From
The Institute of Medical Information Processing, Biometry and Epidemiology, Ludwig-Maximilians-University of Munich, Germany
Chair of Epidemiology: Prof. Dr. Dr. H.-E. Wichmann
and
The Institute of Epidemiology II, Helmholtz Zentrum Muenchen – German Research Center for Environmental Health (GmbH)
Director Adjunct: Prof. Dr. A. Peters

Health effects of air pollution and meteorology: Association with cardiovascular disease in Beijing.

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By
Liqun Liu
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of the Ludwig-Maximilians-University of Munich

Supervisor/Examiner:	Prof. Dr. Annette Peters
Co-Examiners:	apl. Prof. Dr. Dirk Beuckelmann
Co-Supervisor:	Dr. Susanne Breitner
Dekan:	Prof. Dr. med. Dr. h.c. M. Reiser, FACR, FRCR
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1 Summary

Cardiovascular disease (CVD) is now the leading cause of death globally. Non-modifiable risk factors of CVD mainly include advancing age, gender, ethnicity, and heredity. Major modifiable risk factors of CVD include hypertension, abnormal blood lipids, diabetes, obesity, and lifestyle-dependent factors such as physical inactivity, low fruit and vegetable diet, tobacco use and alcohol use. Other modifiable risk factors of CVD include low socioeconomic status (SES), mental illness, and use of certain medication. Environmental factors such as air temperature and air pollutions have also been linked with CVD.

Short-term exposure to heat has been related to cardiovascular mortality showing effects on the same day up to a three days delay. Cold usually showed four to 20 days delayed effects on cardiovascular mortality and morbidity. The exposure-response functions between mortality time-series and temperature measures have been shown to be U-, V- or J-shaped, and the range of temperature corresponding with a minimum mortality was reported to be related with latitude. There is less evidence about the adverse effects of elevated temperature on morbidity, supporting the hypothesis that many heat-related deaths occur in people before they come to medical attention.

Until today, most studies regarding temperature effects on health have been conducted in Europe and the United States; there is a lack of studies for Asian countries. I conducted a study in the urban area of Beijing, China, from January 2003 to August 2005. I obtained daily CVD death counts, daily meteorological data as well as daily concentrations of ambient particulate air pollution. I estimated the effects of two-day and 15-day average temperatures on mortality by using Poisson regression models. I found that both increases and decreases in air temperature were associated with an increased risk of cardiovascular mortality in Beijing. The effects on adult (≥15 years) and elderly (≥65 years) residents were similar. The effects of heat were immediate, while the ones of cold became predominant with longer time lags. The associations were not confounded or modified by the order of the three warm periods included in the study, by heating in winter, or by ambient particulate air pollution.

There is increasing evidence for an association between ambient particulate matter (PM) and CVD during the last decades. PM is an exposure affecting the whole population; although the relative risk could be small, it still has a large public health impact. The exposure-response functions between short-term exposure to PM and cardiovascular mortality and morbidity are considered to be near-linear and without

threshold. Specific chemical compositions of PM are speculated to be responsible for the observed associations. Besides chemical composition, particle characteristics like size are discussed as important measures. Due to the limited availability of appropriate measurement data, there are only few epidemiological studies on short-term associations between daily cardiovascular mortality and morbidity and accurately size-segregated particles.

I conducted two analyses aiming at investigating how daily changes in ambient concentrations of size-segregated particles in Beijing, China, were associated with cardiovascular mortality and emergency room visit (ERV), respectively. I obtained daily CVD death counts and emergency room visit count data, accurately size-segregated particles data as well as meteorological data (potential confounder). I estimated the effects of particles of different size fractions on CVD mortality and morbidity by Poisson regression models including polynomial distributed lag (PDL) models. I found an elevated risk of two-day delayed cardiovascular mortality with the number concentration of sub-micrometer particles. And I found elevated risks for four- to ten-day delayed cardiovascular emergency room visits in association with the number concentration of ultrafine particles (<100nm), as well as of current-day immediate cardiovascular emergency room visits with Aitken mode (30-100nm) and accumulation mode particles (100-1000nm).

2 Zusammenfassung

Kardiovaskuläre Erkrankungen stellen heute die weltweit führende Todesursache dar. Dabei handelt es sich um eine Erkrankung, die durch Arteriosklerose induziert wird (z. B. Herz-Kreislauf-Erkrankungen, Schlaganfall). Zu den nicht-beeinflussbaren Risikofaktoren für kardiovaskuläre Erkrankungen zählen hauptsächlich zunehmendes Alter, Geschlecht, Rasse oder ethnische Herkunft und Vererbung. Modifizierbare Risikofaktoren für kardiovaskuläre Erkrankungen sind hauptsächlich Bluthochdruck, anormale Blutfettwerte, Diabetes, Übergewicht und lebensstil-abhängige Faktoren, wie z.B. Bewegungsmangel, niedriger Obst- und Gemüse-Konsum, Tabakkonsum und Alkoholmissbrauch. Niedriger sozioökonomischer Status, psychische Erkrankungen und die Verwendung bestimmter Medikamente sind weitere modifizierbare Risikofaktoren für kardiovaskuläre Erkrankungen. Auch Umweltfaktoren, wie z.B. Temperatur und Luftverunreinigungen, sind mit kardiovaskulären Erkrankungen in Verbindung gebracht worden.

Kurzfristige Einwirkungen von Hitze können die kardiovaskuläre Mortalität sowohl am selben Tag, als auch mit einer Verzögerung bis zu drei Tage erhöhen. Die Expositions-Wirkungsbeziehung zwischen Mortalität und Temperatur werden häufig als U-, V- oder J- förmig beschrieben, wobei der Komfort-Bereich, in dem die Mortalität am niedrigsten ist, je nach geographischer Breite unterschiedlich sein kann. Negative Auswirkungen von erhöhter Temperatur auf die Morbidität sind nur durch wenige Studien belegt, was auch die Hypothese unterstützen könnte, dass viele Hitze-Todesfälle auftreten, bevor die Menschen in ärztliche Behandlung kommen. Kälte erhöht die kardiovaskuläre Mortalität und Morbidität mit einer Verzögerung von vier bis zu zwanzig Tage. Die Expositions-Wirkungsbeziehungen zwischen Mortalität oder Morbidität und Mehr-Tages-Mittelwerte der Temperatur werden als negativ linear beschrieben.

Bis heute sind die meisten Studien, die Temperatur-Auswirkungen auf die Gesundheit diskutiert haben, in Europa und den USA durchgeführt worden. Daher wurde von Januar 2003 bis August 2005 eine Studie im Stadtgebiet von Beijing, China, durchgeführt. Für diese Studie standen tägliche Anzahlen von kardiovaskulärer Mortalität, tägliche meteorologische Daten, sowie tägliche Konzentrationen von partikulären Luftschadstoffen (als potenzielle Störgrößen) zur Verfügung. Die Auswirkungen von 2-Tage- und 15-Tage-Mittelwerten der Temperatur auf die Mortalität wurden mit Hilfe von Poisson Regressionsmodellen geschätzt. Sowohl eine

Zu- als auch eine Abnahme der Lufttemperatur erhöhte das Risiko für kardiovaskuläre Mortalität in Beijing. Dabei waren die Auswirkungen für Erwachsene (≥ 15 Jahre) und ältere Einwohner (≥ 65 Jahre) ähnlich. Die Auswirkungen von Hitze waren unmittelbar, während Kälte überwiegend mit längeren zeitlichen Verzögerungen wirkte. Die Assoziationen wurden nicht durch die Reihenfolge der drei Warmzeiten in der Studie, von Heizung im Winter, oder durch partikuläre Luftschadstoffbelastung modifiziert.

In den letzten Jahrzehnten konnte eine Assoziation zwischen Feinstaub und den kardiovaskuläre Erkrankungen gezeigt werden. Obwohl nur kleine Effekte beobachtet werden konnten, haben diese durch die Exposition der gesamten Bevölkerung eine große Auswirkung auf die öffentliche Gesundheit. Die Expositions-Wirkungs-Funktionen zwischen kurzfristiger Exposition gegenüber Feinstaub und Mortalität oder Morbidität haben sich als nahezu linear erwiesen. Neben der chemischen Zusammensetzung wird auch die Partikelgröße als wichtige Messgröße diskutiert. Aufgrund der begrenzten Verfügbarkeit geeigneter Messdaten gibt es nur wenige epidemiologische Studien zu kurzfristigen Assoziationen zwischen täglicher kardiovaskulärer Mortalität oder Morbidität und größenspezifisch gemessenen Partikeln.

Wiederum in Beijing, China, wurden zwei Studien durchgeführt, um zu untersuchen, wie tägliche Veränderungen in größenspezifisch unterschiedlichen Partikeln mit kardiovaskulärer Mortalität und Notaufnahmen assoziiert sind. Dazu standen tägliche Anzahlen von kardiovaskulärer Mortalität, von Notaufnahmen aufgrund von kardiovaskulären Problemen, meteorologische Daten (potenzielle Confounders), sowie größenspezifisch gemessene Partikelmasse und –anzahlkonzentration zur Verfügung. Die Auswirkungen von Partikeln unterschiedlicher Größe auf kardiovaskuläre Mortalität und Morbidität wurden mit Poisson-Regressionsmodellen geschätzt unter Verwendung von sogenannten „polynomial distributed lag“-Modellen. Dabei wurde ein erhöhtes Risiko für kardiovaskuläre Mortalität mit einer Verzögerung von zwei Tagen gefunden, das durch erhöhte Anzahlkonzentrationen von Sub-Mikrometer-Partikeln induziert wurde. Es wurde auch eine verzögerte Assoziation zwischen kardiovaskuläre Notaufnahmen und erhöhten Anzahlkonzentrationen von ultrafeinen Partikeln gefunden, sowie ein erhöhtes Risiko am selben Tag, das durch Aitken-Modus und Akkumulationsmodus Partikeln induziert wurde.

3 Introduction

3.1 Background

3.1.1 Cardiovascular diseases

Cardiovascular disease (CVD) is now the number one cause of death globally [1]. Although the term "cardiovascular disease" refers to a class of diseases involving the heart, arteries and veins, it is usually a disease related to atherosclerosis. Atherosclerosis is a condition in which fatty material (e.g. cholesterol) accumulates on the wall of an artery, forms plaques and makes it narrow and hardened. The plaques or a thrombus formed by a sudden rupture of soft plaques could slow or stop blood flow, and result in ischemia or even necrosis of the tissues fed by the artery rapidly. If this happens in coronary arteries, it leads to atherosclerotic coronary heart diseases (CHD, e.g. angina pectoris, myocardial infarction), and in case it happens in arteries to the brain, it leads to a stroke. In 2004, an estimated 17.1 million people died from CVD worldwide, representing 29% of all global deaths; of these deaths, an estimated 7.2 million were due to CHD and 5.7 million were due to stroke [1]. CVD are responsible for 10% of the disability-adjusted life years (DALYs) [2] lost in low- and middle-income countries, and for 18% in high-income countries [3]. In 2006, costs directly and indirectly related to CVD were estimated to be 403.1 billion dollars in the United States [4]. In China, annual direct costs of CVD are estimated to be higher than 40 billion U.S. dollars, or roughly 4% of its gross national income [5].

3.1.2 Cardiovascular risk factors

The non-modifiable risk factors of CVD mainly include advancing age, gender, ethnicity, and heredity.

It was reported that for every 10-year increase in age, both men and women more than double their chances of dying due to CVD [6]. A prospective cohort study of men conducted in the United States showed that the incidence of new CVD continued to increase after the age of 80 [7]. The hypothesized reason is that the age-associated alterations in cardiovascular structure and function superimpose the specific pathophysiological mechanisms on the heart and vascular substrates causing clinical disorders in older individuals [8].

In 1983, it was reported that the age-adjusted death rate for diseases of the heart among all males in the United States (260.4 per 100,000) was twice the rate for all females (132.3 per 100,000) [9]. Nowadays, researchers are aware that CVD affects

almost as many women as men [3], at least among elderly people, as after menopause, the risk for women increases sharply [6]. The reason of a narrowed difference between men and women could be that during the rapid industrialization and urbanization (e.g. in China), social, political, and economic factors have changed the lifestyle of women [10]. Risk factors for CVD in women are now generally the same as in men; some (e.g. tobacco use, high triglyceride level, [3]) are even more dangerous to women. Also, there was possible underestimation of the impact of CVD on women before. It may be attributed to the differences in symptomatology. Women experience more nausea and back pain during a heart attack, while men experience left arm pain and chest pain, which are thought to be the "classic" signs of a heart attack [11].

In the United States, African-Americans have the highest age-adjusted CVD death rate, followed by Whites, Hispanics, and Asians [12]. In the United Kingdom, population of African or South Asian origin are at a particularly high risk of CVD [13]. And it is widely known that family history plays an important role on one's possibility of encountering CVD [3].

The major modifiable risk factors of CVD include hypertension, abnormal blood lipids, diabetes, obesity, and lifestyle-dependent factors such as physical inactivity, low fruit and vegetable diet, alcohol use and tobacco use. Other modifiable risk factors of CVD include low socioeconomic status (SES), mental illness, and use of certain medication. Environmental factors such as air pollution and temperature are also reported to promote CVD.

Hypertension (defined as a systolic blood pressure above 140 mmHg and/or a diastolic blood pressure above 90 mmHg) is one of the most important risk factors. Physical inactivity, obesity as well as low fruit and vegetable diet could all promote hypertension and future CVD; but for 90-95% of hypertension cases (termed "primary hypertension") no medical cause can be found [14]. The risk of CVD doubles for every 10 point increase in diastolic blood pressure or every 20 point increase in systolic blood pressure [3]. In the Canadian Cardiovascular Congress 2004 [15], Dagenais and colleagues presented that Quebec men aged 35 to 64 with a systolic blood pressure between 133 and 140 mmHg were almost twice as likely to have a heart attack or suffer from a sudden cardiac arrest than men whose systolic blood pressure was less than 125 mmHg during a 23-year follow-up, showing that a blood pressure at the top end of the normal range still increases risk. China is a multi-ethnic nation; the prevalence and severity of hypertension are substantially different among ethnic groups [16, 17].

It is easily understood that higher total cholesterol level and triglyceride level in blood make patients more prone to atherosclerosis. Also the type of cholesterol plays a role: low-density lipoprotein (LDL), especially small dense LDL [18], is known to be an atherogenic lipoprotein. People having a total cholesterol level of 240 mg/dL or more, and a LDL level of 160 mg/dL or more are considered to be at high risk of CHD [19]. Kathiresan and colleagues [20] found that a genotype score of nine validated common single-nucleotide polymorphisms (SNPs) associated with modulation in levels of LDL or high-density lipoprotein (HDL) cholesterol was an independent risk factor for incident cardiovascular disease.

The World Diabetes Foundation [21] estimated that in 2010, 285 million people live with diabetes, corresponding to 6.4% of the world's adult population. In China, an epidemic of diabetes has been announced; 92.4 million adults have diabetes (prevalence 9.7%) and 148.2 million have pre-diabetes (prevalence 15.5%) [22]. The American Heart Association [21] considers that people with diabetes are two to four times more likely to develop CVD, including CHD, stroke, peripheral arterial disease and possibly cardiomyopathy. Insulin resistance, one of the underlying metabolic causes of type-2 diabetes, is commonly accompanied by dyslipidemia, hypertension, and prothrombotic factors and could develop from obesity and physical inactivity, which are also major risk factors for CVD [23]. A 6-year prospective cohort study among 78,282 American women aged 54 to 79 years [24] showed that the age-adjusted relative risk (RR) of CVD mortality for women with diabetes was 2.67 (95% confidence interval (CI): 2.20-3.23). A cohort study of a relatively young (≥ 30 years) Middle East population [25] showed that CHD patients with diabetes had a worse prognosis than those without diabetes.

Obesity has become a global epidemic in both adults and children. In the United States, 60% of all adults are currently either obese or overweight [26]; the WHO estimated that by the end of 2010 there are 43 million overweight and obese children under 5 years of age worldwide and 75% of them come from low- and middle-income countries [27]. The Body Mass Index (BMI, body weight (kg) divided by the square of height (m^2)) is commonly used for classifying overweight or obesity. Recent pooled analyses of more than 1.1 million people recruited in 19 cohorts in Asia [28] found a U-shaped association between BMI and the risks of death from CVD. A study [29] showed that a high BMI was associated with lower mortality in elderly heart failure patients when compared with normal weight ones ("obesity paradox"), suggesting that for the elderly parameters such as measures of body composition, fat, and fat-free mass may be

of greater importance than BMI.

Sedentary lifestyle and fast food increase people's risks of high blood pressure, diabetes, overweight or obesity, and high triglycerides, which are all risk factors of CVD. It has been suggested that in China urbanization associated adverse changes in diet and physical activity level might be a reason for the increasing burdens of hypertension, diabetes and high cholesterol level [30]. According to the WHO, worldwide physical inactivity is estimated to cause 20% of CVD and 22% of CHD; low fruit and vegetable intake is estimated to cause 31% of ischemic heart disease and 11% of stroke.

Moderate alcohol consumption has been associated with a lower risk of CHD in healthy people, partly explained by its beneficial effects of raising high-density lipoprotein (HDL) and anti-clotting [31]. Although any type of alcoholic beverage appears beneficial, red wine seems to confer additional health benefits because of the presence of red wine polyphenolic compounds (RWPC) [32]. RWPC are antioxidants which could lower free radical properties, the aggregation of platelet and the thrombotic activities; they are also powerful vasodilators, contribute to the preservation of the integrity of the endothelium and the inhibition of smooth muscle cell proliferation and migration [32]. However, the American Heart Association [19] recommends people who do not drink never to start, as many other ways such as controlling body weight, regular physical activities, and a healthy diet could decrease the risk of CVD, and bring no potential risk of drinking too much or even alcoholism. Too much alcohol intake will increase blood pressure and triglycerides, and elevate the risk for obesity because of the extra calorie intake.

The inverse association between SES and CVD risk in high-income countries is the result of low-income population's life style and behaviour patterns (e.g. higher prevalence of smoking), psychosocial stress caused by chronic life stress, social isolation and anxiety, and less ease of access to health care [33, 3]. Two papers from Canada showed that educational achievement represented SES best [34, 35]. CVD was reported to be associated with both anxiety disorder and mood disorder [36]. Epidemiological studies have consistently shown excess CVD mortality in patients with schizophrenia, bipolar disorder and depression. The excess cardiovascular mortality associated with schizophrenia and bipolar disorder is attributed in part to an increased risk of the modifiable coronary heart disease risk factors e.g. obesity, smoking, diabetes, hypertension and dyslipidaemia [37]. Drug-induced hypertension, cerebrovascular diseases and heart failure have been discussed. A history of elevated blood pressure is a

major risk factor for drug-induced hypertension [38]. Several classes of drugs may precipitate the occurrence of heart failure in patients with pre-existing left ventricular impairment [39].

