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Impact of outdoor air pollution on cardiovascular health in Mainland China

Haidong Kan [a,*], Wei Huang [b], Bingheng Chen [a], Ni Zhao [c]

[a] *Department of Environmental Health, School of Public Health, Fudan University, Box 249, 130 Dong-An Road, Shanghai 200032, China*
[b] *Center for Environment and Health, Peking University, Beijing 100871, China*
[c] *Department of Environmental Sciences and Engineering, School of Public Health, University of North Carolina at Chapel Hill, North Carolina, NC 27514, USA*

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Summary Although China has achieved great progress in ambient pollution reduction in the past two decades, it is still one of the few countries with the worst air pollution levels in the world. In addition to lifestyle choices such as smoking, diet and exercise, exposure to outdoor air pollution is being considered a major determinant of cardiovascular disease in the Chinese population. Numerous epidemiological studies on air pollution and cardiovascular mortality have been conducted in China, using time-series, case-crossover, or cross-sectional designs. The increased cardiovascular mortality risks observed in the Chinese population are similar in magnitude, per amount of pollution, to the risks found in other parts of the world. However, the importance of these increased cardiovascular risks is greater than in North America or Europe, because the air pollution in China is at much higher levels in general and the Chinese population accounts for more than one fourth of the world's total. There has been no air pollution cohort study in China examining the long-term effects of air pollution, nor any published Chinese data assessing the relation between air pollution and cardiovascular morbidity and sub-clinical indicators. Future research in China should focus on a prospective analysis of association between air pollution and cardiovascular disease and the likely underlying pathophysiologic links.

Introduction

As the largest developing country in the world, China has achieved rapid development in the past two

* Corresponding author. Tel./fax: +86 21 64046351.
E-mail address: haidongkan@gmail.com (H. Kan).

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decades. With the advance of economic development, as can be expected, energy consumption increases, so does the degree of urbanization, with more and more people migrating into cities. Alongside energy consumption and urbanization, energy efficiency has improved drastically in China — almost three times better utilization of energy resources in 2000—2002 compared to 1978 [1]. The ambient air quality has improved greatly in a number of Chinese cities through several policy control measures, including relocation of polluting industries, switching to less polluting fuels, enforcement of zoning regulations, stricter emission standards for mobile and stationary sources, better city planning, and increased investment in city infrastructure construction, etc [1]. Although great progress in the control of air pollution has been achieved, China is still one of the few countries with the worst air quality in the world [2].

Coal is still the major source of energy in China, constituting about 75% of all energy sources. Consequently, air pollution in China predominantly consists of coal smoke, with suspended particulate matter (PM) and sulfur dioxide (SO_2) as the principal air pollutants [1]. Moreover, with the rapid increase in the number of motor vehicles in recent years, air pollution in large cities has gradually changed from the conventional coal combustion type to the mixed coal combustion/motor vehicle emission type [1].

In the meantime, with the rapid economic development and consequent improvement in living conditions, nutrition, and health care in China, infant mortality and deaths from infectious diseases have declined. In contrast, non-communicable diseases (NCDs), such as cardiovascular disease and cancer, have placed much more disease burden on the population than ever [3]. It has been estimated that cardiovascular disease is now the leading cause of death in the Chinese population of adults 40 years of age and older, accounting for around 40% of total mortality [3].

Over the last decade, a growing body of human and animal evidence has led to a concern about the potential deleterious effects of ambient air pollution on the cardiovascular system [4,5]. This article is intended to be a systemic review on epidemiologic evidence between outdoor air pollution and cardiovascular disease in China. This review focuses primarily on literature published since 1990, though some earlier studies are referenced to provide context. First, we characterize the level and trend of outdoor air pollution in China; second, we extensively review the effects of short-term and long-term exposure to air pollution on cardiovascular disease; and lastly, we discuss the issues facing research on the effects of air pollution on cardiovascular health in China.

Level and trend of outdoor air pollution in China

Ambient pollution is one of China's most serious environmental problems, and air pollution has been severe for a few decades. Chinese public health and environmental science professionals began studying air pollution-related problems in the early 1950s [1]. Studies conducted in Shenyang, a city in northeastern China, in the fifties showed total suspended particle (TSP) levels sometimes reaching several hundreds to almost 1000 lg/m^3, which was at a level comparable with that during the London fog in 1952 [1,6]. Limited by technical know-how and availability of sophisticated monitoring equipment at that time, these measurements were irregular, non-continuous, and lacked restricted laboratory quality assurance and control.

