to the health impacts of air pollution means that the role of various pollutants on their own or together can be complex to determine. Tong et al. (2018) used a statistical learning method based on Bayesian kernel machine regression to estimate the contribution of joint effects on CVD deaths in Beijing. They showed that there could be interaction between pollutants enhancing cardiovascular mortality. They also found that the main contributing factor varied depending on the lag period used to determine the moving average concentrations, with PM_{2.5} making the biggest contribution for 0–3- or 0–4-day moving averages but not 0–1- or 0–2-day moving averages.

PM_{2.5} and ischemic heart disease in China

An association between increased short-term exposure to PM_{2.5} and ischemic heart disease (IHD) has been shown in several studies conducted in both developed and developing countries (Gouveia et al. 2006; Devos et al. 2015). In China, such associations have also been reported (Table 2). A time series analysis in Hong Kong that assessed effects of fine particles on daily emergency cardiovascular hospitalizations (Qiu et al. 2013) found that an IQR increase in lag01 concentration of PM_{2.5} corresponded to 1.75% (95% CI 0.94–2.57%), 2.61% (1.60–3.64%), and 3.47% (1.84–5.12%) increases of emergency hospital admissions for total circulatory diseases, cardiac diseases, and IHD, respectively.

In Beijing, Xu et al. (2017a) collected daily counts of cardiovascular hospital emergency room visits (ERVs) from ten large hospitals, in which 56,221 cardiovascular ERVs were included. It was estimated that daily mean PM_{2.5} concentration was 102.1 µg/m³ in Beijing in 2015, and every 10 µg/m³ increase in PM_{2.5} was associated with a 0.14% (95% CI 0.01–0.27%) increase in cardiovascular ERVs at lag3. For the analysis of cause-specific ERVs, the estimates of percentage change in daily ERVs each 10 µg/m³ increase in PM_{2.5} were 0.56% (95% CI 0.16–0.95%) for ischemic heart disease (IHD) at lag0–1, 0.81% (95% CI 0.05–1.57%) for heart rhythm disturbances at lag0–1, and 1.21% (95% CI 0.27–2.15%) for heart failure (HF) at lag0, respectively. In addition, this study suggested that the acute effects of PM_{2.5} on IHD varied by temperature with the effect during high-temperature days being significantly higher than that on low-temperature days.

A time series study in Beijing assessed the relationship between PM_{2.5} concentration and IHD morbidity and mortality based on the data of 369,469 IHD cases and 53,247 IHD deaths from the Beijing Monitoring System for Cardiovascular Diseases during 2010 to 2012 (Xie et al. 2015). The group estimated a 10-µg/m³ increase in PM_{2.5} was associated with a 0.27% (95% CI 0.21–0.33%, $p < 2.00 \times 10^{-16}$) increase in IHD morbidity and a 0.25% (95% CI 0.10–0.40%, $p = 1.15 \times 10^{-3}$) increase in IHD mortality on the same day. The study also indicated the dose–response relationships were non-linear, with a steeper dose–response function at lower concentrations and a shallower response at higher concentrations. Such coincidence between the escalation of PM_{2.5} and the increase in IHD morbidity was also demonstrated in Xu et al.'s study (2017b). Using daily IHD hospitalization data and average concentration of PM_{2.5}, they found that a 10-µg/m³ increment increase of PM_{2.5} was associated with an increase in IHD hospitalizations by 0.57% (95% CI 0.46–0.68%). The study (Xu et al. 2017b) suggested that the results could provide important outlook for public health research and management to prevent the increased risk of IHD due to PM by ways of increasing public health awareness and improving government policies.