There has been a huge amount of scientific literature showing an association between smoking (cigarette or other forms) or passive smoking and CVD. Smoking has been estimated to cause about 11% of all deaths due to CVD [40]. The risk of developing an acute cardiac syndrome or chronic lifetime coronary events after second-hand smoke exposure is at least 30% [41]. Research about mechanisms has shown that cigarette smoking could induce vascular oxidative stress, increase oxidative DNA damage in endothelial cells, induce vascular inflammation, and activate the production of circulating monocytes and their adhesion to the endothelium [42]. Reactive oxygen species and the activation of inflammatory pathways play a central role in the accelerated cardiovascular aging in smokers [42]. In 2001, Humphries and colleagues [43] suggested that smoking is a risk factor for CHD, particularly in men carrying the Apo-lipoprotein E4 allele. This may explain why some smokers get heart diseases while others get e.g. lung or bronchial problems.

Over the last decade, ambient air pollution has increasingly been linked with CVD [44]. Recent studies have reported associations of short-term exposure to particularly traffic-related air pollution on adverse outcomes including stroke [45], myocardial infarction [46-48] and disturbances of the autonomic control of the heart [49]. Epidemiological studies have demonstrated a consistent increased risk for cardiovascular events in relation to exposure to present-day concentrations of ambient particulate matter (PM) [44]. For more details about the effects of PM on CVD, please see chapter 3.1.3.

CVD has also been linked with short-term air temperature fluctuation, not only extreme temperature events known as heat waves or cold spells, but also increases or decreases in moderate temperature. For more details about the effects of air temperature variation on CVD, please see chapter 3.1.4.

3.1.3 Particulate air pollution and cardiovascular health

Ambient PM has increasingly been linked with CVD during the last decades [44]. Different size fractions of PM are under investigation: PM with an aerodynamic diameter smaller than 10µm (PM_{10}) or 2.5µm ($PM_{2.5}$ or fine particles), PM with diameters between 2.5µm and 10µm (coarse particles), as well as particles smaller than

100nm (ultrafine particles, UFP) [44]. As a risk factor, air pollution needs to be considered differently than traditional cardiovascular risk factors. Traditional risk factors (e.g. smoking, obesity, race etc.) exert their influences on a limited proportion of population, although in some cases demonstrating large relative risk. Air pollution is a continuous exposure affecting the whole population; although the relative risk could be small, it still has a large public health impact [50].

PM_{10}, $PM_{2.5}$ and coarse particles are typically measured in their mass per volume of air ($\mu g/m^3$), whereas UFP are most often measured by their number (per cm^3) [51]. They have different sources, potential distances of being transported in air, and locations of deposition in human lungs. $PM_{2.5}$ and UFP are of more importance for urban population, as they are predominantly emitted from combustion processes of fossil fuels (high carbon content), e.g. from industry, traffic, power generation (especially diesel engines for UFP). While both $PM_{2.5}$ and UFP can penetrate deep into lungs reaching the alveoli, only UFP are possibly crossing over into the bloodstream. [50]

The shape of the exposure-response functions between short-term exposure to PM and cardiovascular mortality and morbidity is considered to be near-linear and without a threshold [52]. Except for CVD mortality and hospital admissions (morbidity), effects on the cardiovascular system observed for short-term fluctuations of ambient PM also include ischemia and arrhythmia in patients with coronary artery disease, altered heart rate and autonomic control, altered blood pressure, systemic inflammatory response, pro-thrombotic state and endothelial dysfunction [53].

The correlations between fine and coarse particles are typically found to be around or somewhat lower than 0.5 [54]. Both subcategories of PM_{10} (coarse and fine particles) showed short-term effects on cardiovascular mortality or admission, but the significance and magnitude of the effects estimate were inconsistent [54]. So it is hard to determine which one contributes more to the effects of PM_{10}, although several studies showed that the effects of coarse particles on short-term total mortality no longer existed after adjusting for fine particles in a two-pollutant analysis [54]. UFP are supposed to be a great contributor to the observed cardiovascular effects of $PM_{2.5}$, mainly due to the large active surface area and high deposition efficiency in the pulmonary region [55, 56].

With regard to the potential mechanisms through which exposure to PM leads to CVD, there are three main pathways proposed: a) activation of pulmonary receptors

resulting in autonomic nervous system imbalance and the development of dysrhythmias; b) induction of pulmonary and systemic inflammation; c) access of particles or chemical constituents to the systemic circulation [57].

After establishing the associations between PM and CVD, researchers were interested in finding out the constituents of PM which are responsible for their observations. High fractions of nickel, vanadium, selenium and elemental carbon (EC) were reported to increase the risks of $PM_{2.5}$-related CVD mortality and hospitalization [58-60]. Urban UFP contain greater relative amounts of polycyclic aromatic hydrocarbons (PAH) than the bigger fine and coarse particles, which could be one of the reasons that explain UFP's greater redox potential [57]. Coarse particles contain more crustal materials (e.g. silicon, calcium) due to their sources (mechanical grinding, windblown dust, and agricultural activities) [61]. However, the concentrations of particles within the coarse size range in urban environments generally are more influenced by transportation than in rural environments [62].

Due to the limited availability of appropriate measurement data, there are only few epidemiological studies on the short-term associations between daily cardiovascular mortality and more accurately size-segregated particles [63-67]. Nearly all studies on health effects of smaller particles have been conducted in North America and Europe; however, concentration levels in China are very different and there might also be differences in specific sources and particle composition and their proportional contributions to the air pollution mixture which might influence the associations between human health and air pollution.

3.1.4 Air temperature and cardiovascular health

CVD has been linked to climate fluctuation, although uncertainty remains in attributing the expansion of CVD to it, due to the lack of long-term, high-quality datasets as well as the large influence of socio-economic factors and changes in population characters. The Intergovernmental Panel on Climate Change (IPCC) has recommended short-term air temperature fluctuations as a first step for analyzing the association between climate fluctuation and mortality or morbidity [68].

Heat waves but also moderately elevated temperatures contribute to the observed heat-related cardiovascular mortality [69-73]. Different lag times have been reported for the association of heat with cardiovascular mortality; however all lag times were rather immediate, ranging from the same day to three days following a temperature

increase [72-77]. The exposure-response functions between mortality time-series and continuous temperature measures have been shown to be U- or J-shaped, and the range of temperatures corresponding with a minimum mortality ("threshold", "turning point" or "optimum temperature") was reported to be related with latitude, so that the residents of lower latitudes tended to be susceptible only at higher temperature values, indicating a reduced susceptibility to heat [72, 76-78].

Although the short-term effects of high air temperatures on cardiovascular mortality have been well documented, there is much less evidence about the effects of high temperature on morbidity [79]. Several studies on heat waves as well as normal hot weather showed increases in hospital admission for CVD [80-82]. But some other studies showed inconsistent results with negative or no associations between high temperatures and cardiovascular or cerebrovascular hospital admissions [79, 83]. The impact of hot weather on mortality being not paralleled by similar magnitude increases in hospital admissions supports the hypothesis that many heat-related deaths occur in people before they come to medical attention [83].

Excess winter mortality has been well known [84, 85]. Cold spells have been reported to be related to excess mortality mostly attributable to CVD and, in particular, to elderly people [86]. Low temperatures usually showed delayed effects on cardiovascular mortality, from four to 20 days [74, 87-89]. The exposure-response functions between mortality and multiple-day moving averages of temperature were reported to be negative linear [59, 90]. However, the relationship between cold and cardiovascular mortality is not consistent. A study in Yakutsk, Eastern Siberia, where temperature fell even to -48.2°C, found no effect of decreased temperature on ischemic disease mortality, possibly indicating population adaptation to local climate [91].

Exposure to cold is of course also thought to influence cardiovascular morbidity. Studies have shown negative linear correlations between air temperature and the occurrence of myocardial infarctions (MI) and coronary events [92, 93], significant increments of hospitalization due to heart failure in winter compared to summer [94], inverse correlations between temperature and cerebrovascular admission [95, 96] as well as an increase in blood pressure elicited by superficial skin cooling [97]. Some studies were able to separate subgroups and found e.g. stronger cold effects on recurrent MI and coronary events compared with the first attack [92], as well as more excess winter events of intracerebral hemorrhage than subarachnoid hemorrhage and ischemic stroke

[98]. However, protective effects of low temperatures on heart diseases were also reported [99].

High or low air temperature may not really elevate the cardiovascular mortality of a population, but only cause a short-term forward shift in mortality, meaning that the vulnerable people (e.g. elderly people, people with existed chronic diseases) died a few weeks earlier before the time point at which they might die if air temperature hadn't changed. This is referred to as "mortality displacement" [100]. In this case, a decrease in mortality during the subsequent weeks after the high or low temperature period could be observed.

Possible mechanisms through which elevated temperature increases CVD include enlarged skin vessels and facilitated sweat, leading to falling blood pressure, increased cardiac work load and loss of fluid and salt, further leading to haemoconcentration, a "thrombosis promoting" state. The activation of coagulation and inhibition of fibrinolysis lead to diffuse microvascular thrombosis. Besides, heat-induced release of interleukin (IL)-1 or IL-6 into systemic circulation results in damage and hyperactivation of endothelial cells. [67] Possible mechanisms through which low temperature increases CVD include the stimulation of cold receptors in the skin, followed by an upward regulation of the catecholamine level by the sympathetic nervous system and a constriction of the skin vessels to reduce heat loss. Blood pressure increases consequently, and approximately 1L of blood plasma is shifted from skin and legs to central body parts, then removed by urine or shifted to extra-cellular space. The shift of blood plasma leads to haemoconcentration, leading to an increase of the concentrations of red and white blood cells, platelets, certain clotting factors, cholesterol and fibrinogen, as well as blood viscosity, which promotes clotting and thrombosis. Moreover, protein C, which is an anticoagulant, moves out to the extra-cellular space with blood plasma. The rise of blood pressure may lead to oxygen deficiency in the cardiac muscle which might induce myocardial ischemia or arrhythmias. If the rise of blood pressure is too sudden, there is the possibility of vascular spasm and a rupture of an atherosclerotic plaque that induces a thrombus [101-106].

Until today, most studies regarding weather and climate effects on health have been conducted in Europe and the United States; however, there is a lack of data and publications about the temperature-mortality relationship in the Asian region.

3.2 Specific aims

1) To investigate the association between daily air temperature and daily cardiovascular mortality in the urban area of Beijing, China. Moreover, to check which age-group (adult or elderly residents) is affected more by heat or cold in this area, and if air pollution plays a confounding or inter-acting role in the temperature-mortality relationship.

2) To investigate whether daily changes in ambient concentrations of particle size fractions in the sub-micrometer range are associated with cause-specific cardiovascular mortality in different age groups in Beijing, China. Moreover, to better delineate whether particle number, mass, or surface area concentrations may be responsible for the associations, and whether there is a modification of the air pollution effects by air mass origin defined by backward trajectories.

3) To investigate whether daily changes in ambient concentrations of particle size fractions in the range of 3nm to 10μm are associated with cardiovascular emergency room visits in Beijing, China. Moreover, to better delineate whether using particle number or mass concentration may affect the associations.

3.3 Results

3.3.1 Air temperature and cardiovascular health [107]

In the first publication (see chapter 4), I conducted a study aiming at investigating the association between daily air temperature and daily cardiovascular mortality in the urban area of Beijing, China. Moreover, I was interested in the age-group (adult or elderly residents) that is affected more by heat or cold in this area and investigated in addition, if air pollution plays a confounding or inter-acting role in the temperature-mortality relationship.

I conducted the study in the urban area of Beijing, China, from 1 Jan 2003 to 31 Aug 2005 (1,368 km^2, approximately 7,072,000 registered permanent residents, 974 days). I obtained daily death counts due to CVD as well as two subcategories - ischemic heart diseases and cerebrovascular diseases - for adult residents (≥ 15 years) and elderly residents (≥ 65 years). I further obtained daily mean temperature, relative humidity, and barometric pressure as well as daily concentrations of ambient particulate matter with an aerodynamic diameter < 2.5 μm ($PM_{2.5}$) and < 0.1 μm (ultrafine particles, UFP). I estimated the effects of two-day and 15-day average temperatures on mortality by Poisson regression controlling for potential confounders, for warm (April to September) and cold periods (October to March) separately.

All the exposure-response functions between two-day or 15-day average temperature and cardiovascular, ischemic or cerebrovascular mortality showed no obvious U- or J-shape and could be considered linear. The relative risks (RR, with 95% confidence intervals, 95% CI) per 5°C increase of two-day average temperature in the warm period (representing heat effects) associated with cardiovascular, ischemic and cerebrovascular mortality were 1.098 (1.057, 1.140), 1.020 (0.975, 1.067) and 1.047 (1.000, 1.097), respectively, for the adult residents; the RRs for elderly residents were similar, only the one associated with cerebrovascular mortality was a bit higher with 1.064 (1.008, 1.123). The RRs (95% CI) per 5°C decrease of 15-day average temperature in the cold period (representing cold effects) associated with cardiovascular, ischemic and cerebrovascular mortality were 1.057 (1.022, 1.094), 1.123 (1.057, 1.193) and 1.036 (1.002, 1.071), respectively, for the adult residents; the RRs for elderly residents were of similar magnitudes.

The order of the three different warm periods within the whole study period (April to September in 2003: 1st warm period, April to September in 2004: 2nd one, and April to August in 2005: 3rd one) showed no significant interaction with two-day average temperature, and therefore indicates that there was no heat effect modification by potential population adaptation to heat or by possible increasing prevalence of air-conditioning year by year. I also found no interaction between heating and 15-day average temperature after an analysis within the cold period, showing that residential heating didn't modify the cold effect. This might also reflect that the study population exposed themselves to outdoor temperature although they probably spent a lot of time indoors. When considering for confounding by $PM_{2.5}$ or UFP with a lag of two days as the most relevant air pollution lag [108], there were no relevant changes for two-day average temperature effects, and a drop in 15-day average temperature effects on cardiovascular mortality. For more details please see the publication in chapter 4.

In the publication in chapter 4 I additionally estimated the effects of two-day and 15-day average temperatures on respiratory mortality. Elevated air temperature showed effects on respiratory mortality in both warm and cold periods. The effect in warm periods was higher than the one on cardiovascular mortality. The effects were also not modified by the order of the three warm periods or the residential heating in cold periods. Furthermore, the effects did not change after considering lag 2 $PM_{2.5}$ or UFP as confounders.

3.3.2 Particulate air pollution and cardiovascular health [108, 109]

Moreover, I conducted two studies aiming at investigating how daily changes in ambient concentrations of size-segregated particles in Beijing, China were associated with cardiovascular mortality and emergency room visits, respectively. Moreover, I aimed to better delineate whether different types of particle concentrations used may be responsible for the associations. In addition, in the study regarding cardiovascular mortality, I investigated which age-group (adult or elderly residents) is affected more and whether air mass origin modifies the air pollution effect.

The study investigating particulate effect on cardiovascular morality (see second publication in chapter 5) was conducted in the urban area of Beijing, from March 2004 to August 2005 (1,368 km^2, approximately 7,072,000 registered permanent residents, 546 days). I obtained daily cardiovascular death counts as well as two subcategories - ischemic diseases and stroke - for adult residents (≥ 15 years) and elderly residents (≥ 65 years). I also obtained continuously measured particle size-distribution data of particles with a size up to 0.8 μm as well as meteorological and air mass history data. The size-distribution data were converted to particle number, mass, and surface area concentrations (NC, MC and SC, respectively) assuming spherical particles. For this study, I used daily mean NC of Nucleation mode (0.003-0.03 μm) and Aitken mode (0.03-0.1 μm) particles, daily mean MC and SC of two subgroups (0.1-0.3 μm, 0.3-0.8 μm) of accumulation mode particles (ACP, 0.1-0.8 μm), and daily mean NC, MC and SC of particles in the range from 0.003 to 0.8 μm (NC_1, PM_1 and SC_1). I estimated the effects of particle metrics on cardiovascular mortality for single-day lags from 0-3 days and the average of days 0-4 (5-day mean) by Poisson regression controlling for potential confounders.

I could see associations between daily cardiovascular mortality and particle NC in the Aitken mode range as well as NC_1. The strongest associations were found for a delay of two days; the RRs (95%CI) were 4.04 (1.18, 6.98) for lag 2 NC of Aitken mode particles and 4.92 (1.50, 8.45) for lag 2 NC_1, respectively. These 2-days-delayed associations were not confounded by any other particle metrics. When ischemic mortality was analyzed separately, I found a consistent two-days-delayed association with all particle metrics except with NC of Nucleation mode particles. But the associations between ischemic mortality and MC/SC of ACPs as well as PM_1/SC_1 diminished, when adding lag 2 NC of Aitken mode particles in the models. Associations between particle metrics and cardiovascular mortality for elderly people showed similar

effects compared to the results found for the adult population. Associations between cardiovascular and ischemic mortality and particle NC in the Aitken mode range and NC_1 were not modified by air mass origin. Although not statistically significant, results indicated that mortality effects of SC and MC with a lag of two days were stronger for stagnant and southern air masses compared to air masses arriving from northerly directions with average to high wind speed. An increase of 973.7 $\mu m^2/cm^3$ in SC_1 resulted in a 6.6% increase (95% CI: 1.78, 11.55) in ischemic mortality for stagnant and southern air masses compared to a 2.9% increase (-1.20, 7.25) for air masses from northerly directions with average to high wind speed. An increase of 81.8 $\mu g/m^3$ in PM_1 resulted in a mortality increase of 5.9% (1.42, 10.64) for stagnant and southern air masses, compared to 2.4% (-1.66, 6.59). For more details please see publication in chapter 5.

The study investigating particulate effects on cardiovascular emergency room visits (see third publication in chapter 6) was conducted in Beijing (urban and suburban areas), from March 2004 to December 2006 (16,411 km^2, approximately 15,380,000 registered permanent residents, 1033 days). I obtained total cardiovascular as well as severe cardiovascular emergency room visit count data (a combination of ischemic heart diseases, arrhythmia, heart failure and cerebrovascular diseases) (referred as ERVT and ERV, respectively), continuously measured aerosol number size distribution data of particles with a size range of 3 nm to 10 μm as well as meteorological data. The size distribution data were converted to particle number and mass concentrations (NC and MC) assuming spherical particles. I estimated the cumulative lagged effects of particles within different size ranges on ERVT and ERV up to 15 days using polynomial distributed lag (PDL) models. I then quantitatively estimated the effects of 8-day moving average (MA) of particle NC and MC of lags 0-7 and explored the exposure-response functions between the 8-day MA of particle NC or MC and ERVT or ERV by Generalized additive models (GAM) controlling for potential confounders. Both PDL models and GAM are Poisson regression models.

The main results of this study were the four to ten-days delayed effects of NC of UFP on ERVT and ERV, as well as the current-day effects of NC of Aitken mode (the latter two size fractions within UFP range) and accumulation mode (100-300 nm and 300-1000 nm) particles on both outcomes. I could also see significant current-day effects of NC of PM_1. Those effects were dominated by the two size fractions 10-30 nm and 30-50 nm. The IQR of lag 0-7 moving average NC of UFP, PM_1, 10-30 nm particles

and 30-50 nm particles were 9450cm^{-3}, 11270cm^{-3}, 3248cm^{-3} and 2076cm^{-3}, respectively. The RRs (95%CIs) of ERVT associated with per IQR increases then, respectively, were 1.12 (1.05, 1.19), 1.11 (1.04, 1.19), 1.13 (1.06, 1.20) and 1.09 (1.03, 1.15). The RRs (95%CIs) of ERV were 1.10 (1.03, 1.18), 1.10 (1.02, 1.19), 1.10 (1.02, 1.18) and 1.07 (1.00, 1.14). Looking at the fragment with most of the NC or MC data of each exposure-response function plot, only the function associated with the 8-day MA of NC of 3-10 nm particles seemed to show a J-shape; the other functions did not substantially deviate from linearity. The PDL curves for the effects of NC and MC of 100-300 nm and 300-1000 nm particles on ERVT or ERV were quite similar, indicating that particle metrics do not seem to affect the effects of particles in this size range. With regard to each size fraction, the effect of particles on ERVT was in most cases higher than the effect on ERV, except for the NC of 3-10 nm particles.