After China joined the Global Environmental Monitoring System (GEMS) program in the late eighties of the last century, regular systematic monitoring of air pollutants became a routine practice. From a GEMS report published by the United National Environment Programme (UNEP) and World Health Organization (WHO), the ambient SO_2 level in Beijing in the 1980s was around 100—130 lg/m^3, and the TSP level was around 250—450 lg/m^3 [1].

Since the late 1990s, annual average levels of TSP and SO_2 in large cities have been declining slowly despite rapid economic growth in China. For example, from 1990 to 2000, the annual GDP in Shanghai increased from CNY 75,600 million to CNY 455,100 million, while TSP levels decreased from 360 to 156 lg/m^3, a 67% reduction; and SO_2 levels decreased from 95 to 45 lg/m^3, a 53% reduction [1]. Although its ambient air quality has improved substantially, China is still facing the worst air pollution problem in the world. Megacities such as Beijing, Shanghai, and Guangzhou are frequently among the cities in the world with the highest levels of air pollutants [7]. Results from routine monitoring of 360 cities in 2004 revealed that the air quality of nearly 70% of urban areas did not meet the country's national ambient air quality standards (NAAQS), which means that nearly 75% of urban residents were regularly exposed to air considered unsuitable for inhabited areas [8].

Currently, inhalable particles (particles less than 10 lm in aerodynamic diameter, or PM_{10}), SO_2 and nitrogen dioxides (NO_2) are the criteria for pollutants in China. According to China State Environmental Protection Agency, the annual average PM_{10} concentrations for major Chinese cities in 2004 were 102 lg/m^3 in southern cities, 140 lg/m^3 in northern cities, and 121 lg/m^3 in cities nationwide. The annual average concentrations of SO_2 and NO_2 nationwide were 66 lg/m^3 and 38 lg/m^3, respectively [8]. Compared with the Global Air Quality Guidelines set by World Health Organization (PM_{10} annual average: 20 lg/m^3), the PM_{10} levels in Chinese cities are much higher (Fig. 1).

In recent years, the ''gray sky" phenomenon caused by fine particles (particles less than 2.5 lm in aerodynamic diameter, or $PM_{2.5}$) has resulted in increasing public concern, and fine particles existing predominately in urban areas have posed a serious health risk to Chinese residents. In Beijing, the annual average $PM_{2.5}$ concentrations ranged from 96.5 to 106.7 lg/m^3 [9], which was approximately seven times the ambient air quality standard recommended by the US Environmental Protection Agency (15 lg/m^3) and 10 times the WHO Global Air Quality Guideline (10 lg/m^3).

Generally, suspended particulate concentration levels in cities in the north are higher than those in the south of China, while SO_2 concentration levels do not differ much [10]. Air pollution is generally more serious in winter than in summer [10].

Outdoor air pollution has become a major concern for public health in China [11]. A number of researchers have conducted health impact assessments (HIA) of air pollution in China on national [12,13] or subnational geographical scales [14—19]. For instance, Zhang and colleagues calculated the health effects of PM_{10} in 111 Chinese cities, which covered most large and medium-sized cities in China and accounted for more than 70% gross domestic product (GDP) of China in 2004, and estimated that the total economic cost caused by PM_{10} pollution was approximately US$ 29,178.7 million in 2004 [13].

Cardiovascular outcomes from air pollution exposure in China

There is increasing evidence that exposure to higher levels of air pollution is associated with adverse cardiovascular consequences [4,5]. A recent scientific statement from the American Heart Association indicated that short-term or long-term exposure to air pollution is associated with increased risk of cardiovascular disease and death [4]. The cardiovascular outcomes related to air pollution include myocardial ischemia and infarction, ventricular arrhythmia, heart failure exacerbation, and stroke [4]. Air pollutants may adversely affect the cardiovascular system directly and indirectly. Direct effects may occur via agents that readily cross the pulmonary epithelium into the circulation, such as gaseous pollutants (e.g., nitrogen oxides) and possibly ultra-fine particles (UFPs), along with soluble constituents of particles (e.g., transition metals); indirect effects may occur via induction of pulmonary oxidative stress and inflammation, leading to endothelial dysfunction and systemic inflammation [20,21]. All these direct and indirect effects may in turn activate hemostatic pathways and impair vascular function.