Table 2 Ischemic heart disease end points with increased risk associated with PM_{2.5} exposure

Location, etc.	Time period	Outcome	Measure of PM _{2.5} increase	Excess risk (95% CI)	Reference
Short-term exposure					
Hong Kong 612,551 cases	2000–2005	IHD emergency hospital admissions	Lag01, IQR	3.47% (1.84–5.12%)	Qiu et al. (2012)
Beijing 8544IHD (56,221 total cardiovascular ERVs)	2013–2015	IHD emergency room visits (ERVs)	Lag0–1, average increase per 10 µg/m ³	0.56% (0.16–0.95%)	Xu et al. (2017a)
Beijing 369,469 IHD cases; 53, 247 IHD deaths	2010–2012	a) IHD morbidity b) IHD mortality	Same-day exposure, average increase 10 µg/m ³	a) 0.27% (0.21–0.33%) b) 0.25% (0.10–0.40%)	Xie et al. (2015)
Shanghai 188,198 cases	2013–2014	IHD hospitalizations	From lag0 to lag7, average increase 10 µg/m ³	0.25% (0.10–0.39%)	Xu et al. (2017b)
Nationwide (26 large cities) 720,261 cases	2014–2016	IHD hospital admissions	Lag2, IQR	1.7% (1.5–1.9%)	Dai et al. (2018)

Using electronic hospitalization summary reports in 26 large Chinese cities, a multicity case-crossover study (Dai et al. 2018) compared the effects of PM concentrations on IHD in northern China and southern China. As the study showed, PM concentrations were much higher in the north than south. In northern China, an IQR increase in PM_{2.5} concentrations at lag2 days was associated with a 1.8% (95% CI 1.6–2.1%) increase in IHD. Nevertheless, in southern China, negative associations were observed with PM_{2.5} almost at all lag structures indicating that the association is null or negative.

Several recent studies in different parts of China have shown an association between PM_{2.5} and acute myocardial infarctions (AMIs) (see Table 3). In Shanghai, Wang et al. (2016) assessed 972 patients from the emergency medical service documents covering the 2013–2014 in the Pudong District. It was found that the mean urban background levels of PM_{2.5} was associated with an increased risk of AMIs, with an OR (95% CI) of 1.16 (1.03–1.29). In addition, the

study suggested that more AMIs occurred during 6:00–18:00 when people were more likely to be outdoors and during November, December, and January when the pollution level was high. The study was consistent with that of Yu et al. (2018) conducted in Guangzhou province, in which it was found that a 10-µg/m³ increment in concentrations of PM_{2.5} was associated with an increase of 1.636% (95% CI 0.537–2.740%) in AMI.

Based on 2749 patients from Chaoyang District, Beijing, hospitalized with AMI in Anzhen Hospital, Zhang et al. (2016) estimated the transient effects of PM_{2.5} on risk of EDVs for AMI, ST-elevation myocardial infarction (STEMI), and non-ST-elevation myocardial infarction (NSTEMI). The result showed that each 10-µg/m³ increment of PM_{2.5} concentration (1-day lagged) was associated with an increased risk of EDVs for STEMI (OR 1.05; 95% CI 1.00–1.11), especially in patients aged ≥ 65 years. However, no association of PM_{2.5} concentration with overall AMI or

Table 3 Acute myocardial infarction end points with increased risk associated with PM_{2.5} exposure

Location etc	Time period	Outcome	Measure of PM _{2.5} increase	Excess risk, Hazard Ratio (OR) or Hazard Ratio (HR) (95% CI)	Reference
Short-term exposure					
Guangzhou 5545 cases	2015–2016	Daily MI morbidity	2-day cumulative, average increase 10 µg/m ³	1.636% (0.537–2.740%)	Yu et al. (2018)
Shanghai 972 cases	2013–2014	AMI morbidity	Lag0–1, average increase 10 µg/m ³	OR = 1.16 (95% CI 1.03–1.29)	Wang et al. (2016)
Beijing 2749 cases	2014	EDVs for AMI and its subtypes a) AMI b) ST-elevation myocardial infarction (STEMI) c) non-ST-elevation myocardial infarction (NSTEMI)	Lag1, average increase 10 µg/m ³	a) No association b) 1.05 (1.00–1.11) c) No association	Zhang et al. (2016)
Long-term exposure					
Tianjin 598 patients with AMI	2013–2014	Major adverse cardiovascular events (MACEs)	a) Five groups based on National Air Quality Classification Standard b) Better vs worse air quality	a) HR = 1.622 (95% CI 1.352–1.947) b) HR = 3.255 (95% CI: 1.2008–5.276)	Zang and Qi (2017)

NSTEMI was found. The findings indicated that studies of the association between $PM_{2.5}$ and AMI should consider AMI subtypes, lag times, and individual characteristics.