3.4 Discussion and conclusions

1) Both increases and decreases in air temperature are associated with an increased risk of cardiovascular mortality in Beijing. The effects of heat were immediate while the ones of cold became predominant with longer time lags. These findings are in agreement with the findings of studies conducted in Europe and the United States. The heat effect I found is smaller then what Chung et al. [72] found in Beijing, but is comparable to what Almeida et al. [73] found in Lisbon, a city with similar latitude as Beijing. The cold effect I found is smaller then what Analitis et al. [89] found in Europe. In our study, the temperature effects on adult (≥15 years) and elderly (≥65 years) residents were similar. And the associations were not confounded or modified by ambient particulate air pollution.

2) There is an elevated risk of cardiovascular mortality or ischemic mortality (when analyzed separately) in Beijing from short-term exposure to particulate air pollution in the sub-micrometer range. The observed effects of the number concentration (NC) of particles are not confounded by other particle metrics; while the observed effects of the mass (MC) or surface area concentrations (SC) of particles diminished when adding the NC in the models. The associations between particle metrics and cardiovascular mortality for elderly people were similar compared to the results found for the adult population. Associations between cardiovascular and ischemic mortality and the sub-micron particles were not substantially modified by air mass origin. The pronounced effect of NC of sub-micron particles I found is in agreement with other

previous studies [63, 66, 110-112].

3) The analyses showed an elevated risk of cardiovascular emergency room visits in Beijing associated with short-term exposure to particulate air pollution. In particular, delayed effects of NC of UFP and immediate effects of NC of Aitken mode and accumulation mode particles were observed. If compared with the results from other studies [63, 66, 67, 108], my observed UFP effect on cardiovascular emergency room visits was more delayed. But my observed immediate effects of sub-micron particles were comparable to what Branis et al. [64] reported in their study of cardiovascular hospital admissions in Prague.

4 Associations between air temperature and cardio-respiratory mortality in the urban area of Beijing, China: a time-series analysis

Authors: Liqun Liu, Susanne Breitner, Xiaochuan Pan, Ulrich Franck, Arne Marian Leitte, Alfred Wiedensohler, Stephanie von Klot, H-Erich Wichmann, Annette Peters, Alexandra Schneider

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Associations between air temperature and cardio-respiratory mortality in the urban area of Beijing, China: a time-series analysis

Liqun Liu[1,2,3*], Susanne Breitner[1,2], Xiaochuan Pan[3*], Ulrich Franck[4], Arne Marian Leitte[4], Alfred Wiedensohler[5], Stephanie von Klot[1], H-Erich Wichmann[2,6], Annette Peters[1] and Alexandra Schneider[1]

Abstract

Background: Associations between air temperature and mortality have been consistently observed in Europe and the United States; however, there is a lack of studies for Asian countries. Our study investigated the association between air temperature and cardio-respiratory mortality in the urban area of Beijing, China.

Methods: Death counts for cardiovascular and respiratory diseases for adult residents (≥15 years), meteorological parameters and concentrations of particulate air pollution were obtained from January 2003 to August 2005. The effects of two-day and 15-day average temperatures were estimated by Poisson regression models, controlling for time trend, relative humidity and other confounders if necessary. Effects were explored for warm (April to September) and cold periods (October to March) separately. The lagged effects of daily temperature were investigated by polynomial distributed lag (PDL) models.

Results: We observed a J-shaped exposure-response function only for 15-day average temperature and respiratory mortality in the warm period, with 21.3°C as the threshold temperature. All other exposure-response functions could be considered as linear. In the warm period, a 5°C increase of two-day average temperature was associated with a RR of 1.098 (95% confidence interval (95%CI): 1.057-1.140) for cardiovascular and 1.134 (95%CI: 1.050-1.224) for respiratory mortality; a 5°C decrease of 15-day average temperature was associated with a RR of 1.040 (95%CI: 0.990-1.093) for cardiovascular mortality. In the cold period, a 5°C increase of two-day average temperature was associated with a RR of 1.149 (95%CI: 1.078-1.224) for respiratory mortality; a 5°C decrease of 15-day average temperature was associated with a RR of 1.057 (95%CI: 1.022-1.094) for cardiovascular mortality. The effects remained robust after considering particles as additional confounders.

Conclusions: Both increases and decreases in air temperature are associated with an increased risk of cardiovascular mortality. The effects of heat were immediate while the ones of cold became predominant with longer time lags. Increases in air temperature are also associated with an immediate increased risk of respiratory mortality.

Background

In recent years, concern on the effects of meteorological factors on population health has increased. Research started by exploring the effects of weather, since its relationship with certain health outcomes is relatively easy to be investigated compared to rather long-term climate changes. The Intergovernmental Panel on Climate Change (IPCC) has recommended short-term air temperature fluctuations as one of the main markers for analyzing the association between climate and mortality or morbidity [1].

So far, the association between air temperature and mortality has been investigated in various locations of the world, either by simple descriptive statistics or by time-series or case-crossover approaches. Results obtained from heat wave events formed most of the existing evidence of heat effects on mortality from 1970s until today [2].

* Correspondence: liqun.liu@helmholtz-muenchen.de; xcpan@hsc.pku.edu.cn
[1]Helmholtz Zentrum Muenchen, German Research Center for Environmental Health, Institute of Epidemiology II, Neuherberg, Germany
[3]Peking University Health Science Center, School of Public Health, Beijing, China
Full list of author information is available at the end of the article

The 2003 European heat wave and 2006 California heat wave are two prominent recent events. Excess deaths in early August 2003 were speculated to be at least 33,120 for Western Europe [3] (maximum "% excess death" was found to be 60% for France from 1 to 20 August, 2003 [4]); while 655 (6%) excess deaths were estimated for California from 15 July to 1 August, 2006 [5]. However, not only heat waves but also increases in moderate temperature contribute to the observed heat-related mortality. Exposure-response functions between mortality time-series and continuous temperature measures have shown V-, U- or J-shaped associations, and the range of temperature corresponding with a minimum mortality ("threshold", "turning point" or "optimum temperature") was reported to be related with latitude [6,7]. The residents of lower latitudes tended to be more vulnerable only at higher temperature values, indicating less susceptibility to heat [8-10].

Excess winter mortality has been well known (which may have also caused that in recent years, particularly in the light of global warming, there were fewer studies particularly focusing on cold spells or temperature decreases). The Eurowinter study [11] found that annual excess deaths due to cold ranged from 408 to 1,617 for eight European regions on days colder than 18°C. Barnett et al. [12] compared coronary events occurring in the coldest 25% of periods with those occurring in the rest of periods among the WHO MONICA project population and found an overall increase. In a recent large multi-centre European study (PHEWE, 15 cities), Analitis et al. [13] found that a 1°C decrease in 16-day-average minimum apparent temperature was associated with 1.25%-3.30% increases of total or cause-specific mortalities.

Until today, most studies regarding weather and climate effects on health have been conducted in Europe and the United States; however, there is a lack of data and publications about the temperature-mortality relationship in the Asian region. For this reason, we conducted the present study aiming at investigating the association between daily air temperature and daily cardiovascular as well as respiratory mortality in the urban area of Beijing, China. Moreover, we were interested in the age-group that is affected the most by heat or cold in this area and investigated in addition, if air pollution plays a role in the temperature-mortality relationship.

Material and methods

Study area and period

We conducted the study in the urban area of Beijing, China, from 1 Jan 2003 to 31 Aug 2005 (974 days). Beijing is located on the North China Plain surrounded by mountains of 1000-1500 m in altitude to the west, north, and northeast, while Bohai Sea on the southeast side. Typical warm temperate semi-humid continental monsoon climate brings Beijing hot, humid summers and cold, dry winters. Springs and autumns are both of relatively short duration. The urban area of Beijing is about 1,368 km^2 consisting of eight districts (see Figure 1) with approximately 7,072,000 registered permanent residents [14].

Mortality data

We obtained mortality data in the Beijing urban area for adult residents (≥ 15 years) from Beijing Centers for Diseases Control and Prevention (CDC). We calculated daily death counts for adults (referring as "the whole population") as well as for individuals of 65 years and older. Daily death counts included deaths due to cardiovascular (ICD-10 code: I00-I99), respiratory (J00-J99), and cardiorespiratory (I00-J99) diseases. We further considered death counts for ischemic heart diseases (I20-I25) and cerebrovascular diseases (I60-I69), which were the two major cardiovascular subcategories. Influenza and pneumonia (J10-J18) and chronic lower respiratory diseases (J40-J47), the two major respiratory subcategories, were not analyzed because of too small counts.

Meteorological and air pollution data

Daily meteorological data were available from China Meteorological Data Sharing Service System (station 54511, located at N39°48' E116°28' in the south eastern part of Beijing within Daxing District, see Figure 1) and included daily mean temperature, relative humidity, and barometric pressure. We further calculated apparent temperature (a measure of individually perceived discomfort due to a combination of temperature and humidity) [15]. Daily mean meteorological data from another measurement station (Houhai, located in the centre of Beijing, see Figure 1) was gathered from an internet weather service (Weather Underground 2011) as well, but contained missing values. The Pearson correlation coefficients for valid days between the two data sources were 0.995, 0.967 and 0.999 for daily air temperature, relative humidity and barometric pressure, respectively, indicating a good agreement.

Daily mass concentrations of ambient particulate matter with an aerodynamic diameter <2.5 μm ($PM_{2.5}$) and number concentrations of ambient particles with an aerodynamic diameter <0.1 μm (ultrafine particles, UFP) were obtained from a joint cooperation between Peking University, Beijing, China, and Leibniz-Institute for Tropospheric Research, Leipzig, Germany [16]. The measurement station for aerosol size distribution data is located on Peking University campus area in the north western part of Beijing (see Figure 1). The number size distribution was used to calculate number concentrations of UFP, and mass concentrations of $PM_{2.5}$ assuming spherical particles with a mean particle density of 1.5 g cm^{-3}. Details are described

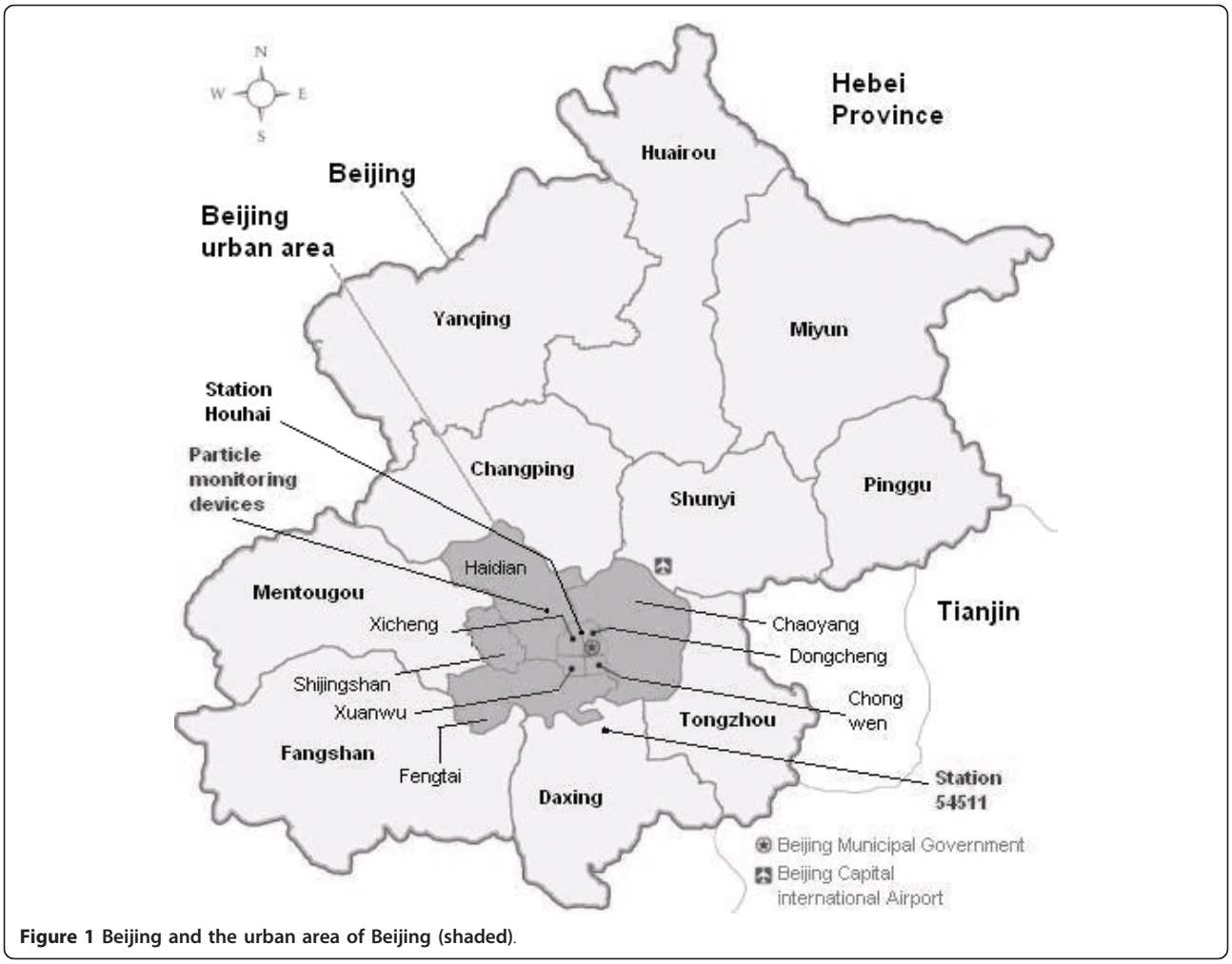

Figure 1 Beijing and the urban area of Beijing (shaded).

elsewhere [17]. Particle data were available only from March 2004 on.

Statistical analyses

We used generalized semi-parametric Poisson regression to model the natural logarithm of the expected daily death counts as a function of the predictor variables. Penalized splines were used to allow for non-linear confounding and temperature effects. Data were analyzed using the package "mgcv" version 1.4-1.1 in the statistical software R version 2.7.2 (R Development Core Team, 2008).

We explored the effects of air temperature on mortality within warm period (April to September) and cold period (October to March) separately.

In a first step, a base model was built without air temperature exposure for each category of mortality individually (see Additional file 1, Table S1). To control systematic variations over time, we considered long-term trend as well as dummy variables for season, day of the week (DOW), and public holidays as potential confounders. As potential meteorological confounders we considered daily mean relative humidity and barometric pressure with the same type of lag as the temperature term. To ensure sufficient adjustment for season and other meteorological parameters, time trend and relative humidity were forced into all models. Season, day of the week, public holidays and barometric pressure were only included if they improved model fit. As a criterion to guide the selection of degrees of freedom (DF) for trend, we used the minimization of the absolute value of the sum of the partial autocorrelation function (PACF) of the model's residuals for a fixed number of lags [18]. Model selection for the other confounders was carried out by minimizing the Generalized Cross Validation (GCV) criterion [19].

We considered the mean of lags 0 to 1 and of lags 0 to 14 for air temperature exposure. The focus on these averages was chosen on the basis of previous studies conducted in Europe, Northern America, and other places around the world [13,20-22]. Firstly, we added them to the base models and estimated the exposure-response functions for temperature effects using penalized splines

with four knots. Then, if the function was linear or almost linear, temperature effects were directly presented as relative risk (RR) of death per 5°C increase if positive linear or decrease if negative linear, respectively. If the function was non-linear, we selected a temperature breakpoint (which we commonly call "threshold") by minimizing the Akaike Information Criterion (AIC) for a range of different threshold values. Then for a J-shaped function, only the temperatures above the threshold were used for effect estimation. In this case, temperature effects were presented as relative risk (RR) of death per 5°C increase in temperature above the threshold.

After having explored the effects of air temperature on mortality for the whole population as described above, we repeated the same procedure for mortality of elderly people (65 years and above) only.

Furthermore, we applied polynomial distributed lag (PDL) models [23] to avoid problems related to co-linearity among lagged exposure variables. We investigated the lagged effects of air temperature up to 29 days on the whole population as well as the elderly people (65 years and above), for warm period and cold period. We constrained the shape of the distributed lag curve to follow a polynomial of 5^{th}-order in order to get a flexible functional form.

Sensitivity analyses

We used different threshold temperatures for a J-shaped function for the whole population and the elderly people. All other sensitivity analyses were done only for the whole population. Sensitivity analyses included the use of different values of smoothness for the functions of time trend. We also estimated the exposure-response functions using apparent temperature instead of mean air temperature, again considering two-day and 15-day averages. Moreover, we re-analyzed the air temperature effects on mortality for the shorter warm (April to September 2004 plus April to August 2005) or cold (March 2004 plus October 2004 to March 2005) period, during which the ambient particle data was available. We then also included the concentrations of $PM_{2.5}$ or UFP linearly as additional adjustments using a lag of two days, as this seemed to be the most appropriate lag for the association between air pollution and mortality (Breitner S et al. Unpublished work).

Results

Mortality data

There were 14,723 cardiovascular and 3,150 respiratory deaths in the warm period, while 17,493 and 4,007 in the cold period. Table 1 presents descriptive statistics for daily death counts by cause and age groups, for warm and cold periods. Deaths occurred within individuals of 65 years and older were 83% to 88% of all cases due to each cause. Daily death counts followed a seasonal pattern with peaks in winters and troughs in summers in the whole population as well as the aged people, while daily death counts for the group of 15 to 64 years had no obvious seasonal pattern (see Additional file 1, Figure S1).

Meteorology and air pollution

The descriptions of daily meteorological parameters and air pollutants by time period are shown in Table 2. Daily mean temperature, relative humidity, and barometric pressure also followed seasonal patterns, but each with different directions and magnitudes. Due to the fact that air pollution data was only available for a shorter time period, we couldn't confidently detect a seasonal pattern within this data (see Additional file 1, Figure S2).

Regression results

Among all the exposure-response functions (Figure 2 and Additional file 1, Figure S3) between two-day or 15-day average temperature and mortality of the whole population due to different causes, only the association between 15-day average temperature and mortality due to respiratory diseases in the warm period showed J-shaped curve (Figure 2), all the other functions could be considered as linear. The exposure-response functions for the elderly population had similar shapes (data not shown).