Mortality is often considered the most important outcome associated with air pollution exposure. In China, numerous epidemiologic studies have measured increases in cardiovascular mortality associated with air pollution. Among them, time-series

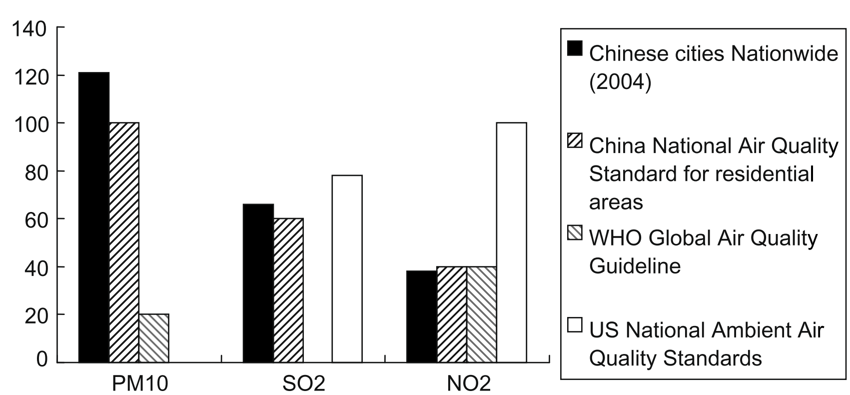

Fig 1 Comparison of the $PM_{10}/SO_2/NO_2$ levels in Chinese cities and International/National Air Quality Standards. US Environmental Protection Agency revoked the annual PM_{10} standard in 2006; World Health Organization did not include an annual average standard for SO_2 in the Global Air Quality Guideline.

or case-crossover studies captured the acute effects of air pollution by examining the association between daily death numbers and daily or multi-day changes in air pollution, while the cross-sectional studies revealed that long-term exposure to air pollution might lead to an increased risk of death in the population. However, compared to relatively complete data on air monitoring, data on the association between air pollution and cardiovascular disease are very limited in China. In terms of suspended particulates, scarcity of data on PM_{10} or fine particles ($PM_{2.5}$) in most cities further hinders the value of such studies. Though no published data in China have assessed cardiovascular morbidity or sub-clinical parameters in relation to air pollution, a few panel studies are underway examining the association between air pollution and sub-clinical parameters.

Short-term exposure and cardiovascular mortality

To assess the association between short-term exposure to air pollution and cardiovascular mortality, several time-series and case-crossover studies were conducted in large Chinese cities, including Beijing, Shenyang, Chongqing, Shanghai, Wuhan, and Taiyuan.

The relationship between air pollution and daily cardiovascular mortality was examined in two large residential areas of Beijing, with a population of 1,419,123 in 1989 [22,23]. Very high concentrations of SO_2 (mean = 102 lg/m^3, maximum = 630 lg/m^3) and TSP (mean = 375 lg/m^3, maximum = 1003 lg/m^3) were observed in these areas. A highly significant association was found between SO_2 and daily cardiovascular mortality. The risk of cardiovascular mortality was estimated to increase by 11% (95% CI: 5—16%) with each doubling in SO_2 concentration. The association of TSP with cardiovascular mortality was positive but not significant. In the season-specific analysis, both SO_2 and TSP were found to be significant predictors of cardiovascular mortality in summer; in winter, SO_2 was again significantly associated with increased mortality, but no positive association was found between TSP and mortality.

Shenyang, a heavily industrialized city, is the capital of Liaoning Province, which is located in north-eastern China. Xu et al. analyzed daily mortality data in Shenyang in 1992 to identify possible associations with ambient SO_2 and TSP [24]. During the study period, both TSP concentrations (mean = 430 lg/m^3, maximum = 1141 lg/m^3) and SO_2 concentrations (mean 197 = lg/m^3, maximum = 659 lg/m^3) far exceeded the WHO's recommended criteria. Locally weighted regression analysis showed a significant association of daily mortality with TSP: the risk of cardiovascular mortality increased by an estimated 2.1% (95% CI 0.4—3.8%) with a 100 lg/m^3 concentration increase in TSP. SO_2 was not significantly related with cardiovascular death in Shenyang.