Zang and Qi (2017) implemented a retrospective analysis of a total of 598 patients in Tianjin who were divided into five groups according to the National Air Quality Classification Standard and then divided into two groups according to better and worse air quality. After 1-year follow-up, the study found that with the increase of the concentration of $PM_{2.5}$, the incidence of major adverse cardiovascular events (MACEs) was higher in patients 1 year after AMI. In the five groups, HR was 1.622 (95% CI 1.352–1.947; $p = 0.000$) and, in the two groups, HR was 3.255 (95% CI 2.008–5.276; $p = 0.000$), suggesting that the poor air quality could worsen the condition of patients.

Beside hospital emergency room/department visits for cardiovascular disease, numbers of out-of-hospital heart attack cases, especially cardiac arrest, manifest the acute effects of $PM_{2.5}$ on people with heart disease. Cardiac arrest is defined as the cessation of cardiac mechanical activity and the subsequent cessation of blood circulation (Mozaffarian et al. 2016). To assess the effects of air pollution on out-of-hospital cardiac arrests (OHCAs), Xia et al. (2017) obtained health data from nationwide emergency medical service database and analyzed 4720 OHCA cases. After adjustment for humidity and temperature, they found that the highest odds ratios of OHCA for a $10\text{-}\mu\text{g}/\text{m}^3$ increase in $PM_{2.5}$ were observed at lag1 (1.07; 95% CI 1.04–1.10), with significant associations with advanced age (aged ≥ 70 years) (1.09; 95% CI 1.05–1.13) and stroke history (1.11; 95% CI 1.06–1.16), supporting the statement that increased $PM_{2.5}$ exposure contributes to triggering OHCA.

$PM_{2.5}$ and stroke in China

As a subtype of CVD, stroke risk is adversely impacted by $PM_{2.5}$ (Table 4). The modified health risk of stroke associated with $PM_{2.5}$ and PM_{10} was examined in a case-crossover study in 26 Chinese cities by Liu et al. (2017a). Using hospital admission for stroke, the group examined 278,980 hospital admissions for ischemic stroke and 69,399 for hemorrhagic strokes separately from 2013 to 2015. The results showed an IQR in $PM_{2.5}$ and PM_{10} in northern China corresponded to a 1.0% (95% CI 0.7%, 1.4%) and 0.7% (95% CI, 0.3%, 1.2%) increase in ischemic stroke admissions at lag3 days, respectively, indicating the levels of $PM_{2.5}$ and PM_{10} are significantly associated with increased risk of ischemic stroke and $PM_{2.5}$ has a greater adverse effect on ischemic strokes. The different adverse effects of particular size on stroke have been also illustrated in the study of Lin et al. (2016b) in Guangzhou. The group assessed 9066 stroke deaths and found significant association between hemorrhagic stroke mortality with

various PM fractions, including PM_{10} , $PM_{2.5}$, and PM_{1} . It was found that excess risks (ERs) per IQR increase in lag2 days in PM_{10} , $PM_{2.5}$, and PM_{1} were 7.18% (95% CI 1.62–13.05%), 6.62% (95% CI 1.28–12.25%), and 8.74% (95% CI 1.33–16.68%), respectively, and the risk estimate of PM on hemorrhagic stroke mortality was more significant. By analyzing $PM_{2.5}$ chemical constituents, the same group found that organic carbon (OC), elemental carbon (EC), sulfate, nitrate, and ammonium were all significantly associated with stroke mortality.

In Beijing, the capital of China, Zhang et al. (2018b) detected a significant association between short-term increased $PM_{2.5}$ with stroke mortality using daily $PM_{2.5}$ concentration from an ecological study. Each $10\text{-}\mu\text{g}/\text{m}^3$ increase of $PM_{2.5}$ was associated with an increase of mortality: 0.27% (95% CI 0.12–0.43%) for cerebrovascular diseases, 0.23% (95% CI 0.04–0.42%) for ischemic stroke, and 0.37% (95% CI 0.07–0.67%) for hemorrhagic stroke. It was estimated in the same study that if the annual mass concentration of $PM_{2.5}$ could achieve the standard of WHO Air Quality Guidelines ($10\text{ }\mu\text{g}/\text{m}^3$), around 400 stroke deaths will be avoided per year in Beijing. Different from other studies (Zeng et al. 2018; Tian et al. 2018), Zhang et al. (2018b) did not find evidence indicating that gender or age can modify the effect of $PM_{2.5}$ on stroke in subgroup analysis.