Based on the AIC, it appeared that 21.3°C was the most appropriate threshold temperature for the one J-shaped relationship. The RRs of mortality associated with mean temperature by time period and age group are shown in Table 3. In the warm period, heat effects were found for two-day average temperature and mortality due to all causes except for ischemic heart diseases. The strongest one was seen for respiratory mortality of the whole population. For elderly people, the RRs were lower for respiratory mortality, higher for cerebrovascular mortality, and almost the same amount for cardiovascular and cardiorespiratory mortality compared to the whole population. Heat effect was also found for 15-day average temperature and respiratory mortality, but with slightly higher effect size for elderly people. In the cold period, heat effects were also found, for both two-day and 15-day average temperature and respiratory mortality, also with higher effect size for the whole population compared to the elderly. Cold effects were found between 15-day average temperature and mortality due to all the other four causes, as well as between two-day average temperature and ischemic heart diseases mortality. The sizes of the effects for elderly people were all lower, although not much, compared to those for the whole population.

Figure 3 and Additional file 1, Figure S4 together show polynomial distributed lag curves with daily mean

Table 1 Descriptive statistics of daily death counts in the urban area of Beijing by time period, age group, and cause of death

	Whole population								65+ years							
	Warm period				Cold period				Warm period				Cold period			
Cause of death (ICD-10 code)	Mean ± SD	Min	Median	Max	Mean ± SD	Min	Median	Max	Mean ± SD	Min	Median	Max	Mean ± SD	Min	Median	Max
Cardiovascular diseases (I00-I99)	28 ± 9	8	29	51	38 ± 8	17	38	70	24 ± 7	6	24	44	32 ± 7	13	32	62
Respiratory diseases (J00-J99)	6 ± 3	0	6	17	9 ± 4	0	8	25	5 ± 3	0	5	15	8 ± 3	0	8	22
Ischemic heart diseases (I20-I25)	12 ± 4	1	12	26	16 ± 4	5	16	35	10 ± 4	0	10	23	14 ± 4	4	13	31
Cerebrovascular diseases (I60-I69)	12 ± 5	2	12	26	16 ± 5	4	16	33	10 ± 4	1	10	23	14 ± 4	3	13	29
Cardiorespiratory diseases (I00-J99)	34 ± 10	10	35	62	47 ± 10	23	47	85	29 ± 9	9	29	54	40 ± 9	18	40	75

temperature for mortality of the whole population due to all causes. In the warm period, heat effects were always observed within the first five days, whereas a delayed cold effect was observed only for cardiovascular mortality and disappeared with a lag of about two weeks. It is debatable if the described "delayed cold effect" is real or also partly reflects a harvesting effect (mortality displacement) following the heat effect that might have led to an accumulation of premature deaths in the susceptible subpopulation. In the cold period, a heat effect was also observed for respiratory mortality. Apparent one to eight days delayed cold effects were observed for cardiovascular, cerebrovascular and cardiorespiratory mortality, showing no significant following harvesting effect. The polynomial distributed lag curves restricted to the elderly population were similar to the ones for the whole population (data not shown).

Sensitivity analyses

The exposure-response curves for the whole population obtained by using different values of smoothness for the functions of time trend were quite robust (data not shown). When using different threshold temperatures (21.1, 21.2 and 21.4-21.7°C), the effects of 15-day average temperature on respiratory mortality of the whole population as well as the elderly people in the warm period all became slightly weaker; the size of the effect on elderly people was still higher than the one on the whole population (data not shown). The exposure-response functions for apparent temperature were similar to the ones derived from the mean temperature analyses (data not shown).

The exposure-response curves for the whole population during the shorter period showed almost no change compared to those in Figure 2 as well as in Additional

Table 2 Descriptive statistics of meteorological parameters and air pollutants in the urban area of Beijing by time period

Time period	Meteorological parameter/air pollutant	Mean ± SD	Min	1st Qu	Median	3rd Qu	Max
Warm	Air temperature (°C)	22.6 ± 4.8	6.9	19.8	23.3	26.2	32.1
period	Apparent temperature (°C)	23.6 ± 6.8	4.3	19.2	24.5	29.0	37.7
	Relative humidity (%)	60.5 ± 18.1	10	48	63	74	95
	Barometric pressure (hPa)	005.0 ± 59.5	989	1001	1005	1009	1023
	$PM_{2.5}$ (μg/m^3) [a]	105.7 ± 66.8	9.9	53.6	98.4	138.2	436.7
	UFP (number/cm^3) [a]	23940 ± 9442	9024	16920	21890	29310	73010
Cold	Air temperature (°C)	3.4 ± 6.3	-9.1	-1.5	2.3	8.2	18.7
Period	Apparent temperature (°C)	2.9 ± 5.5	-8.0	-1.3	1.9	6.4	18.1
	Relative humidity (%)	47.8 ± 20.8	12 31	46	63	96	
	Barometric pressure (hPa)	1021.0 ± 65.4	999	1016	1021	1025	1037
	$PM_{2.5}$ (μg/m^3) [a]	122.0 ± 94.6	13.9	47.5	90.3	184.4	413.4
	UFP (number/cm^3) [a]	30940 ± 10637	13460	24120	29150	35550	76280

a. Particulate air pollution data were available only for the period from March 2004 on.

$PM_{2.5}$: particulate matter (PM) with an aerodynamic diameter <2.5 μm.

UFP: ultrafine particles, particles with an aerodynamic diameter <0.1 μm.

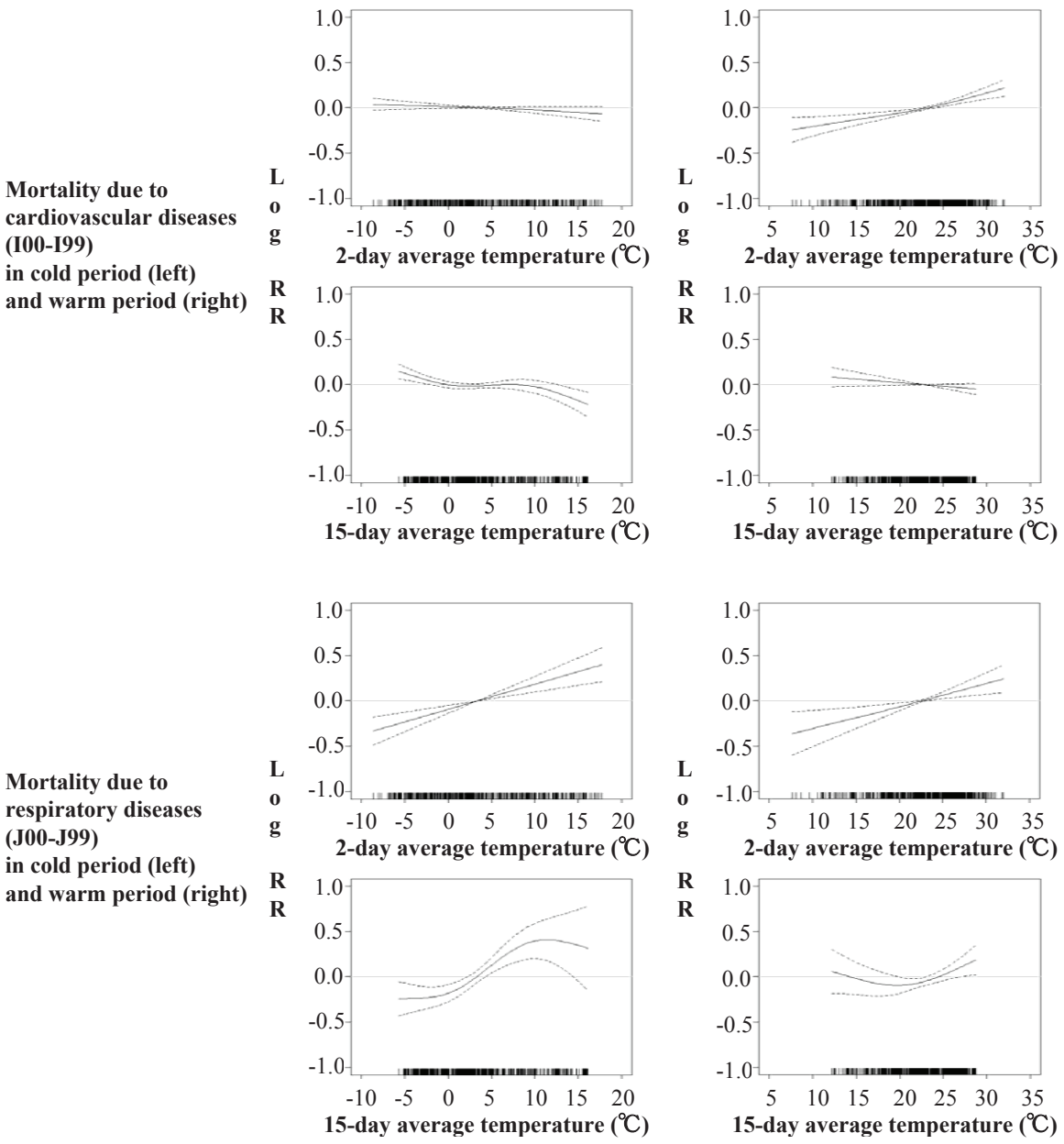

Figure 2 Exposure-response functions (together with 95% CIs) for two-day and 15-day average temperature and daily mortality of the whole population due to cardiovascular and respiratory diseases in the urban area of Beijing, by warm/cold period.

file 1, Figure S3, although the 95%CI of some curves became wider (data not shown). The correlations between temperature and $PM_{2.5}$ as well as UFP by time period are presented in Additional file 1, Table S2. As shown in Additional file 1, Table S3, compared with the effects obtained without adjustment for particle air pollution, there were no relevant changes for the effects of two-day average temperature after controlling for lag 2 of $PM_{2.5}$ or UFP, either in warm or in cold period. The effects of 15-day average temperature on cardiovascular and cardiorespiratory mortality in the warm period dropped and became non-significant after controlling for lag 2 of $PM_{2.5}$ or UFP; while which in the cold period only dropped after controlling for lag 2 of $PM_{2.5}$.

Discussion

Summary

We only observed J-shaped association between 15-day average temperature and respiratory mortality in the warm period; the other associations did not diverge from linearity. Immediate heat effects could be seen on every outcome in the warm period, even on respiratory

Table 3 Relative risks (RR, with 95% confidence intervals (CI)) of daily mortality in association with a 5°C increase of 2-day average temperature or a 5°C decrease of 15-day average temperature in the urban area of Beijing, by time period, age group and cause of death

	Warm period		Cold period	
	RR (95%CI) per 5°C increase of 2-day average temperature	RR (95%CI) per 5°C decrease of 15-day average temperature	RR (95%CI) per 5°C increase of 2-day average temperature	RR (95%CI) per 5°C decrease of 15-day average temperature
Whole population				
Cardiovascular disease (I00-I99)	1.098(1.057,1.140) *	1.040(0.990,1.093)	0.982(0.958,1.007)	1.057(1.022,1.094) *
Respiratory disease (J00-J99)	1.134(1.050,1.224) *	0.937(0.899,0.976) *[a]	1.149(1.078,1.224) *	0.851(0.767,0.944) *
Ischemic heart diseases (I20-I25)	1.020(0.975,1.067)	0.997(0.915,1.087)	0.947(0.914,0.982) *	1.123(1.057,1.193) *
Cerebrovascular diseases (I60-I69) Cardiorespiratory diseases (I00-J99)	1.047(1.000,1.097) *	1.025(0.950,1.106)	0.980(0.954,1.007)	1.036(1.002,1.071) *
	1.114(1.076,1.153) *	1.033(0.968,1.101)	1.009(0.983,1.035)	1.057(1.006,1.111) *
65+ 65+ years				
Cardiovascular disease (I00-I99)	1.093(1.048,1.139) *	1.038(0.978,1.101)	0.994(0.965,1.023)	1.054(1.016,1.093) *
Respiratory disease (J00-J99)	1.080(1.010,1.154) *	0.931(0.890,0.973) *[a]	1.128(1.056,1.204) *	0.887(0.798,0.988) *
Ischemic heart diseases (I20-I25)	1.016(0.968,1.067)	0.978(0.888,1.077)	0.954(0.920,0.990) *	1.116(1.046,1.191) *
Cerebrovascular diseases (I60-I69)	1.064(1.008,1.123) *	1.008(0.928,1.095)	0.999(0.961,1.038)	1.031(0.978,1.087)
Cardiorespiratory diseases (I00-J99)	1.117(1.075,1.160) *	1.010(0.941,1.084)	1.025(0.997,1.054)	1.042(1.001,1.085) *

a. Threshold model for a threshold of 21.3°C.

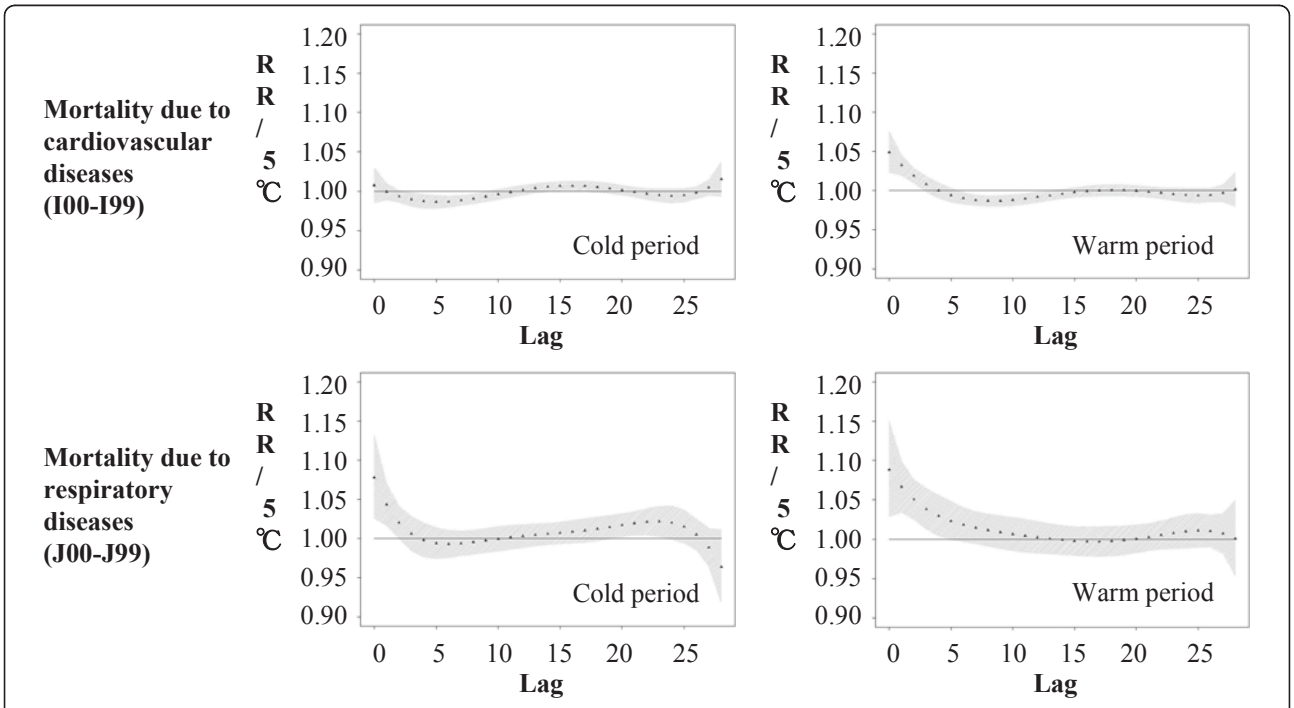

Figure 3 Relative risks (together with 95% CIs) of mortality of the whole population due to cardiovascular and respiratory diseases in association with a 5°C increase of temperature obtained with polynomial distributed lag models. Models were estimated with lags up to 29 days using a fifth degree polynomial for the cold period and the warm period. Indicated in each plot are the overall 29-day relative risks.

mortality in the cold period; while in the cold period, prolonged cold effects could be seen on every outcome except for respiratory mortality. Previous studies also found immediate heat effects and delayed cold effects [24-26]. The strongest immediate heat effect in the warm period was found in association with respiratory mortality, stronger for the whole population than for elderly people (65 years and older). However, the prolonged heat effect on respiratory mortality, as well as the immediate heat effects on cardiovascular, cerebrovascular and cardiorespiratory mortality in the warm period appeared with similar magnitudes for the two age groups. The strongest cold effect in the cold period was found in association with ischemic heart diseases mortality, with similar effect magnitudes for the whole as well as the elderly population. The prolonged cold effects on cardiovascular, cerebrovascular and cardiorespiratory mortality in the cold period appeared also with similar magnitudes for the two age groups. When considering $PM_{2.5}$ or UFP with lag 2 as confounders, there were no relevant changes for two-day average temperature effects, and a drop in 15-day average temperature effects on cardiovascular and cardiorespiratory mortalities

Heat effects

For the J-shaped exposure-response function, we found 21.3°C as our most appropriate threshold temperature. Curriero et al. [9] got 19°C to 21°C as "minimum mortality temperature" for New York (NY), Philadelphia (PA), Baltimore (MD), Washington, D.C., U.S., while Ballester et al. [27] got 22°C to 25°C for Valencia, Spain. Those cities are all located on similar latitudes (from 38° 54'N to 40°54'N) as Beijing (39°54'N), and "turning-point temperatures" were all close to each other. However, both authors observed V-shaped temperature-mortality functions.

For the convenience of comparison, we re-calculated the percentages based on a 1°C increase in lag 0-1 average temperature in the warm period, which resulted in 2.5% and 1.9% increases in respiratory and cardiovascular mortality, respectively. A study conducted in four Asian cities including Beijing reported by Chung et al. [7] found much higher threshold temperature (31°C) and temperature effect estimates (10.5% and 7.6% per 1°C increase, respectively). The fact that they used daily apparent temperature and also included the entire Beijing (including the suburban area with approximately 4,100,000 inhabitants, the fifth national census in 2000, http://www.stats.gov.cn/tjsj/ndsj/renkoupucha/2000pucha/pucha.htm) as their study area might be the reasons for the differences. However, Almeida et al. [28] reported estimates which are more comparable to ours in their study in Lisbon (38°42'N), Portugal (1.7% and 2.4% per 1°C increase, respectively) using also daily apparent temperature. There are also studies pointing out heat effect on ischemic mortality [26,29], which has not been found in our results.

Similar to the present study, several authors [7,27,30,31] observed greater effect on respiratory mortality than on cardiovascular mortality. In our dataset, daily death counts due to chronic lower respiratory diseases accounted for approximately half of respiratory diseases. However, our explorative analysis revealed that the magnitude of effect on chronic lower respiratory diseases mortality was as high as 98% of respiratory diseases mortality (data not shown). This may reflect that health status of people suffering from chronic respiratory diseases rapidly deteriorates during hot periods [31], which should be kept in mind and considered as priority when setting up preventive strategies during heat events.

After an analysis within the warm period, we found that the order (April to September in 2003 is the 1st warm period, April to September in 2004 is the 2nd one, and April to August in 2005 is the 3rd one.) showed no significant interaction with two-day average temperature, and therefore indicates that there was no heat effect modification by potential population adaption to heat or by possible increasing prevalence of air-conditioning year by year.