In 1995, daily mortality in a district of Chongqing was analyzed from January through December using daily ambient $PM_{2.5}$ and SO_2 data [25]. The mean concentrations of $PM_{2.5}$ and SO_2 were 147 lg/m^3 ($n = 365$, maximum = 666 lg/m^3) and 213 lg/m^3 ($n = 213$, maximum = 571 lg/m^3), respectively. The relative risk of cardiovascular mortality on the third day after a 100 lg/m^3 increase in mean daily SO_2 was 1.20 (95% CI 1.11—1.30). The estimated effects of mean daily SO_2 on cardiovascular risk remained after controlling for $PM_{2.5}$; however, the association for $PM_{2.5}$ was negative and statistically insignificant on all days. Compared with SO_2, $PM_{2.5}$ had less daily measurement, and thereby less statistical power to detect its association with mortality. This is one of the only two population-based studies examining the health effects of $PM_{2.5}$ in China [25,26].

Kan and Chen assessed the relationship between outdoor air pollution and daily mortality from June 2000 to December 2001 in Shanghai [27]. In the single-pollutant models, an increase of 10 lg/m^3 of PM_{10}, SO_2 and NO_2 corresponded to 0.3% (95% CI 0.1—0.6%), 1.3% (95% CI 0.4—2.2%), and 1.8% (95% CI 0.7—2.8%) increased cardiovascular mortality risk, respectively. In the multiple-pollutant models, the associations between SO_2 and cardiovascular mortality were not affected by the inclusion of other pollutants; for PM_{10} and NO_2, however, the inclusion of other pollutants possibly weakened the associations between these two pollutants and cardiovascular mortality, suggesting that SO_2 may be more important than particulate matter as a health risk in Shanghai. The authors also conducted a case-crossover analysis based on the same data [28], and found similar results with this time-series analysis.

Few studies in China have assessed the health effects of ozone (O_3). Given the changes in air pollution types from conventional coal combustion to the mixed coal combustion/motor vehicle emissions in China's large cities, it is worthwhile to investigate the association between O_3 and mortality outcomes in the country. Zhang et al. conducted a time-series study to investigate the relation between O_3 and daily mortality in warm and cold seasons in Shanghai using 4 years of daily data (2001—2004) [29]. O_3 was significantly associated with cardiovascular mortality in the cold season in Shanghai but not in the warm season. In the whole-year analysis, an increase of 10 lg/m^3 of 2-day average O_3 corresponded to 0.53% (95% CI, 0.10—0.96%) increase in cardiovascular mortality. In the cold season, the estimates increased to 1.53% (95% CI, 0.54—2.52%). In the warm season, they did not observe significant associations for cardiovascular mortality. Multipollutant models indicated that the association between O_3 and cardiovascular mortality was not confounded by PM_{10} or by SO_2; however, after adding NO_2 into the model, the association of O_3 with cardiovascular mortality became statistically insignificant.

In China, $PM_{2.5}$ and $PM_{10-2.5}$ are not yet the criteria air pollutants, and their monitoring data are scarce. Few epidemiological studies in China have assessed the health effects of $PM_{2.5}$ and $PM_{10-2.5}$ simultaneously. Kan et al. conducted a time-series study to examine the association of short-term exposure to $PM_{2.5}$ and $PM_{10-2.5}$ with daily mortality in Shanghai, China from March 4, 2004 to December 31, 2005 [26]. The average concentrations of $PM_{2.5}$ and $PM_{10-2.5}$ were 56.4 lg/m^3 and 52.3 lg/m^3 in the study period, and $PM_{2.5}$ constituted around 53.0% of the PM_{10} mass. They found that $PM_{2.5}$ was associated with the death rate from cardiovascular disease in Shanghai. A 10 lg/m^3 increase in the 2-day moving average concentration of $PM_{2.5}$ corresponded to 0.41% (95% CI 0.01%, 0.82%) increase in cardiovascular mortality. They did not find a significant association of $PM_{10-2.5}$ with cardiovascular mortality.