Likewise, exploring data from 2013 to 2016 including daily mean concentration of air pollution and daily data on stroke mortality in six subtropical cities in Guangzhou province, Wang et al. (2018) examined the city-specific acute effects of daily PM_{10} , $PM_{2.5}$, and $PM_{10-2.5}$ across different lag days (log0 to log3) and multiday lags (log01, log02, and log03). The analysis of lag-specific associations between particulate matters and stroke mortality demonstrated that the increased stroke mortality at lag03 date was most significant. In addition, the study used attributable mortality (AM) and attributable fraction (AF) as indicators to illustrate the mortality burden based on the estimated effects of particulate matters at lag03, the result of which showed that 5.57% (95% CI 4.21–6.96%) of the overall stroke mortality could be attributable to $PM_{2.5}$. The corresponding ER in total stroke mortality in the six cities was 3.07% (95% CI 2.35–3.79%) for $PM_{2.5}$, and sensitivity analyses showed that adverse effect of $PM_{2.5}$ on ischemic stroke was higher than hemorrhagic stroke.

In recent years, a greater number of studies in China further focused on the health effect of $PM_{2.5}$ on the subtype of stroke, especially ischemic stroke. For example, Guo et al.'s study (2017) in Guangdong, with a total of 95,562 attack admissions for ischemic stroke included in this study, assessed the ischemic stroke risk ratio of the same-day exposure to $PM_{2.5}$, which was estimated to be 1.0270 (95% CI 1.0177–1.0368) with an IQR increase in the concentration level of $PM_{2.5}$ in single-pollutant model. Moreover, based on hospital stroke admissions in 2014–2016 from the national database covering up to

Table 4 Cerebrovascular end points with increased risk associated with PM_{2.5} exposure

Location, etc.	Time period	Outcome	Measure of PM _{2.5} increase	Excess risk, hazard ratio (OR), or hazard ratio (HR) (95% CI)	Reference
Short-term exposure					
Gansu 25,790 cases	2014–2017	Cerebrovascular mortality	Lag4, average increase per 10 µg/m ³	1.22% (0.11–2.35%)	Wu et al. (2019)
26 cities case-crossover 348,379 cases: IS: 278,980; HS: 69,399	2013–2015	Hospital admissions for stroke	Lag3, IQR	1.0% (0.7–1.4%)	Liu et al. (2017a)
Guangzhou 9066 cases	2007–2011	a) Ischemic stroke b) Hemorrhagic stroke	Lag2, IQR	a) No association b) 6.62% (1.28–12.25%)	Lin et al. (2016b)
Beijing 48,122 cases: IS 32,799; HS 13,051	2014–2016	a) Stroke mortality b) Ischemic stroke c) Hemorrhagic stroke	Average increase per 10 µg/m ³	a) 0.27% (0.12–0.43%) b) 0.23% (0.04–0.42%) c) 0.37% (0.07–0.67%)	Zhang et al. (2018b)
6 cities 54,236 cases: IS: 31,457 HS: 22,779	2013–2016	Stroke mortality	Lag3, average increase per 10 µg/m ³	3.07% (2.35–3.79%)	Wang et al. (2018)
Guangdong 95,562 cases	2013–2015	Ischemic stroke	Same-day exposure, IQR	1.027% (1.018–1.037%)	Guo et al. (2017)
172 cities 2,032,667 cases	2014–2016	Hospital stroke admissions	Average increase per 10 µg/m ³	0.34% (0.2–0.48%)	Tian et al. (2018)
Beijing 63,956 cases	2010–2012	Ischemic stroke	Average increase per 10 µg/m ³	0.31% (95% CI 0.17–0.45%)	Tian et al. (2017)
Chengdu 84, 535 cases	2013–2015	Stroke mortality	Average increase per 10 µg/m ³	0.69% (0.01–1.38%)	Zeng et al. (2018)
Nationwide 1356 cases	2013–2015	First stroke	Average increase per 10 µg/m ³	OR = 1.049 (95% CI 1.038–1.061)	Guan et al. (2018)
Long-term exposure					
Hong Kong 66,820 aged 65+ 6733 cases	1998–2001 to 2010	First stroke	Average increase per 10 µg/m ³	HR = 1.14 (95% CI 1.02–1.27)	Qiu et al. (2017)
Nationwide 12,291 ischemic stroke patients	2007–2008	Nationwide	Average increase per 10 µg/m ³	HR = 1.05 (95% CI 1.02–1.09)	Chen et al. (2019)