Cold effects

After re-calculation of the cold effects in the cold period, we found 1.1% and 2.3% increases in cardiovascular and ischemic heart disease mortality of our whole study population associated with 1°C decrease in 15-day average temperature, respectively. Analitis et al. [13] reported a higher estimate (a 1°C decrease induced a 1.7% increase in cardiovascular mortality in cold seasons) within the PHEWE project, which might be attributed to their use of a 16-day average of minimum apparent temperature. Moreover, the PHEWE project included very cold northern cities such as Helsinki and Stockholm. However, the Eurowinter study [11] found that people in cold regions such as Finland did not experience more winter excess mortality than people in mild regions such as London; Donaldson et al. [32] observed no excess ischemic heart disease mortality as temperature fell from 10.2°C to -48.2°C in Yakutsk, eastern Siberia. Both findings reflect the possibility of population acclimatization to climate and maybe also to future climate changes. However, the associations of mortality with environmental temperatures are also strongly modified by behavioural and social factors (e.g. clothing, housing conditions) [33]. In Beijing, the residential heating system works every year from November 15th to next March 15th, regardless of outside temperatures. However, we found no interaction between heating and 15-day average temperature after an analysis

within the cold period, showing that residential heating didn't modify the cold effect. This might also reflect that the study population exposed themselves to outdoor temperature although they probably spent a lot of time indoors.

Our study showed effects of increasing temperature on respiratory mortality even during cold season. This is contrary to our initial hypothesis, although the same situation has been observed by Kunst et al. [34] in The Netherlands. We therefore investigated the exposure-response functions between 2-day or 15-day average temperature and mortality due to influenza and pneumonia (J10-J18) and chronic lower respiratory diseases (J40-J47) (data not shown). Interestingly, we observed different effects regarding the two mortality categories. Whereas a decrease in temperature was associated with an increase in mortality due to influenza and pneumonia (as expected), we found opposite effects for mortality due to chronic lower respiratory diseases. In a previous study, Hampel et al. [35] have reported differences in the associations between a temperature decrease and several blood markers of inflammation and coagulation in patients with coronary diseases and patients with pulmonary diseases. They hypothesized that there might be different disease patterns as well as patient characteristics and medication responsible for the observed differences in the effects. Nevertheless, although we have no hint of a higher misdiagnosis for respiratory deaths than for deaths due to other causes, we cannot rule out this possibility.

Mechanism

Some studies [36,37] have shown that respiratory mortality increases more for individuals of 65 years and older compared to the general population when air temperature increases. One possible explanation is that aged people, especially COPD patients, are likely to have bad excess heat dissipation through circulatory adjustment. The heat stress increases their risk of developing pulmonary vascular resistance secondary to peripheral pooling of blood or hypovolemia [38]. However, our results didn't show a higher risk for respiratory mortality in individuals of 65 years and older, although half of the respiratory deaths in our study period were due to chronic lower respiratory diseases (J40-J47, mainly COPD, data not shown). It can be speculated that aged people in Beijing pay more attention and expose themselves less to heat. Possible mechanisms through which high temperature increases cardiovascular mortality include enlarged skin vessels and facilitated sweat, leading to falling blood pressure, increased cardiac work load and loss of fluid and salt, further leading to haemoconcentration [39], a "thrombosis promoting" state. The activation of coagulation and inhibition of fibrinolysis lead to diffuse microvascular thrombosis. Besides, heat-induced release of interleukin (IL)-1 or IL-6 into systemic circulation results in damage and hyperactivation of endothelial cells.

When temperature decreases, the cold receptors in skin are stimulated, the sympathetic nervous system regulates the catecholamine level to increases [40] and then the skin vessels constrict to reduce heat loss. Blood pressure increases consequently, and approximately 1l of blood plasma is shifted from skin and legs to central body parts, then removed by urine or shifted to extra-cellular space. The shift of blood plasma leads to haemoconcentration, then the concentrations of red and white blood cells, platelets, certain clotting factors, cholesterol and fibrinogen, as well as blood viscosity all go up, promoting clotting and thrombosis. Moreover, protein C, which is an anticoagulant, moves out to the extra-cellular space with blood plasma. The rise of blood pressure may lead to oxygen deficiency in the cardiac muscle which might induce myocardial ischemia or arrhythmias. If the rise of blood pressure is too sudden, there is the possibility of vascular spasm and a rupture of an atherosclerotic plaque that induces a thrombus [39,41-43].

Strengths and limitations

This study was based on a population as large as seven million inhabitants, among which the daily cardiorespiratory death count reached 40. This ensured the statistical power of the analysis. Moreover, we did sensitivity analyses by including $PM_{2.5}$ or UFP concentration levels as confounders. Both $PM_{2.5}$ and UFP [44] have been shown to be associated with mortality. As Beijing is known as one of the most polluted cities of the world, controlling for these two air pollutants was an important strength of the present study. Some other studies [36,45,46] also considered $PM_{2.5}$, PM_{10} or black smoke as confounders.

However, there are also limitations of the present study. Firstly, we got both, the meteorological and the air pollution data from only one monitoring station, which may lead to misclassification of the exposure level. This misclassification is non-differential and should bias the effect estimates towards the null. However, further data on daily meteorological parameters from an internet service (Weather Underground 2011) was obtained for a station located in the center of Beijing. Data from the two sources showed a good agreement (Pearson correlation coefficient >0.99 for air temperature). Secondly, ozone is a potentially important confounder to heat effect, but we had no such data for a sensitivity analysis.

Conclusions

Our results add to the evidence that both increases and decreases in air temperature are associated with an increased risk of cardiovascular mortality. The effects of heat were immediate while the ones of cold became predominant with longer time lags. The increase in air

temperature also immediately elevated the risk for respiratory mortality.

Additional material

Additional file 1: This file contains three additional tables and four additional figures to the manuscript. They are: - Additional file, Table S1. Confounders included in each base model - Additional file, Table S2. Correlations between air temperature and $PM_{2.5}$ as well as UFP in the urban area of Beijing - Additional file, Table S3. Relative risks (RR, with 95% confidence intervals (CI)) of daily mortality by cause of death and time period in association with a 5°C increase of 2-day average temperature or 5°C decrease of 15-day average temperature in the urban area of Beijing, before and after adjusting for $PM_{2.5}$ or UFP (linearly with the same moving averages as the temperature term, or linearly with lag 2) in the confounder model - Additional file, Figure S1. Daily death counts by cause of death and age group - Additional file, Figure S2. Daily mean air temperature, relative humidity, barometric pressure, and concentration of $PM_{2.5}$ and UFP - Additional file, Figure S3. Exposure-response relationships (together with 95% confidence intervals) for 2-day and 15-day average temperatures and daily mortality of the whole population due to ischemic heart diseases, cerebrovascular diseases and cardio-respiratory diseases in the urban area of Beijing, by time period - Additional file, Figure S4. Relative risks (together with 95% confidence intervals) of mortality of the whole population due to ischemic heart diseases, cerebrovascular diseases and cardiorespiratory diseases in association with a 5°C increase of temperature obtained with polynomial distributed lag models. Models were estimated with lags up to 29 days using a 5th degree polynomial for the cold period and the warm period. Indicated in each plot are the overall 29-day relative risks

List of abbreviations

PDL models: Polynomial Distributed Lag models; 95%CI: 95% Confidence Interval; ICD-10: International Classification of Diseases 10th Revision; $PM_{2.5}$: Particulate matter with an aerodynamic diameter <2.5 μm; UFP: Particulate matter with an aerodynamic diameter <0.1 μm; DOW: Day of the week; PACF: Partial Autocorrelation Function; DF: Degree of freedom; GCV: Generalized Cross Validation; RR: Relative Risk; COPD: Chronic Obstructive Pulmonary Disease; IL: Interleukin.

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Author details

[1]Helmholtz Zentrum Muenchen, German Research Center for Environmental Health, Institute of Epidemiology II, Neuherberg, Germany. [2]Ludwig-Maximilians-University Munich, IBE Chair of Epidemiology, Munich, Germany. [3]Peking University Health Science Center, School of Public Health, Beijing, China. [4]Helmholtz Centre for Environmental Research - UFZ, Core Facility Studies, Leipzig, Germany. [5]Physics Department, Leibniz Institute for Tropospheric Research (IfT), Leipzig, Germany. [6]Helmholtz Zentrum Muenchen, German Research Center for Environmental Health, Institute of Epidemiology I, Neuherberg, Germany.

Authors' contributions

LL performed the statistical analyses and drafted the manuscript. SB guided the statistical analyses and the interpretation of the results substantially, and revised the manuscript substantially and critically. XP was substantially involved in the acquisition of mortality, meteorological and air pollution data, and revised the manuscript critically. UF and AML were involved in the acquisition of respiratory mortality data, and revised the manuscript critically. AW was involved in the acquisition of air pollution data, and revised the manuscript critically. SvK guided the statistical analyses and revised the manuscript critically. HEW was substantially involved in the study design and revised the manuscript critically. AP was substantially involved in the study design, and guided the interpretation of the results, and revised the manuscript critically. AS guided the statistical analyses and the interpretation of the results substantially, and revised the manuscript substantially and critically. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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Additional file, Table S1. Confounders included in each base model *

Population and Outcome	Confounders						
	trend	season	day of the week (DOW)	public holiday	relative humidity	barometric pressure	other
Whole population							
Cardiovascular diseases (I00-I99)	penalized spline		dummy variable	dummy variable	penalized spline		
Respiratory disease (J00-J99)	penalized spline	dummy variable	dummy variable		penalized spline		
Ischemic heart diseases (I20-I25)	penalized spline	dummy variable	dummy variable		penalized spline		
Cerebrovascular diseases (I60-I69)	penalized spline	dummy variable	dummy variable		penalized spline		death count due to cereborvascular diseases of lag 1, linear
Cardiorespiratory disease (I00-J99)	penalized spline		dummy variable	dummy variable	penalized spline		
65+ years							
Cardiovascular diseases (I00-I99)	penalized spline		dummy variable	dummy variable	penalized spline		
Respiratory disease (J00-J99)	penalized spline	dummy variable	dummy variable		penalized spline		
Ischemic heart diseases (I20-I25)	penalized spline	dummy variable	dummy variable		penalized spline		
Cerebrovascular diseases (I60-I69)	penalized spline	dummy variable	dummy variable		penalized spline		death count due to cereborvascular diseases of lag 1, linear
Cardiorespiratory disease (I00-J99)	penalized spline	dummy variable	dummy variable	dummy variable	penalized spline		

***** We used the same confounder models for the warm and cold periods; for the sensitivity analysis we only re-adjusted the DF for trend in every model, because of less days, on which the air pollution data was available.

Additional file, Table S2. Correlations between air temperature and $PM_{2.5}$ as well as UFP in the urban area of Beijing

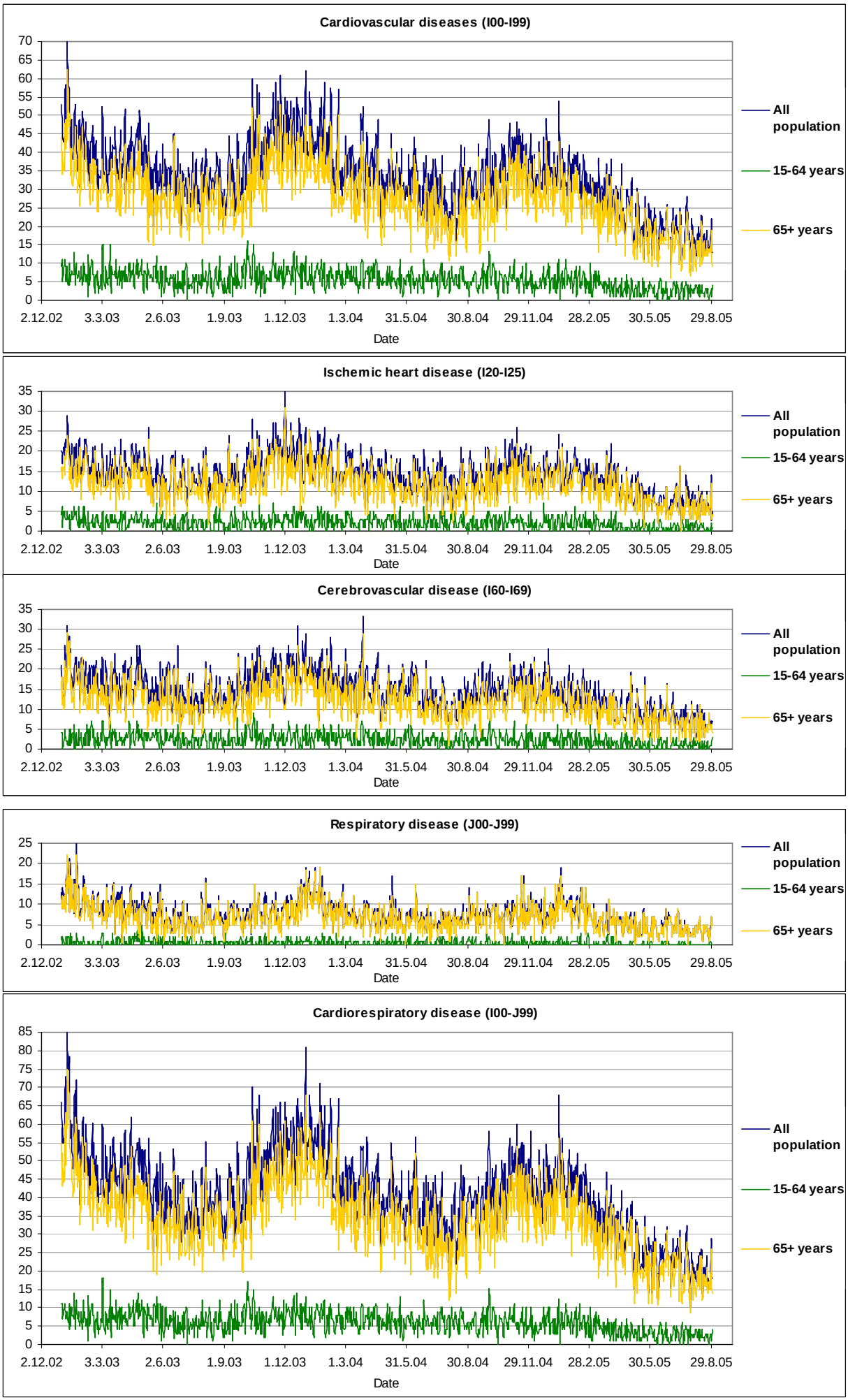
	$PM_{2.5}$ ($\mu g/m^3$)	UFP (number/cm^3)
Warm period		
Air temperature (℃)	0.222	-0.297
$PM_{2.5}$ ($\mu g/m^3$)		-0.348
Cold period		
Air temperature (℃)	0.092	-0.028
$PM_{2.5}$ ($\mu g/m^3$)		-0.417

Additional file, Table S3. Relative risks (RR, with 95% confidence intervals (CI)) of daily mortality by cause of death and time period in association with a 5°C increase of 2-day average temperature or 5°C decrease of 15-day average temperature in the urban area of Beijing , before and after adjusting for $PM_{2.5}$ or UFP (linearly with the same moving averages as the temperature term, or linearly with lag 2) in the confounder model

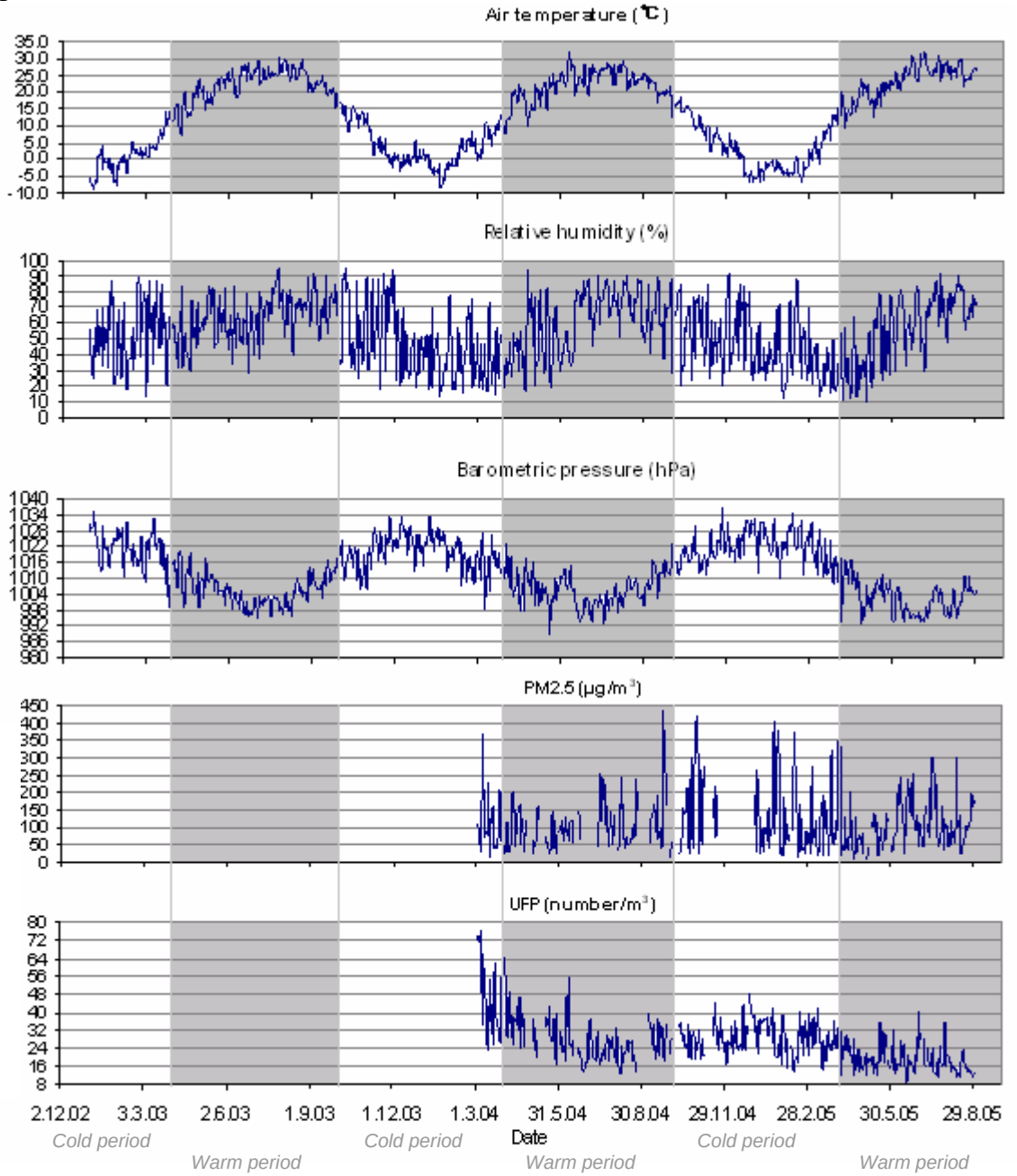
	Warm period		Cold period	
	RR (95%CI) per 5°C **increase** of 2-day average temperature	RR (95%CI) per 5°C **decrease** of 15-day average temperature	RR (95%CI) per 5°C **increase** of 2-day average temperature	RR (95%CI) per 5°C **decrease** of 15-day average temperature
The whole population				
No adjustment for air pollutants				
Cardiovascular disease (I00-I99)	1.066(1.016,1.118) *	1.192(1.051,1.352) *	0.969(0.945,0.994) *	1.101(1.003,1.209) *
Respiratory disease (J00-J99)	1.079(0.992,1.174)	0.940(0.891,0.991) *[a]	1.100(0.995,1.216)	0.930(0.769,1.125)
Ischemic heart diseases (I20-I25)	0.999(0.941,1.061)	1.064(0.964,1.175)	0.981(0.945,1.018)	1.004(0.947,1.066)
Cerebrovascular diseases (I60-I69)	1.069(1.007,1.136) *	1.033(0.936,1.141)	0.978(0.941,1.016)	1.018(0.974,1.065)
Cardiorespiratory diseases (I00-J99)	1.083(1.036,1.133) *	1.103(1.002,1.215) *	1.009(0.983,1.035)	1.057(1.006,1.111) *
$PM_{2.5}$ (linearly with lag 2)				
Cardiovascular disease (I00-I99)	1.082(1.024,1.144) *	1.068(0.991,1.150)	0.982(0.930,1.037)	1.041(0.944,1.147)
Respiratory disease (J00-J99)	1.079(0.986,1.181)	0.929(0.877,0.984) *[a]	1.105(0.963,1.267)	0.907(0.702,1.172)
Ischemic heart diseases (I20-I25)	1.003(0.939,1.070)	1.029(0.938,1.129)	0.962(0.920,1.005)	1.021(0.946,1.103)
Cerebrovascular diseases (I60-I69)	1.072(1.004,1.144) *	1.000(0.899,1.113)	1.001(0.956,1.048)	1.002(0.953,1.054)
Cardiorespiratory diseases (I00-J99)	1.105(1.050,1.164) *	1.069(0.987,1.158)	1.010(0.950,1.074)	1.013(0.898,1.143)
UFP (linearly with lag 2)				
Cardiovascular disease (I00-I99)	1.080(1.027,1.136) *	1.052(0.990,1.118)	0.970(0.944,0.998) *	1.118(1.006,1.242) *
Respiratory disease (J00-J99)	1.078(0.988,1.177)	0.933(0.880,0.989) *[a]	1.115(1.000,1.244) *	1.049(0.958,1.148)
Ischemic heart diseases (I20-I25)	1.020(0.957,1.086)	1.017(0.929,1.113)	0.971(0.933,1.011)	1.023(0.961,1.190)
Cerebrovascular diseases (I60-I69)	1.073(1.008,1.142) *	1.016(0.914,1.129)	0.987(0.946,1.029)	1.005(0.957,1.055)
Cardiorespiratory diseases (I00-J99)	1.094(1.045,1.146) *	1.064(0.990,1.142)	1.010(0.963,1.059)	1.077(0.970,1.194)

a. Threshold model for a threshold of 21.3°C.