Qian et al. examined the associations of daily cause-specific mortality with daily mean concentrations of PM_{10} in Wuhan, China using 4 years' data (2001—2004) [30]. There are approximately 4.5 million residents in Wuhan who live in the city core area of 201 km^2. The authors used the generalized additive model to analyze pollution, mortality, and covariate data, and found consistent associations of PM_{10} with mortality with the strongest on lag 0 day. Every 10 lg/m^3 increase in PM_{10} daily concentration at lag 0 day was significantly associated with an increase in cardiovascular (0.51%; 95% CI 0.28—0.75%) and stroke (0.44%; 95% CI 0.16—0.72%) mortality. In general, these associations were stronger among the elderly than among the young. The authors suggested a linear no threshold exposure-response relationship between PM_{10} and cardiovascular mortality in Wuhan [30].

In another published report, Qian and colleagues examined the associations of short-term exposure to gaseous pollutants with mortality in Wuhan [31]. They found consistent associations between NO_2 and mortality with the strongest on the same day. Every 10 lg/m^3 increase in NO_2 daily concentration on the same day was associated with an increase in cardiovascular (1.65%; 95% CI: 0.87—2.45%), stroke (1.49%; 95% CI: 0.56—2.43%), cardiac (1.77%; 95% CI: 0.44—3.12%), and cardiopulmonary mortality (1.60%; 95% CI: 0.85—2.35%). Examination of exposure-response curves suggested no-threshold linear relationships between daily mortality and NO_2, where the NO_2 concentrations ranged from 19.2 to 127.4 lg/m^3. SO_2 and O_3 were not associated with daily cardiovascular mortality in Wuhan.

Stroke is now one of the leading causes of death in China [3]. In Zhabei District of Shanghai, Kan et al. conducted a time-series study of acute stroke mortality and air pollution [32]. A total of 2426 stroke deaths were included in the analysis, accounting for 24.7% of the total non-accidental deaths in the study region. Approximately 3.3 people died from stroke each day during the study period. The authors found after significant association of stroke mortality with PM_{10} and NO_2, but not with SO_2. Each increase of 10 lg/m^3 in PM_{10}, SO_2 and NO_2 corresponded to 0.8% (95% CI 0—1.6%), 1.7 (95% CI −0.2%, 3.6%) and 2.9% (95% CI 0.1%, 5.7%) increase in stroke mortality.

Diabetes is known to be a chronic disease characterized by adverse consequences to the cardiovascular system. Therefore, diabetics have been suspected to be at higher risk of air pollution-related health events. Recently the relation has been investigated and confirmed as positive in Canada [33,34] and USA [35,36]. In China, diabetes has become one of the major causes of death, and mortality from diabetes has increased sharply during the past two decades [3]. In Shanghai, Kan and coworkers conducted a time-series study to assess the association between air pollution and daily mortality from diabetes [37]. Death records were collected for all individuals who lived in the Zhabei district of Shanghai and died from diabetes from January 1, 2001, to December 31, 2002. Each increase of 10 lg/m^3 in PM_{10}, SO_2, or NO_2 was found to correspond, respectively, to a 0.6% (95% CI: 0, 1.2%), 1.1% (95% CI: −1.0%, 3.2%), or 1.3% (95% CI: 0—2.6%) increase in mortality from diabetes. The air pollutants were also observed to have a greater effect on diabetics than on nondiabetics.

Identification of the specific pollutants contributing most to the health hazard of the air pollution mixture may have important implications for environmental and social policies. In China, however, many researchers have reported controversial findings. For example, in Beijing and Chongqing, it was SO_2, but not TSP nor $PM_{2.5}$, that was significantly associated with daily cardiovascular mortality [22,23,25]; in Shenyang, however, TSP, but not

SO_2, was a significant predictor of cardiovascular death. This controversy may reflect the different characteristics of the study sites as well as differences in analytic techniques used in various studies. It is also worth noting that the observed health effects attributed to the ambient gaseous pollutants, e.g. SO_2 and NO_2, might result from exposure to particles [38,39].

Furthermore, in contrast to studies conducted in North America, some Chinese studies reported associations for gaseous pollutants independent of particles [22,23,25,27–29,31], suggesting that factors other than particle indicators are important in the air pollution mixture in China. At present, we cannot conclude that SO_2 and NO_2 are proxies of particles or the components of particles, and SO_2 and NO_2 may have a direct short-term effect on mortality in China. However, a consistent, significant effect of SO_2 and NO_2 on mortality observed in the Chinese literature suggests that the role of outdoor exposure to gaseous pollutants may differ from that in other parts of the world and is thus worthy of further investigation.