0.28 billion people who received Urban Employee Basic Medical Insurance, Tian et al. (2018) examined the association between air pollution and daily ischemic stroke admission nationwide. A two-stage method was used to estimate the effects of air pollution in specific cities and combine all the estimates of 172 cities in China. The results demonstrated that an increase of 10 µg/m³ of PM_{2.5} was associated with a 0.34% (95% CI 0.20–0.48%) increase of hospital admissions for ischemic stroke. After controlling for calendar time, relative humidity, public holidays, and day of the week, further subgroup exploration showed that the effect estimates were greater in cities with lower air pollutant levels and higher air temperatures, as well as in elderly subpopulations. The same study explained that high temperature could consistently enhance the effects of air pollution, while the positive effect modification of long-term air pollutant levels was less consistent, indicating that high temperature might exert greater modifying effects on the associations than long-term air pollution levels.

More recently, the association between short-term changes in PM_{2.5} and first hospital admission for ischemic stroke in Beijing was assessed in 63,956 first hospital admissions for ischemic stroke that were identified from Beijing Medical Claim Data for Employees during 2010 to 2012 (Tian et al. 2017). The exposure–response relationship between PM_{2.5} and admissions for ischemic stroke was approximately linear, with a relatively stable response at lower concentrations (< 100 µg/m³) and a steeper response at higher concentrations. A 10-µg/m³ increase in the same-day PM_{2.5} concentration was associated with a 0.31% (95% CI 0.17–0.45%, $p < 1.57 \times 10^{-5}$) increase in the daily admissions for ischemic stroke.

Zeng et al. (2018) studied the impact of haze in Chengdu in the Sichuan basin, during which the atmosphere warms with altitude and cool air gets trapped at lower altitudes due to the local geography. Using environmental and daily morbidity of stroke data (2013–2015), the study estimated the daily mean concentration of PM_{2.5} to be 75.9 µg/m³ with 38% of the observed days exceeding the Grade II national standards,

75 $\mu\text{g}/\text{m}^3$ for 24-h mean levels and concluded that same-day exposure to $\text{PM}_{2.5}$ was associated with the onset of stroke. For females, every 10 $\mu\text{g}/\text{m}^3$ increase of $\text{PM}_{2.5}$ contributed to 0.80% percent change of onset; for the group of age less than 65, a 0.78% higher risk increase of $\text{PM}_{2.5}$ was observed.

A more specific study on differential susceptibility by Guan et al. (2018) assessed association between individual stroke risk and exposure to $\text{PM}_{2.5}$ based on data of 1356 first-ever stroke events derived from the China National Stroke Screening Survey (CNSSS) database ($n = 1,292,010$). A significant association between first-ever stroke and $\text{PM}_{2.5}$ was found; for each 10 $\mu\text{g}/\text{m}^3$ increase of $\text{PM}_{2.5}$ exposure, the odds ratio was 1.049 (95% CI 1.038, 1.061). The size of association, varied considerably according to individual-specific characteristics including demographic, lifestyle, and medical history factors, ranging OR = 0.966 (95% CI 0.920–1.013) to 1.145 (95% CI 1.080–1.215) among Chinese adults.