Additional file, Figure S1. Daily death counts by cause of death and age group

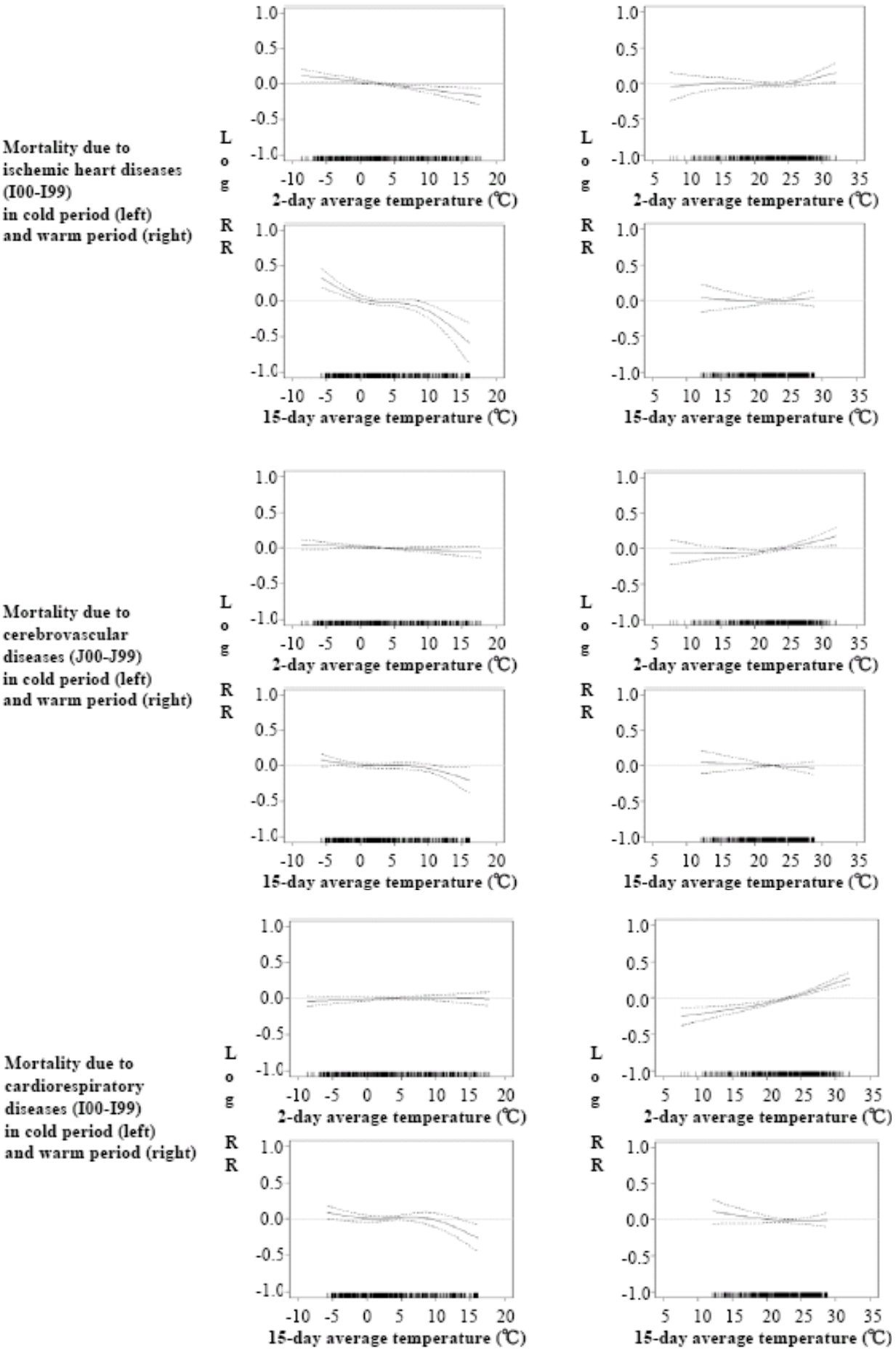


Additional file, Figure S2. Daily mean air temperature, relative humidity, barometric pressure, and concentration of $PM_{2.5}$† and UFP†

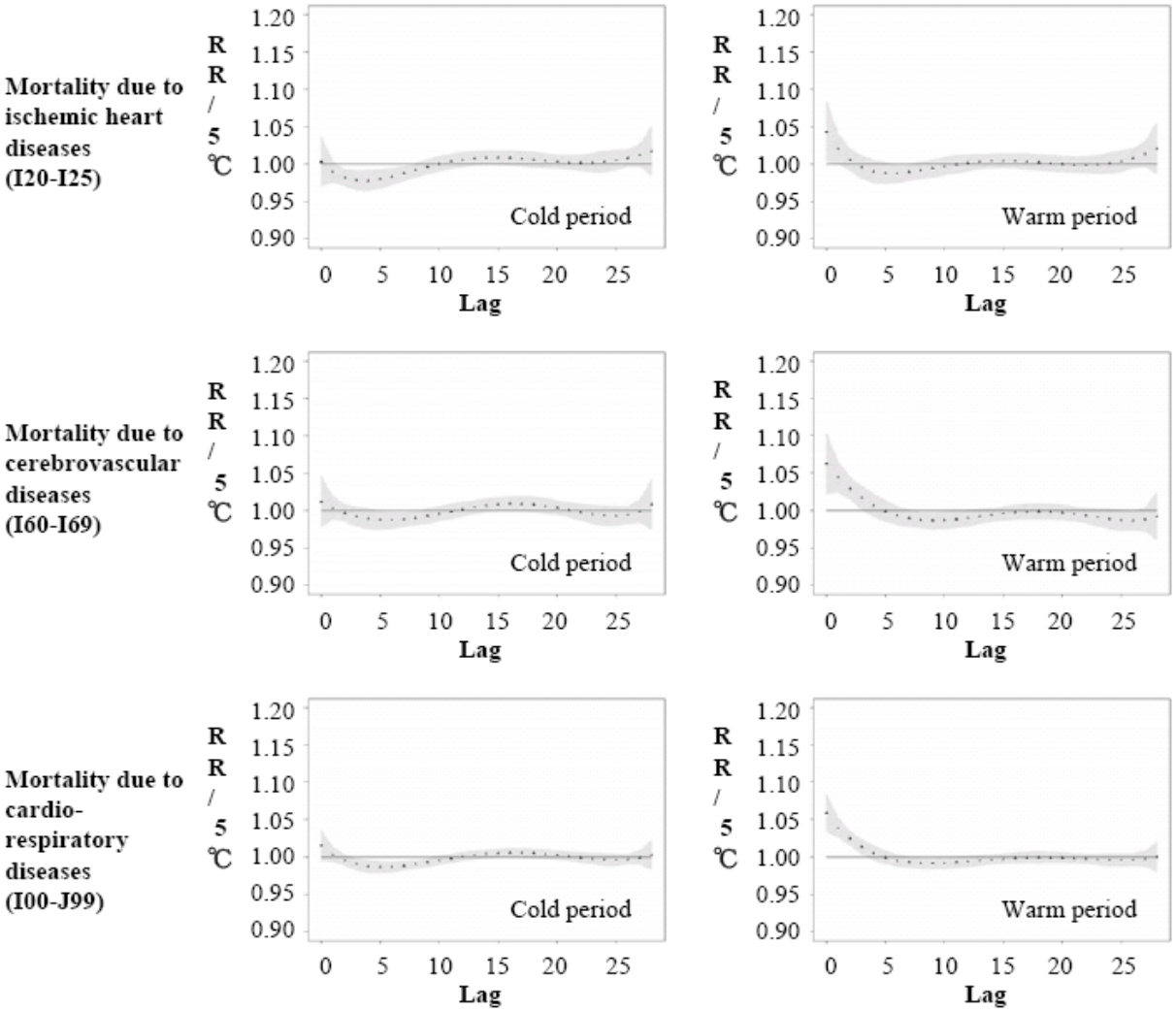


† Particle data were available only for the period March 2004 until August 2005.

Additional file, Figure S3. Exposure-response relationships (together with 95% confidence intervals) for 2-day and 15-day average temperatures and daily mortality of the whole population due to ischemic heart diseases, cerebrovascular diseases and cardio-respiratory diseases in the urban area of Beijing, by time period



Additional file, Figure S4. Relative risks (together with 95% confidence intervals) of mortality of the whole population due to ischemic heart diseases, cerebrovascular diseases and cardiorespiratory diseases in association with a 5° C increase of temperature obtained with polynomial distributed lag models. Models were estimated with lags up to 29 days using a 5th degree polynomial for the cold period and the warm period. Indicated in each plot are the overall 29-day relative risks



5 Sub-micrometer particulate air pollution and cardiovascular mortality in Beijing, China

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Sub-micrometer particulate air pollution and cardiovascular mortality in Beijing, China

Susanne Breitner [a,b,*], Liqun Liu [a,b,c], Josef Cyrys [a,d], Irene Brüske [e], Ulrich Franck [f], Uwe Schlink [f], Arne Marian Leitte [f], Olf Herbarth [f,g], Alfred Wiedensohler [h], Birgit Wehner [h], Min Hu [i], Xiao-Chuan Pan [c], H-Erich Wichmann [b,e], Annette Peters [a,j]

[a] Helmholtz Zentrum München - German Research Center for Environmental Health, Institute of Epidemiology II, Neuherberg, Germany
[b] Ludwig-Maximilians-Universität München, IBE Chair of Epidemiology, Munich, Germany
[c] Peking University, Health Science Center, School of Public Health, Beijing, China
[d] University of Augsburg, Environmental Science Center, Augsburg, Germany
[e] Helmholtz Zentrum München - German Research Center for Environmental Health, Institute of Epidemiology I, Neuherberg, Germany
[f] Helmholtz Centre for Environmental Research — UFZ, Core Facility Studies, Leipzig, Germany
[g] University of Leipzig, Leipzig, Germany
[h] Leibniz Institute for Tropospheric Research (IfT), Leipzig, Germany
[i] Peking University, College of Environmental Sciences and Engineering, State Key Joint Laboratory of Environmental Simulation and Pollution Control, Beijing, China
[j] Focus Network Nanoparticles and Health (NanoHealth), Helmholtz Zentrum München - German Research Center for Environmental Health, Neuherberg, Germany

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ABSTRACT

Background: While the link between particulate matter and cardiovascular mortality is well established, it is not fully investigated and understood which properties of the aerosol might be responsible for the health effects, especially in polluted mega-city areas.
Objectives: Our goal was to explore the association between daily cardiovascular mortality and different particle metrics in the sub-micrometer range in Beijing, China.
Methods: We obtained daily counts of cause-specific cardiovascular deaths in the Beijing urban area for the period March 2004 to August 2005. Concurrently, continuous measurements of particle number size distributions were performed. Particle number concentrations (NC) between 0.003 μm and 0.8 μm were converted to particle mass and surface area concentrations assuming spherical particles. Semi-parametric Poisson regression models adjusting for trend, seasonality, day of the week, and meteorology were used to estimate immediate, delayed and cumulative particle effects. Additionally, effect modification by air mass origin was investigated.
Results: We observed associations between daily cardiovascular mortality and particle NC for a 2-days delay. Moreover, nearly all particle metrics showed 2-days delayed associations with ischemic heart disease mortality. The strongest association was found for particle NC in the size range 0.03–0.1 μm (7.1% increase in daily mortality with a 95%-confidence interval of 2.9%–11.5%, per an increase of 6250 particles/cm^3). Results for surface and mass concentrations with a lag of two days indicated effect modification by air mass origin, whereas effects of particle NC were not modified.
Conclusions: Results show an elevated risk of cardiovascular mortality in Beijing from short-term exposure to particulate air pollution in the sub-micrometer range. Results also indicate that locally produced smaller particles and regionally transported particles may exhibit different effects in Beijing.

Abbreviations: ACP, accumulation mode particles; CDC, Center for Disease Control; CPC, Condensation Particle Counter; CI, confidence interval; DF, degrees of freedom; DMA, Differential Mobility Analyzer; GCV, generalized cross validation; ICD-10, International Classification of Disease, Tenth Revision; IQR, interquartile range; MC, mass concentrations; MC_1, particle MC for particles in the range below 0.8 μm; PAH, polycyclic aromatic hydrocarbons; PACF, partial autocorrelation coefficient; PKU, Peking University; PM, particulate matter; PM_{10}, particulate matter with an aerodynamic diameter <10 μm; $PM_{2.5}$, particulate matter with an aerodynamic diameter <2.5 μm; PM_1, particulate matter with an aerodynamic diameter <1 μm; NC, number concentrations; NC_1, particle NC for particles in the range below 0.8 μm; SC, surface area concentrations; SC_1, particle SC for particles in the range below 0.8 μm; TDMPS, Twin Differential Mobility Particle Sizer; UFP, ultrafine particles (particles with an aerodynamic diameter <0.1 μm).

* Corresponding author at: Helmholtz Zentrum München - German Research Center for Environmental Health, Institute of Epidemiology II, Ingolstaedter Landstr. 1, 85764 Neuherberg, Germany. Tel.: +49 89 3187 4481; fax: +49 3187 3380.
E-mail address: susanne.breitner@helmholtz-muenchen.de (S. Breitner).

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1. Introduction

Cardiovascular morbidity and mortality have been associated with mass concentrations of particulate matter (PM) with an aerodynamic diameter smaller than 10 μm or 2.5 μm (PM_{10} or $PM_{2.5}$, respectively) (Brook et al., 2010; Pope and Dockery, 2006). Nevertheless, questions remain regarding the physical or chemical properties of PM responsible for the health effects. Besides chemical composition, particle characteristics like size, number concentration, and surface area are discussed to determine the potential to induce inflammatory injury, oxidative damage, and other biological effects (Brook, 2008; Valavanidis et al., 2008).

In particular, ultrafine particles (particles with an aerodynamic diameter less than 100 nm; UFP) may contribute to the observed health effects because of their high particle number concentrations and larger active surface area; thus, having a high deposition efficiency in the pulmonary region (Brook, 2008; Delfino et al., 2005; Pekkanen and Kulmala, 2004; Peters et al., 2006). UFP can be further divided into two subfractions: Nucleation mode particles and Aitken mode particles. Nucleation mode particles are often defined as particles with an aerodynamic diameter less than <0.03 μm, whereas Aitken mode particles are then defined as particles with an aerodynamic diameter between 0.03 and 0.1 μm; see, for example, Halonen et al. (2009) or Peters et al. (2009) (it should be noted, however, that there are also studies using different size ranges for Nucleation mode and Aitken mode particles; see, for example, Yue et al., 2009 or Branis et al., 2010). Both sub-fractions differ in dynamics and may also have varying effects on health. Nucleation mode particles mainly result from gas-to-particle conversion of different chemical compounds. Aitken mode particles, on the other hand, are directly emitted from combustion processes, such as soot particles from car traffic. They may also result from condensational growth and coagulation of nucleation mode particles. Aerosols in the accumulation mode (0.1–0.8 μm; ACP) are generally produced by the coagulation of smaller particles and by the heterogeneous nucleation of condensable vapors onto existing aerosol particles.

Due to the limited availability of appropriate measurement data, there are only few epidemiological studies on the short-term associations between daily cardiovascular mortality and more accurately size-segregated particles (Atkinson et al., 2010; Branis et al., 2010; Halonen et al., 2009; Peters et al., 2009; Stölzel et al., 2003). Nearly all studies on health effects of smaller particles have been conducted in North America and Europe; there remains a need for replicating these findings in China, as there are different concentration levels. There might be also differences in specific sources and their proportional contributions to the air pollution mixture, which might influence size distribution and chemical composition of particles and the associations between particles and human health.

This study aimed to investigate whether daily changes in ambient concentrations of particle size fractions in the sub-micrometer range are associated with cause-specific cardiovascular mortality in different age groups in Beijing, China. Moreover, we aimed to better delineate whether particle number, mass, or surface area concentrations may be responsible for the associations. Additionally, we investigated modifications of air pollution effects by air mass origin defined by backward trajectories.

2. Material and methods

2.1. Study area and period

The study was conducted in the urban area of Beijing, China, from March 4, 2004 to August 31, 2005 (546 days). Beijing is located about 150 km southeast of the Bohai Sea, and is surrounded by mountains in the north, northwest, and west. In 2005, the Beijing urban area comprised eight districts with a total area of about 1368 km^2 and had a population size of approximately 10 million inhabitants (Beijing Municipal Bureau of Statistics, 2006) [Appendix A, Fig. A.1].