Long-term exposure and cardiovascular mortality

Although daily time-series and case-crossover studies continue to suggest short-term acute effects of air pollution, they provide little information about the degree of life shortening, pollution effects on long-term mortality or morbidity, and the role of pollution in inducing or accelerating the progress of chronic diseases [40]. Several prospective cohort studies in North America and Europe have evaluated the effects of long-term exposure to outdoor air pollution on cardiopulmonary mortality [41–48]. However, it is unknown whether the findings from low air pollution exposure settings in developed countries apply to China, where the characteristics of outdoor air pollution and the sociodemographic status of local residents are different from those in developed countries.

Compared with short-term association studies, there are even fewer studies in China examining the association between long-term exposure to air pollution and cardiovascular mortality. So far, there has been no cohort mortality study in China; however, some limited cross-sectional mortality evidence exists from which we can draw some preliminary conclusions about potential long-term mortality effects.

In Beijing, Zhang and colleagues used ecological analysis to assess the relationship between long-term exposure to ambient air pollution and mortality [49]. All the data on environmental measures and related factors, population size and number of deaths were collected from the eight districts in Beijing from 1980 to 1992. In this study SO_4^{2-} was selected as a main indicator of air pollution because SO_4^{2-} levels were significantly correlated with daily mean concentrations of SO_2 and NO_2, annual coal combustion, number of households using gas fuel, counts of motor vehicles and population density in Beijing. Statistically significant correlations were observed between SO_4^{2-} concentration and cardiovascular mortality; the mean correlation coefficients were 0.79 for males and 0.84 for females. Moreover, correlations were found not only between the current SO_4^{2-} concentration and cardiovascular mortality, but also for SO_4^{2-} levels measured up to 12 years prior to death, which may suggest long-term effects of air pollution.

Wang et al. examined the chronic effects of air pollution on cardiovascular mortality in Shenyang using an ecological cross-sectional analysis [50]. In the study area, the annual daily averages for TSP in the high-, medium-, and relatively low-pollution areas were 518, 477, and 361 lg/m^3, respectively; and for SO_2 were 235, 128, and 64 lg/m^3, respectively. The results showed that there were significant differences in mortality from cerebrovascular and cardiovascular diseases among these areas.

As a major iron and steel industry base, and surrounded by mountains, Benxi is one of the most polluted cities in China. Jin and colleagues studied the association of air pollution and mortality in Benxi using an ecological cross-sectional design [51]. The total population studied was 667,553. Annual daily average concentrations of TSP and SO_2 varied from 290–620 lg/m^3 to 160–240 lg/m^3, respectively. The results showed that each increase of 100 lg/m^3 of TSP was associated with a 24% (95% CI 8–41%) increase in cardiovascular mortality. No significant association was found for SO_2.

The estimates from the cross-sectional analysis mentioned above are difficult to interpret, due to the lack of information on potential confounders such as smoking, diet, or socioeconomic status. In any case, these cross-sectional studies provide some descriptive indication of an air pollution effect that could be greater than the effect found in the time-series literature.

Summary and recommendations

Increasing evidence suggests that ambient air pollutants may have a short-term and long-term effect on cardiovascular outcomes in China [1]. The increased cardiovascular mortality risks observed in the Chinese population are similar in magnitude, per amount of pollution, to the risks found in other parts of the world [52,53]. However, the importance of these increased cardiovascular risks is greater than in North America or Europe, because the air pollution in China is at much higher levels in general. Moreover, the overall burden of cardiovascular disease attributable to air pollution in China would be larger than in any other country in the world, due to its overall population which accounts for more than one fourth of the world's total.

Most Chinese studies discussed above were ecological in nature, thus limiting the power for causal inference. In addition, no published data assessed the relation between air pollution and cardiovascular morbidity and sub-clinical indicators. Future research will need to clarify the life-time course of these effects with full control of potential confounders (e.g. prospective cohort studies), to examine the relevance of cumulative exposure, as well as to identify the most susceptible time periods and populations, genetic-environment interaction, and pathophysiologic links between air pollution and cardiovascular disease for the Chinese population. Last but not least, pollution needs to be reduced, and air quality and health need to be monitored for trends and consequences.

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