Dong et al. (2018) determined that $\text{PM}_{2.5}$ can also moderate associations of stroke risk for other pollutants. To investigate the acute effect of NO_2 and SO_2 on IS and IS-related death in five urban districts in Changzhou between 2015 and 2016, they estimated the percentage change (95% CI) in daily IS counts and deaths with an IQR increase in air pollutant levels for different single or multiple lag days in both single-pollutant and two-pollutant models. The study found that for daily IS counts, the estimated effects of NO_2 and SO_2 were more significant when adjusted for $\text{PM}_{2.5}$ and PM_{10} . Young individuals (< 65 years old) had a higher IS mortality risk for $\text{PM}_{2.5}$, PM_{10} , NO_2 , and CO.

The aforementioned studies suggested that in China, short-term $\text{PM}_{2.5}$ exposure is associated with increased stroke mortality and morbidity. In addition, several recent cohort studies in China have indicated the long-term effect of $\text{PM}_{2.5}$ on stroke. A cohort study in Hong Kong (Qiu et al. 2017) collected data from 66,820 old people (65+) whose first occurrence of emergency hospital admission for stroke was during 1998–2001 (baseline) and followed up to 2010. A total of 6733 cases of incident stroke, of which 3526 (52.4%) were ischemic and 1175 (17.5%) were hemorrhagic, were identified. The results showed the HR for every 10 $\mu\text{g}/\text{m}^3$ higher $\text{PM}_{2.5}$ concentration was 1.14 (95% CI 1.02–1.27) for all incident stroke. However, long-term $\text{PM}_{2.5}$ exposure had different associations according to stroke subtype, with a statistically significant HR (1.21, 95% CI 1.04–1.41) for ischemic stroke and no significant association for hemorrhagic stroke (HR 0.90, 95% CI 0.70–1.17). The effect tended to be greater at older ages for those aged > 70 and was higher for less educated people and current smokers.

Similarly assessing the prolonged effects of air pollution, while different from most studies whose outcome is stroke mortality or hospital admission, a few studies examined the adverse effects of air pollution on survival after stroke. Chen et al. (2019) followed 12,291 ischemic stroke patients for

1 year, and during the process, 1649 deaths were identified. After controlling for potential confounders, significant associations were observed between exposure to $\text{PM}_{2.5}$ and incident fatal ischemic stroke, with the corresponding HR of 1.05 (95% CI 1.02–1.09). The authors concluded that pre-stroke exposure to $\text{PM}_{2.5}$ in China was associated with increased incident fatal ischemic stroke in the year following an ischemic stroke.

Discussion

As the concerns over the adverse effects of air pollution on human health increases, more and more relevant studies have been reported worldwide, suggesting that air pollution, especially $\text{PM}_{2.5}$ is one of the largest environmental causes of cardiovascular disease and death (Lozano et al. 2012). China, the biggest developing country, was observed to have much higher particular matter levels, which might lead to a more conspicuous relationship between exposure and adverse cardiovascular events. The review of recent studies in China, from 2013 onwards, demonstrated that exposure to $\text{PM}_{2.5}$ is indeed associated with adverse cardiovascular health effects, including cardiovascular mortality, stroke, and IHD in China.

Although the evidence for the association between air pollution and CVD is strong and growing in volume, there are currently only a few studies focusing on the role of specific chemical constituents in particulate matter. Exploring the relationship between the elemental composition of $\text{PM}_{2.5}$ and cardiovascular disease in emergency department patients, Huang et al. (2017) assessed the correlation between emergency admissions for cerebral hemorrhage, cerebral infarction, TIA (transient ischemic attack), coronary heart disease, and $\text{PM}_{2.5}$ concentrations of chemical element compositions and PM_{10} in Changsha, Hunan. The study suggested that concentration rises of nickel, zinc, and lead elements for $\text{PM}_{2.5}$ in Changsha city were related to the increase of ED for cerebral hemorrhage. With each additional IQR increase of Ni, Zn, and Pb concentrations in $\text{PM}_{2.5}$, the values of OR of cerebral hemorrhage were 1.826 (95% CI 1.031–3.233), 1.568 (95% CI 1.015–2.423), and 1.682 (95% CI 1.010–2.800), respectively. Therefore, future research should focus on identification and quantification of chemical compounds present in ambient air particles for a better understanding of the mechanism by which particulate matter causes health effects. To what degree is it that the concentrations of fine particulate matter themselves or their components contribute to these effects, or do $\text{PM}_{2.5}$ act as surrogate markers for other components of air pollution, such as gaseous pollution?