2.2. Mortality data

Cardiovascular death count data for adult residents (age ≥15 years) were obtained from the Beijing Center for Disease Control (CDC) for the urban area of Beijing. The Beijing CDC provided data including five-year age groups and the code for the underlying cause of death which was classified according to the International Classification of Disease, 10th Revision (ICD-10). Cardiovascular mortality was divided into the following causes: cardiovascular diseases (ICD-10: I00–I99), ischemic diseases (ICD-10: I20–I25), and stroke (ICD-10: I60–I69). We did not consider further disease-specific analysis due to the low number of cases in the relevant subgroups. Age-specific death counts were combined to adult mortality (age ≥15 years) as well as mortality of elderly people (age ≥65 years).

2.3. Air pollution and meteorological data

Data on particle number size distribution were taken on the campus area of the Peking University (PKU), located in the Haidian district in the north western part of Beijing [Appendix A, Fig. A.1]. The setup of the measurement station was already described in detail elsewhere (e.g. Wehner et al., 2004, 2008). The measurement station can be classified as an urban background station (Wehner et al., 2004) and is a few hundred meters away from a major road, the fourth ring road. The campus is primarily a residential and commercial area without any industrial or agricultural activities. Local emission sources within a radius of 1 km were vehicular traffic, fuel combustion by domestic cooking and heating, and construction. Average particle number size distributions at the PKU measurement site and another regional measurement site, located around 50 km to the south of the PKU, were shown to be similar in summer (Yue et al., 2009), especially during regional pollution periods, confirming that the PKU measurement site may be considered as an urban background station.

In this study, we obtained data on number size distributions in the size range between 0.003 and 0.8 μm. A Twin Differential Mobility Particle Sizer (TDMPS) system (Birmili et al., 1999) was used to sample the size distributions between 0.003 and 0.8 μm (mobility diameter). In this instrument, aerosol particles are charged in a bipolar diffusion charger, leading to a size-dependent charge equilibrium. For each particle size, the fractions of positively and negatively as well as for uncharged, singly and multiple charged particles are known. In a Differential Mobility Analyzer (DMA), fractions of particles with the same electrical mobility are selected by scanning the voltage between the electrodes of the capacitor. The mobility distribution is determined by measuring the number concentration of the selected electrical mobilities by a Condensation Particle Counter (CPC). Knowing the bipolar charged distribution and the transfer function of the DMA, the real number size distribution can be calculated. The TDMPS used in this study consists of two mobility size spectrometers. The measured mobility distribution were merged here and then inverted as once to the number size distribution. Losses by diffusion of particles smaller 0.1 μm were corrected after the inversion to obtain the final number size distribution. A low-flow PM_{10} inlet was used to minimize contamination by large dust particles and data were corrected for sedimentation within the inlet line (Wehner et al., 2004).

To ensure the data quality, checks of the TDMPS systems were done on a regular base. First, the flow rates of the DMAs and CPCs were checked weekly. Flow sensors were recalibrated if necessary. Furthermore, sizing of the mobility size spectrometers were checked every three month using latex particles of 200 as an independent check of the sheath air flow of the DMA. The accuracy of the date was about +/−10% in terms of the concentration and 2% in terms of sizing. The relative humidity within the systems was kept below 30%

by adding a silica-gel dryer in the inlet line and also in the sheath air cycle to reduce dependence of measured properties on relative humidity (Wu et al., 2008) and avoid condensation of water in the inlet systems during warm and humid days, especially during summertime.

Number size distributions were converted to particle number concentrations (NC), particle surface area concentrations (SC) assuming spherical particles (Leitte et al., 2011) and then to particle mass concentrations (MC) assuming a density of 1.5 g/cm³ (Wehner et al., 2008). For the present analysis, we computed daily means of these particle metrics for several size ranges: 0.003–0.03 μm (Nucleation mode), 0.03–0.1 μm (Aitken mode), 0.1–0.3 μm, 0.3–0.8 μm, and 0.003–0.8 μm.

As shown in Fig. 1, particles in the ultrafine range were mainly represented by number, whereas ACP (0.1–0.8 μm) were mostly represented by mass and surface area. Based on these proportions, for Nucleation and Aitken mode particles we only analyzed NC in association with mortality, whereas for ACP we only investigated MC and SC.

Daily meteorological data were available at two locations, one in a distance of about 400 m from the air sampling site, the second in a distance of about 30 km of the air measurement station (China meteorological data sharing service system, World Meteorological Organization (WMO) station number 54511, see Appendix A, Fig. A.1). The data obtained included average daily temperature and relative humidity and were highly correlated (Spearman correlation coefficients between the two data sources were around 0.99). As the weather data obtained nearby the particle monitoring site contained missing values, we used data from the WMO station.

Data on air mass history could be obtained from an analysis by Wehner et al. (2008). Back-trajectories with a length of 72 h were used to determine the origin of air masses. Classification of the back-trajectories by cluster analysis was applied which resulted in 6 different clusters (cluster 1–cluster 6). Clusters 1–4 represent air masses arriving from northerly directions with average to high wind speed, while clusters 5 and 6 consist of air masses coming from the south with low wind speed to stagnant conditions.

2.4. Statistical analysis

2.4.1. Statistical model

We used quasi-likelihood estimation within the context of Poisson semi-parametric regression models to model the natural logarithm of the expected daily death counts as a function of the predictor variables.

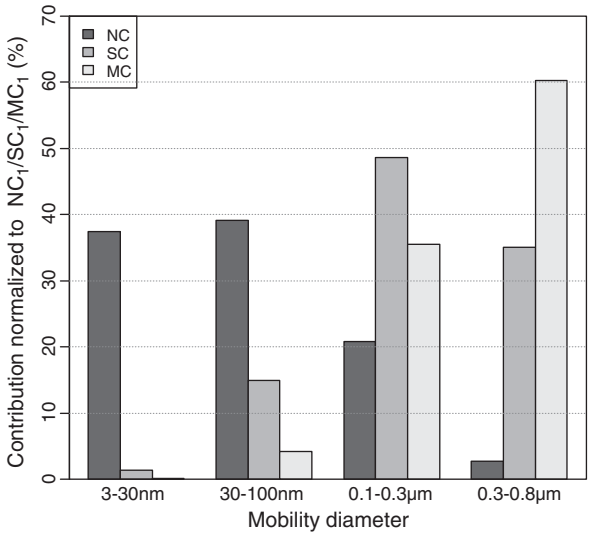

Fig. 1. Particle size ranges and contributions to number (NC), surface (SC), and mass (MC) concentration.

Penalized splines based on B-spline bases were used to allow for non-linear confounding effects (Eilers and Marx, 1996).

In a first step, a base model was built without air pollutants. To control for systematic variation over time, we introduced a time trend and seasonality term as well as dummy variables for day of the week and public holidays. As other potential confounders we considered daily mean air temperature and relative humidity.

To ensure sufficient adjustment for season and meteorology, time trend and air temperature were forced into the base model. The absolute value of the sum of the partial autocorrelation function (PACF) was used to guide the selection of degrees of freedom (DF) for time trend (Touloumi et al., 2006). Model selection for the other confounder variables was carried out by minimizing the Generalized Cross Validation (GCV) criterion (Wood, 2006). For the meteorological parameters we considered lags 0 to 14, the mean of lags 0 and 1, the mean of lags 0–4, and the mean of lags 0–14.

In the final confounder model, the number of DF for the smooth function of time trend was re-adjusted, as many of the meteorological variables exhibit seasonal patterns themselves and, hence, capture part of the observed seasonal trends in the outcome (Touloumi et al., 2004). The final confounder model consisted of smooth functions of trend, 2-day average air temperature (representing the effect of higher temperatures), 15-day average air temperature (representing the effect of colder temperatures), and same-day relative humidity as well as day of the week.

In the last step of the analysis, particle metrics were added separately to the models and associations estimated linearly. We analyzed single-day lags from 0 to 3 days, and the average of days 0–4 (5-day mean). We also investigated the associations between air pollution and cardiovascular mortality for elderly people (≥65 years) only. Further, two-pollutant models examined the independent effects of particle metrics. To avoid problems with collinearity, these analyses were only conducted when the pollutants' inter-correlation was <0.5. Lags with the absolute greatest single-day effect were included in these two-pollutant models. Finally, we also investigated modification of the particle metric effects by air mass origin. For our analyses, we defined a dummy variable with ones when air masses were classified into stagnant and southern air masses (clusters 5 and 6 obtained by Wehner et al. 2008) versus zeros when air masses arrived from northerly directions with average to high wind speed (clusters 1 to 4). Interaction terms were added to the models in order to estimate the particle effects of the corresponding subgroups. We used a likelihood ratio test to determine whether there were indeed differences between the subgroups.

2.4.2. Sensitivity analyses

To explore the robustness of the models, we performed sensitivity analyses using different values of smoothness for the functions of time trend and air temperature, but also a different air temperature measure, apparent temperature. Moreover, we excluded all days, which have been previously identified as days with dust events (Wu et al., 2009). We further checked the exposure–response functions for deviations from linearity. Therefore, we replaced the linear term of the particle metrics with a fixed 4DF regression spline. A likelihood ratio test with 3DF that compares the original main model with the smoothed model and visual inspection were used to assess whether the smoothed exposure–response curve resembles a straight line. Additionally, we compared different values of smoothness by the generalized cross-validation (GCV) score.

Data were analyzed using the package "mgcv" version 1.5.5 in the statistical software R version 2.9.2 (R Development Core Team, 2009). Effect estimates are presented as percent change in mortality together with 95% confidence intervals (CI) based on an increase in air pollution concentrations from the first to the third quartile [interquartile range (IQR)].

3. Results

3.1. Descriptives

Overall, there were 15,769 cardiovascular deaths during the study period from March 4, 2004 to August 31, 2005. Ischemic heart diseases and cerebrovascular diseases were the two major death causes for cardiovascular mortality; each category accounted for around 42% of the deaths. Elderly people (≥65 years) accounted for at least 75% for all causes of death.

Descriptive parameters of death counts, particle metrics, and meteorological data are provided in Table 1. Daily death counts and meteorological variables followed a seasonal pattern (data not shown). The time series of size-segregated particle NC, MC, and SC contained some gaps due to measurement equipment maintenance. Overall, 11% of the TDMPS measurements were missing (Table 1). For Aitken mode particles, there were almost no differences in NC when air masses came from different directions (Table 1), whereas for particles in the range below 0.8 μm (NC_1) NC were slightly higher for stagnant and southern air masses. The same pattern was seen for SC and MC of particles below 0.8 μm (SC_1 or MC_1, respectively).

Most of the particle number concentration (76.5%) was in the UFP fraction, with nearly same proportions for Nucleation particles and Aitken mode particles (37.4% and 39.1%, respectively) (Fig. 1). In contrast, most of the surface area (83.7%) and nearly all mass (95.7%) were attributable to particles in the size range of 0.1–0.3 μm and 0.3–0.8 μm.

Nucleation mode particles were not correlated with Aitken mode particles (Spearman correlation coefficient $r = 0.17$) and moderately negatively correlated with nearly all other air pollution parameters and relative humidity ($-0.55 \leq r \leq -0.67$, see Appendix A, Table A.1). Aitken mode particles and particles in the range below 0.8 μm (NC_1) were not or only slightly correlated with all other parameters, whereas MC and SC were highly correlated with each other in the accumulation mode range.

3.2. Regression results

Regression results showed an association between daily cardiovascular mortality and particle NC in the Aitken mode range as well as NC_1 (Table 2). We observed the strongest associations for a delay of two days. When mortality due to ischemic heart diseases was separately analyzed, we found a consistent 2-days-delayed association with all particle metrics except with particle NC in the nucleation mode range (Table 2). Cerebrovascular mortality only had borderline significant associations with particle NC (data not shown) with a delay of two days as well as with the 5-day average.

Associations between particle metrics and cardiovascular mortality for elderly people (≥65 years) showed similar effects compared to the results found for the adult population (Fig. 2). The same was the case for mortality due to ischemic heart diseases (Fig. 2) as well as for mortality due to cerebrovascular diseases (data not shown).

Two-pollutant models showed that the association between cardiovascular mortality and Aitken mode particles as well as particle NC in the range below 0.8 μm (NC_1) was not confounded by any other particle metrics (Table 3). For Aitken mode particles, risk estimates in ischemic heart disease mortality were also essentially unchanged or only decreased slightly, while the effects for SC and MC diminished (Table 3). In two-pollutant models with NC of particles in the range below 0.8 μm (NC_1) associations for all particle metrics slightly decreased, but were still significant.

Associations between cardiovascular and ischemic heart disease mortality and particle NC in the Aitken mode range and in the range below 0.8 μm (NC_1) were not modified by air mass origin (Fig. 3). In contrast, results indicated that mortality effects of SC and MC with a lag of two days were stronger for stagnant and southern air masses

Table 1
Descriptive statistics for mortality counts, particle number (NC), particle surface (SC), and particle mass (MC) concentrations, and meteorological parameters in the urban area of Beijing, China, from March 2004 to August 2005.

	Min	25%	50%	75%	Max
Deaths					
Cardiovascular disease (I00–I99)	8	23	30	35	54
Coronary heart disease (I20–I25)	1	9	12	15	26
Cerebrovascular disease (I60–I69)	2	9	12	15	33
Pollutants [a]					
NC Nucleation mode (<0.03 μm) [cm^{-3}]	2522	6917	10,430	17,120	61,930
NC Aitken mode (0.03–0.1 μm) [cm^{-3}]	2103	10,130	13,260	16,380	31,080
NC_1 (<0.8 μm) [cm^{-3}]	12,370	26,900	33,500	40,690	86,820
SC 0.1–0.3 μm [$\mu m^2\ cm^{-3}$]	67.1	350.8	567.0	819.6	2076.0
SC 0.3–0.8 μm [$\mu m^2\ cm^{-3}$]	35.6	192.4	400.2	679.1	2631.0
SC_1 (<0.8 μm) [$\mu m^2\ cm^{-3}$]	137.5	713.3	1155.0	1687.0	4849.0
MC 0.1–0.3 μm [$\mu g/m^3$]	3.2	16.2	27.8	40.2	105.1
MC 0.3–0.8 μm [$\mu g/m^3$]	4.1	22.5	47.3	80.4	319.4
MC_1 (<0.8 μm) [$\mu g/m^3$]	8.0	42.1	78.4	123.9	422.9
Pollutants [a] — Air mass origin					
NC Aitken mode (0.03–0.1 μm) [cm^{-3}]					
Southern and stagnant air masses	2135	9516	12,500	16,500	30,500
Northerly directions with average to high wind speed	2103	10,270	13,390	16,410	28,970
NC_1 (<0.8 μm) [cm^{-3}]					
Southern and stagnant air masses	12,720	27,090	35,500	41,470	86,820
Northerly directions with average to high wind speed	15,020	26,200	33,100	40,550	78,640
SC_1 (<0.8 μm) [$\mu m^2\ cm^{-3}$]					
Southern and stagnant air masses	147.8	829.2	1181.0	1728.0	4849.0
Northerly directions with average to high wind speed	144.3	700.7	1148.0	1682.0	4796.0
MC_1 (<0.8 μm) [$\mu g/m^3$]					
Southern and stagnant air masses	9.2	48.9	82.0	136.8	405.0
Northerly directions with average to high wind speed	8.8	40.5	78.0	123.9	422.9
Meteorological variables					
Air temperature [°C]	−7.1	7.60	18.7	24.3	32.1
Relative humidity [%]	10.0	36.0	56.0	73.0	93.0

[a] 11% of the daily values are missing.

Table 2
Percentage of change (95%-confidence interval) in cardiovascular (ICD-10 I00–I99) and ischemic heart disease (ICD-10 I20–I25) mortality per an interquartile[a] increase in pollutants in Beijing, from March 2004 to August 2005.[b]

Air pollutant and lag	Cardiovascular mortality % Change (95% CI)		Ischemic heart disease mortality % Change (95% CI)	
Nucleation mode (<0.03 μm) [cm^{-3}]				
0	0.75 (−2.35;3.96)		3.57 (−1.21;8.58)	
1	0.74 (−2.02;3.57)		2.33 (−1.88;6.73)	
2	1.16 (−1.39;3.78)		−1.57 (−5.29;2.30)	
3	1.52 (−0.98;4.07)		0.45 (−3.29;4.34)	
5 d-average	2.13 (−1.80;6.22)		1.68 (−4.14;7.85)	
Aitken mode (0.03–0.1 μm) [cm^{-3}]				
0	0.30 (−2.63;3.31)		−0.70 (−5.01;3.80)	
1	−1.48 (−4.44;1.58)		−2.04 (−6.38;2.50)	
2	4.04 (1.18;6.98)	***	7.13 (2.91;11.52)	***
3	1.57 (−1.22;4.43)		3.17 (−0.93;7.43)	
5 d-average	2.99 (−0.66;6.77)		3.99 (−1.03;9.25)	
NC_1 (<0.8 μm) [cm^{-3}]				
0	0.59 (−2.93;4.24)		0.86 (−4.40;6.41)	
1	0.21 (−3.2;3.78)		1.19 (−4.01;6.66)	
2	4.92 (1.50;8.45)	***	6.59 (1.50;11.93)	**
3	2.79 (−0.57;6.27)		3.78 (−1.17;8.99)	
5 d-average	4.19 (−0.76;9.37)	*	5.30 (−1.77;12.88)	
SC 0.1–0.3 μm [$\mu m^2\ cm^{-3}$]				
0	−0.56 (−3.38;2.35)		−3.32 (−7.39;0.93)	
1	0.38 (−2.18;3.00)		−0.32 (−4.03;3.53)	
2	0.93 (−1.42;3.34)		4.47 (1.05;8.01)	**
3	−0.27 (−2.56;2.06)		1.36 (−1.99;4.82)	
5 d-average	0.24 (−2.72;3.29)		1.22 (−2.72;5.32)	
SC 0.3–0.8 μm [$\mu m^2\ cm^{-3}$]				
0	−0.59 (−3.18;2.07)		−3.5 (−7.27;0.42)	
1	0.52 (−1.69;2.70)		1.30 (−1.95;4.67)	
2	0.41 (−1.66;2.50)		3.71 (0.71;6.79)	**
3	−1.05 (−3.03;0.97)		−0.40 (−3.31;2.59)	
5 d-average	−0.48 (−3.49;2.63)		0.85 (−3.34;5.23)	
SC_1 (<0.8 μm) [$\mu m^2\ cm^{-3}$]				
0	−0.59 (−3.36;2.26)		−3.61 (−7.61;0.56)	
1	0.42 (−2.02;2.93)		0.54 (−3.03;4.23)	
2	0.85 (−1.41;3.16)		4.51 (1.24;7.89)	***
3	−0.68 (−2.85;1.53)		0.52 (−2.65;3.79)	
5 d-average	−0.01 (−3.07;3.15)		1.25 (−2.87;5.55)	
MC 0.1–0.3 μm [$\mu g/m^3$]				
0	−0.57 (−3.40;2.33)		−3.50 (−7.58;0.76)	
1	0.43 (−2.11;3.03)		−0.18 (−3.87;3.66)	
2	0.86 (−1.48;3.26)		4.47 (1.06;8.01)	**
3	−0.34 (−2.61;1.99)		1.24 (−2.10;4.70)	
5 d-average	0.13 (−2.87;3.23)		1.16 (−2.87;5.36)	
MC 0.3–0.8 μm [$\mu g/m^3$]				
0	−0.61 (−3.18;2.03)		−3.40 (−7.14;0.49)	
1	0.46 (−1.73;2.70)		1.31 (−1.90;4.64)	
2	0.33 (−1.71;2.42)		3.54 (0.58;6.58)	**
3	−1.07 (−3.03;0.92)		−0.46 (−3.33;2.50)	
5 d-average	−0.53 (−3.52;2.55)		0.82 (−3.33;5.15)	
MC_1 (<0.8 μm) [$\mu g/m^3$]				
0	−0.63 (−3.34;2.15)		−3.64 (−7.55;0.45)	
1	0.47 (−1.87;2.86)		0.99 (−2.43;4.53)	
2	0.52 (−1.65;2.73)		4.00 (0.867.23)	**
3	−0.93 (−3.00;1.19)		−0.02 (−3.07;3.11)	
5 d-average	−0.37 (−3.47;2.84)		−0.72 (−3.26;5.45)	

[a] Interquartile range for nucleation mode: single lags = 10,203 cm^{-3}, 5-day average = 7448 cm^{-3}; Aitken mode: single lags = 6250 cm^{-3}, 5-day average = 4150 cm^{-3}; NC_1: single lags = 13,790 cm^{-3}, 5-day average = 12,060 cm^{-3}; SC 0.1–0.3 μm: single lags = 468.8 $\mu m^2\ cm^{-3}$, 5-day average = 265.9 $\mu m^2\ cm^{-3}$; SC 0.3–0.8 μm: single lags = 486.7 $\mu m^2\ cm^{-3}$, 5-day average = 361.9 $\mu m^2\ cm^{-3}$; SC_1: single lags = 973.7 $\mu m^2\ cm^{-3}$, 5-day average = 630.2 $\mu m^2\ cm^{-3}$; MC 0.1–0.3 μm: single lags = 24.0 $\mu g/m^3$, 5-day average = 14.0 $\mu g/m^3$; MC 0.3–0.8 μm: single lags = 57.9 $\mu g/m^3$, 5-day average = 43.4 $\mu g/m^3$; MC_1: single lags = 81.8 $\mu g/m^3$, 5-day average = 58.1 $\mu g/m^3$.