To date, there have been a limited number of studies in China estimating long-term health effects of $\text{PM}_{2.5}$. Previously, several studies in other countries have found that

the mortality of long-term exposure of $PM_{2.5}$ was ten times higher than that of short-term exposure (Dockery et al. 1993; Pope et al. 2004). It is likely that more data from cohort studies in China will emerge in the coming years, which will likely highlight the impact of high pollution levels in certain regions of China.

Methodological advances are also welcomed as these may help to elucidate the interactions between pollution and specific conditions. Although daily mean concentration is widely used as exposure indicators to estimate $PM_{2.5}$, a study (Guo et al. 2018) showed that daily mean concentrations might insufficiently represent the true exposure level because of the diurnal variations of air pollutants and various human activity patterns, while daytime or rush-hour concentrations may lead to better estimations of acute effect of $PM_{2.5}$. Lin et al. (2018) used DECH to address concerns that the commonly used measurement indicator; daily mean concentration could underestimate the mortality risk. Therefore, the application of advanced methodological approaches to future studies may help to pin down the most significant aspects of air pollution contributing to disease risk, especially for acute events such as heart attack and stroke.

Exposure measurement is notoriously difficult for air pollution studies, with compromises between geographically wide estimates of exposure and sample size needed to be made in many studies. The difference and relationship between measured $PM_{2.5}$ and actual $PM_{2.5}$ need further clarification. The data used by most Chinese studies was obtained from local environmental monitoring stations or the U.S. embassy station, which, on the one hand, may not be totally verified or validated, and, on the other hand, may only represent the general levels of outdoor air pollution rather than the actual $PM_{2.5}$ levels. In addition, the impact of other factors such as socio-economic traits and meteorological conditions may vary from region to region. Consequently, a suggestion for the improvement of environmental policy is to establish systematic $PM_{2.5}$ monitor network across the country and to consider regional and population variations more carefully. In particular, studies related to $PM_{2.5}$ exposure on cardiovascular health are largely centered in highly urbanized megacities, particularly in Beijing, Shanghai, Guangzhou, or regions with high $PM_{2.5}$ pollution, like Taiyuan. In contrast with urban cities, the number and scope of studies in rural areas or remote areas with relative small population, like Gansu (Wu et al. 2019) and Yanbian Korean Autonomous Prefecture (Zhang et al. 2018a), are still much fewer.

Indoor pollution from domestic heating and cooking, as well as smoking, might also have significant effects on people's cardiovascular health, so the measurement of indoor $PM_{2.5}$ would help to reduce risk of confounding. Likewise, the PM air quality standards and control measures are based on the report of outdoor air pollution from monitor stations, which might ignore the possible health threat of indoor

pollution. So it is recommended that the government should consider the function of indoor $PM_{2.5}$ when making environmental standards and relative protective approaches to minimize these adverse effects; meanwhile, the public should improve awareness of self-protection even when they are indoors.

China has been developing rapidly in recent years. Urbanization, accompanied with increased industrialization, emissions from waste, biomass burning, as well as vehicle exhaust, has led to considerable increase of $PM_{2.5}$ in China during the past several years. By investigating the nexus between urbanization and the air pollution-related health, Liu et al. (2017b) found a 1% increase in urbanization was associated with a 0.32%, 0.14%, and 0.50% increase in $PM_{2.5}$ -related mortality of lung cancer, stroke, and ischemic heart disease, indicating that the launch of China's new national urbanization plan may result in worse $PM_{2.5}$ -related health effects. Under these circumstances, some studies accessing the public health benefits of reducing $PM_{2.5}$ in China emphasized the significant of air quality improvement. For instance, Chen et al. (2017) created an annual air quality surface with a land use regression (LUR) model to evaluate avoided cases of mortality and morbidity in Tianjin, assuming the achievement of China's current air quality daily and annual standards (no. GB3095-2012). It was estimated in the study (Chen et al. 2017) that if the daily average $PM_{2.5}$ was reduced to the daily Class II standard ($75 \mu\text{g}/\text{m}^3$), the avoided deaths for cardiovascular disease would be 2000 (95% CI 920–3100) per year and the monetary values were 180–4800 million yuan per year in 2015 in Tianjin; if the annual average $PM_{2.5}$ was reduced to the annual Class II standard ($35 \mu\text{g}/\text{m}^3$), the avoided deaths for cardiovascular disease were 1400 (95% CI 640–2100) and the monetary values were 130 to 3400 million yuan.

To eliminate the concerns over the health effects of $PM_{2.5}$ in general public and obtain the benefit of addressing $PM_{2.5}$ issues, Chinese government must take a series of effective actions. Some improvement of policy-making has been achieved by government and found really helpful in reducing the detrimental impact of air pollution and remedying people's health state. A time series study (Su et al. 2016) in Beijing observed adverse effects of $PM_{2.5}$ on cardiovascular ERV before Beijing Olympics using polynomial distributed lag (PDL) models and found that an IQR increase in $PM_{2.5}$ was associated with an overall RR of 1.022 (95% CI 0.990–1.057). However, modification occurred on account of some main air pollution control policies taken during the period of Olympics; as the study showed, cardiovascular ERV in association with air pollution increases in the non-Olympics period while no effects were observed during the Olympics period and the difference for $PM_{2.5}$ was statistically significant. In addition, "The Airborne Pollution Prevention and Control Action Plan (2013–2017)," the goal of which is to reduce 25% of PM emissions from 2012 levels by the year 2017,

was established by the government to improve air quality through installing emissions-cutting exhaust filters, reducing coal use, tightening vehicle emission standards, etc. (Sheehan et al. 2014). Although air quality daily and annual standards in China (no. GB3095-2012) have played an essential role in the last 7 years since 2012, stricter standards need establishing to improve air quality, such as primary-level standard. The government could decide more appropriate standards by referring to WHO guidelines and the standards used by other countries. For example, in 2013, the EPA (Environmental Protection Agency) in the USA published a new regulation for PM in which the annual primary standards for PM_{2.5} were reduced to 12 µg/m³ from the previous criterion of 15 µg/m³. And several recent studies (Yin et al. 2017; Ye et al. 2019) exploring the shape of exposure–response relation of PM_{2.5} against cause-specific mortality and morbidity and the saturation point of PM_{2.5} might also provide evidence for standards setting and environmental policy-making. Meanwhile, as has mentioned before, China is a vast county with uneven levels of PM_{2.5}; therefore, the standards should be adjusted to better adapt to regional conditions.

Moreover, support from industry and public combined with policy-making is necessary in addressing the challenge from PM_{2.5} air pollution. The industries should enhance social responsibilities to comply with relative guidelines and control the emission of pollution by means of developing new technologies, such as gasoline particular filters. Meanwhile, the public could develop personal awareness to take timely protective measures when necessary and help improve air quality, corresponding to policy requirements. For example, wearing masks and using air purifiers especially in high-polluted areas and when warning saturation point is reported reduce the usage of power-wasting vehicles and burning of biomass for cooking and heating indoors and adopt more environmentally friendly travel and living habits. By working together, government, industry, and the general population can cooperate to reduce hazardous pollution.

Conclusion

Here, we have summarized findings from an ever increasing number of studies that highlight the adverse impact of PM_{2.5} on cardiovascular health in China. Focusing on one aspect of air pollution, PM_{2.5}, which may on the one hand be directly involved as a causative risk factor in at least some end points and on the other hand may be a surrogate for other pollutants contributing to the mechanism of disease, the results of the various studies to date provide strong evidence for the role of ambient air pollution in cardiovascular disease risk. While further studies, in particular on long-term effects of PM_{2.5} exposure, will add to the knowledge base, the existing evidence from China and elsewhere supports the need for a

reduction in such pollution in order to reduce the incidence of cardiovascular disease. This is particularly important in China, where recent rapid economic advances have led to high levels of air pollution in many parts of the country.

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