[b] Models adjusted for trend, weekday, temperature (2-day average and 15-day average), and relative humidity (lag 0).

* p-value < 0.10.

** p-value < 0.05.

*** p-value < 0.01.

compared to air masses arriving from northerly directions with average to high wind speed, although the interaction term was not statistically significant. An increase of 973.7 $\mu m^2\ cm^{-3}$ in the SC of particles below 0.8 μm (SC_1) resulted in a 5.7% increase (95% CI: 0.18%; 11.41%) in ischemic heart disease mortality for stagnant and southern air masses compared to a 2.8% increase (95% CI: −1.38%; 7.21%) for air masses from northerly directions with average to high wind speed. Moreover, an increase of 81.8 $\mu g/m^3$ in the MC of particles below 0.8 μm (MC_1) resulted in a mortality increase of 5.17% (95% CI: 0.01%; 10.60%) for stagnant and southern air masses, while for air masses from northerly directions with average to high wind speed we observed a 2.3% increase (95% CI: −1.79%; 6.59%).

3.3. Sensitivity analyses

We performed a number of sensitivity analyses (Appendix A, Table A.2), resulting in only slight changes of the risk for mortality.

Different values of smoothness for the exposure–response relationships between particle NC and mortality and corresponding likelihood ratio tests indicated linear exposure–response relationships (data not shown).

4. Discussion

We observed adverse associations between particle NC and cardiovascular mortality for a 2-days delay. Moreover, all particle parameters except particle NC below 30 nm showed 2-days-delayed associations with ischemic heart disease mortality. The strongest association was found for NC of particles in the size range 0.03–0.1 μm. This association also did not change when adjusting for other particle metrics. Mortality effects of particle NC were not modified by air mass origin. In contrast, results for SC and MC with a lag of two days indicated stronger effects for stagnant and southern air masses compared to air masses arriving from northerly directions with average to high wind speed.

There are only a small number of studies on cardiovascular mortality that also have considered particle NC. Studies conducted in Erfurt, Germany, reported delayed increases of 5.1% (95% CI: −1.0;11.5) as well as of 3.1% (95% CI: 0.2;6.0) in cardiovascular mortality per increases of 12,690 cm^{-3} (Wichmann et al., 2000) and 9743 cm^{-3} particles (Peters et al., 2009; Stolzel et al., 2007) in the size range of 0.01–0.1 μm. Moreover, a recent study reported that out of a larger number of particle metrics, only particle NC was associated with cardiovascular mortality (increase of 2.2% (95% CI: 0.6;3.8) per increase of 10,166 cm^{-3} particles), although the increase was seen more immediately with a lag of one day (Atkinson et al., 2010). In our study, particle NC showed a delayed association with cardiovascular mortality. For comparative purposes, we re-calculated our results based on an increase of 10,000 particles/cm^3 which resulted in a 6.5% (95% CI: 1.9;11.4) increase in cardiovascular mortality in association with Aitken mode particles and a 3.5% (95% CI: 1.1;6.1) increase for NC_1, respectively. In contrast, Branis et al. (2010) and Halonen et al. (2009) did not find any association between particle NC and cause-specific mortality, including cardiovascular mortality, for the Czech Republic and Finland, respectively. We did not find any association between cardiovascular mortality and particle MC and SC which is, for MC, in agreement with the studies conducted in Erfurt (Peters et al., 2009; Stolzel et al., 2007), but in contrast to a study recently conducted in Barcelona (Perez et al., 2009).

For ischemic heart disease mortality the strongest associations were seen for NC of particles; a result also found by Forastiere et al. (2005) who showed a significant increase of out-of-hospital coronary deaths in Rome, Italy, in association with an increase in same-day UFP. Moreover, our results also indicated delayed associations with sub-micrometer particle MC and SC. Note that we did not measure active particle surface area directly on a continuous scale, but only could obtain calculated surface area concentrations by converting particle numbers. Nevertheless, toxicological studies report that surface area plays an important role in determining the biological activity of particles (Brook, 2008; Valavanidis et al., 2008).

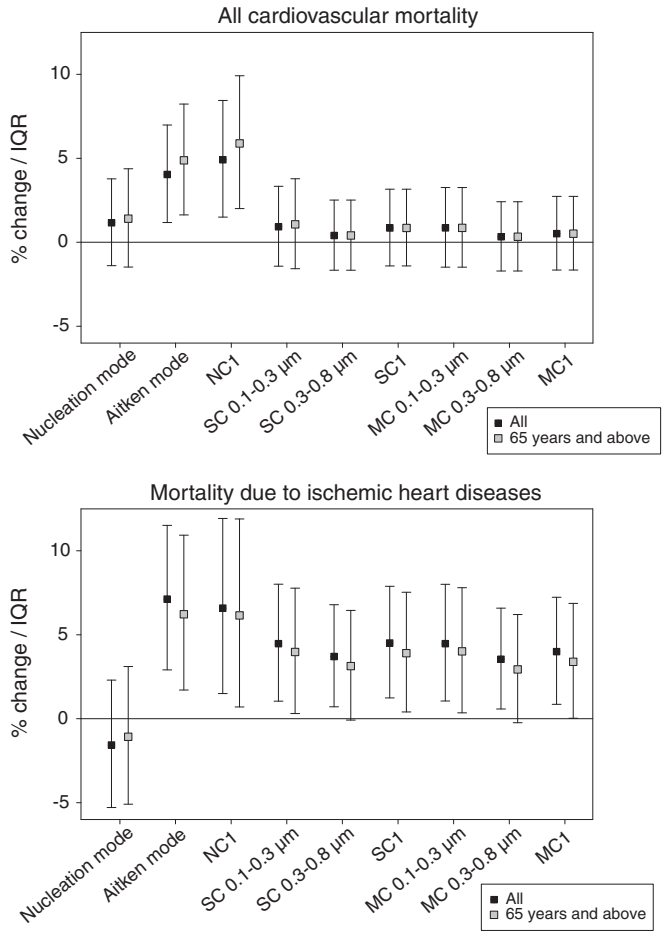

Fig. 2. Percentage of change (95%-confidence interval) in cause- and age-specific cardiovascular mortality per an interquartile [a] increase in particle metrics in Beijing [b], from March 2004 to August 2005. [a] Interquartile range for nucleation mode: 10,203 cm^{-3}; Aitken mode: 6250 cm^{-3}; NC_1: 13,790 cm^{-3}; SC 0.1–0.3 µm: 468.8 $µm^2$ cm^{-3}; SC 0.3–0.8 µm: 486.7 $µm^2$ cm^{-3}; SC_1: 973.7 $µm^2$ cm^{-3}; MC 0.1–0.3 µm: 24.0 $µg/m^3$; MC 0.3–0.8 µm: 57.9 $µg/m^3$; MC_1: 81.8 $µg/m^3$. [b] Beijing urban area.

Table 3
Percentage of change (95%-confidence interval) in cardiovascular (ICD-10 I00–I99) and ischemic heart disease (ICD-10 I20–I25) mortality per an interquartile[a] increase in pollutants with a lag of 2 days in Beijing, from March 2004 to August 2005[b]. Two-pollutant models[c].

Air pollutant	Cardiovascular mortality %change (95% CI)	Ischemic heart disease mortality %change (95% CI)
	Two-pollutant	Two-pollutant
Aitken mode	4.29 (1.40;7.26)***	7.03 (2.76;11.48)***
Nucleation mode	1.67 (−0.90;4.31)	−0.55 (−4.33;3.38)
Aitken mode	4.52 (1.27;7.88)***	5.84 (1.00;10.91)**
SC 0.1–0.3 µm	−0.82 (−3.43;1.85)	1.99 (−1.88;6.02)
Aitken mode	4.06 (1.16;7.06)***	6.26 (1.97;10.73)***
SC 0.3–0.8 µm	−0.10 (−2.17;2.02)	2.66 (−0.37;5.78)*
Aitken mode	4.24 (1.15;7.43)***	5.68 (1.09;10.47)**
SC_1	−0.42 (−2.81;2.04)	2.59 (−0.94;6.26)
Aitken mode	4.42 (1.24;7.69)***	5.81 (1.09;10.75)**
MC 0.1–0.3 µm	−0.70 (−3.24;1.91)	2.19 (−1.59;6.11)
Aitken mode	4.07 (1.17;7.06)***	6.32 (2.03;10.78)***
MC 0.3–0.8 µm	−0.15 (−2.20;1.95)	2.53 (−0.45;5.61)*
Aitken mode	4.13 (1.17;7.18)***	6.04 (1.66;10.61)***
MC_1	−0.28 (−2.49;1.98)	2.58 (−0.67;5.92)
NC_1	4.83 (1.36;8.42)***	5.31 (0.15;10.73)**
SC 0.1–0.3 µm	0.34 (−2.02;2.75)	3.60 (0.12;7.20)**
NC_1	4.91 (1.49;8.45)***	6.17 (1.11;11.48)**
SC 0.3–0.8 µm	0.38 (−1.67;2.47)	3.43 (0.46;6.50)**
NC_1	4.83 (1.39;8.39)***	5.43 (0.33;10.80)**
SC_1	0.43 (−1.82;2.74)	3.82 (0.52;7.22)**
NC_1	4.84 (1.38;8.41)***	5.40 (0.26;10.80)**
MC 0.1–0.3 µm	0.34 (−2.00;2.74)	3.67 (0.21;7.24)**
NC_1	4.92 (1.50;8.45)***	6.21 (1.15;11.53)**
MC 0.3–0.8 µm	0.32 (−1.70;2.39)	3.29 (0.35;6.32)**
NC_1	4.89 (1.46;8.43)***	5.91 (0.8;11.24)**
MC_1	0.35 (−1.80;2.55)	3.56 (0.43;6.7)**

[a] Interquartile range for nucleation mode (<0.03 µm): 10,203 cm^{-3}; Aitken mode (0.03–0.1 µm): 6250 cm^{-3}; NC_1 (<0.8 µm): 13,790 cm^{-3}; SC 0.1–0.3 µm: 468.8 $µm^2$ cm^{-3}; SC 0.3–0.8 µm: 486.7 $µm^2$ cm^{-3}; SC_1 (<0.8 µm): 973.7 $µm^2$ cm^{-3}; MC 0.1–0.3 µm: 24.0 $µg/m^3$; MC 0.3–0.8 µm: 57.9 $µg/m^3$; MC_1 (<0.8 µm): 81.8 $µg/m^3$.
[b] Models adjusted for trend, weekday, temperature (2-day average and 15-day average), and relative humidity (lag 0).
[c] Two-pollutant models were only conducted when the pollutants' inter-correlation was <0.5.
* p-value<0.10.
** p-value<0.05.
*** p-value<0.01.

We found no consistent associations between sub-micrometer particle metrics and cerebrovascular mortality; a finding which is supported by a study conducted in Helsinki, Finland (Halonen et al., 2009). However, Perez et al. (2009) found an increase of 5.6% (95% CI: 0.3;11.3) in cerebrovascular mortality for a 10 $µg/m^3$ increase of MC_1 in a study conducted in Barcelona.

In models controlling for other particle metrics, particle NC showed an independent effect of other particle metrics which is in agreement with other studies (Atkinson et al., 2010; Peters et al., 2009). Associations for particle MC and SC generally diminished when controlling for NC of Aitken mode particles, but showed only slight changes in association with ischemic heart disease mortality when controlling for NC_1.

The associations between particle SC and MC and cardiovascular mortality were elevated for stagnant and southern air masses. It has been shown that during days with higher air pollution air masses mostly arrive from densely populated and industrial regions south and south-east of Beijing (Massling et al., 2009; Wehner et al., 2008). These slow-moving air masses highly influence the accumulation mode aerosol in Beijing and in the whole China Plain by aged regional aerosol and secondary aerosol production (Wiedensohler et al., 2009). Chemically and physically altered particles transported by air masses from regions south and south-east of Beijing might be responsible for the stronger associations observed in our study. On the other hand, when air masses arrive from Central Asia the lowest particle MC is observed in Beijing (Wehner et al., 2008; Zhang et al., 2010). Health effects of particle NC on cardiovascular mortality were not modified by air mass origin. These results indicate that locally produced ultrafine particles and regionally transported ACP may exhibit different effects in Beijing.

Overall, results point to a strong role of particles in the Aitken mode range. It has been shown that particle NC of Aitken mode particles such as soot are strongly influenced by traffic emissions, which is also the case in Beijing (Wu et al., 2008). Therefore, these soot particles may contain a significant amount of polycyclic aromatic hydrocarbons (PAH) and toxic metals, through which they may negatively affect human health (Branis et al., 2010; Ning and Sioutas, 2010).

There were on average 29 daily deaths due to cardiovascular diseases in our study period which ensured the statistical power of the analysis. Moreover, we thoroughly adjusted for meteorological confounder variables as well as time trend to rule out the possibility that the detected associations resulted from meteorological influences or seasonal differences. Additional sensitivity analyses indicated that our final models seemed to be conservative and stable with respect to the choice of the model parameters.

Nevertheless, this study also has some limitations. Many of the metrics under investigation may vary considerably in space. Therefore, a greater amount of measurement error due to greater spatial variability could be present in this study as we only had

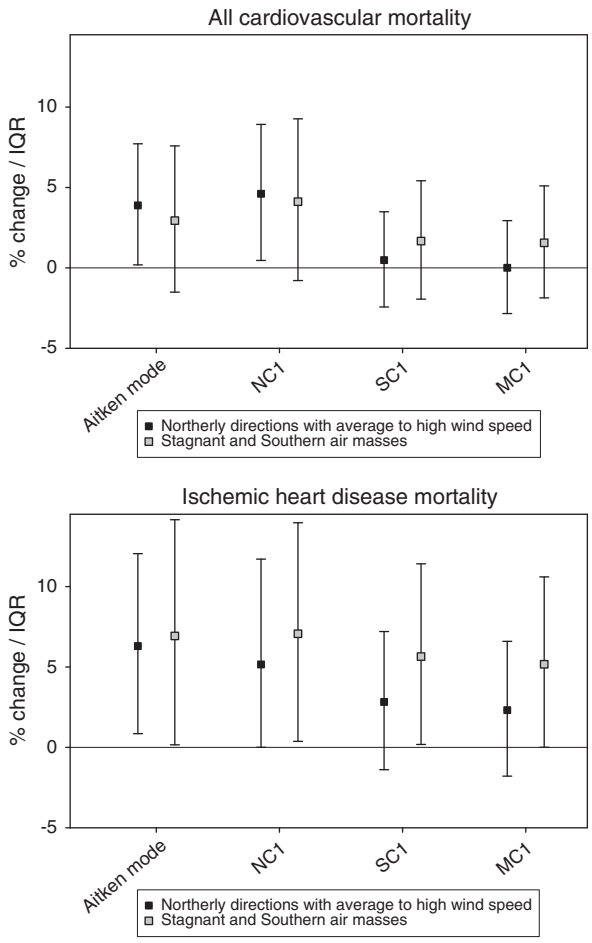

Fig. 3. Percentage of change (95%-confidence interval) in cardiovascular (ICD-10 I00–I99) and ischemic heart disease (ICD-10 I20–I25) mortality per an interquartile [a] increase in particle metrics in Beijing [b], from March 2004 to August 2005. Effect modification by air mass origin. [a] Interquartile range for nucleation mode: 10,203 cm^{-3}; Aitken mode: 6250 cm^{-3}; NC_1: 13,790 cm^{-3}; SC 0.1–0.3 μm: 468.8 μm^2 cm^{-3}; SC 0.3–0.8 μm: 486.7 μm^2 cm^{-3}; SC_1: 973.7 μm^2 cm^{-3}; MC 0.1–0.3 μm: 24.0 $\mu g/m^3$; MC 0.3–0.8 μm: 57.9 $\mu g/m^3$; MC_1: 81.8 $\mu g/m^3$. [b] Beijing urban area.

measurements of one urban background station to characterize exposure over an entire community. However, concurrent measurements of particles in the ultrafine range at different sites within one city often have shown good correlations over time despite differing magnitudes in space. This suggests that a background site might well represent the exposure of the average population with respect to UFP if the site is carefully chosen (Aalto et al., 2005; Cyrys et al., 2008; Peters et al., 2005; Puustinen et al., 2007). To the extent that there is classical measurement error inherent, it has been shown that it is highly unlikely to bias away from the null even in the presence of covariates (Zeger et al., 2000). Therefore, measurement error in our particle metrics would likely attenuate the true association. As one would expect greater exposure misclassification by a single monitoring site for locally produced particles such as UFP than for regionally transported particles, the fact that the present study did identify larger associations between locally generated particles and cardiovascular mortality, compared to MC in the accumulation mode range or PM_1, point to an important role of locally produced particles on daily mortality.

We used a variety of particle metrics for the analyses as different metrics may point toward differing properties of the aerosol and also represent different sources of air pollution. However, by testing a set of particle metrics the possibility that some effects might have occurred by chance cannot be excluded. Because some of the metrics are closely correlated, we considered especially consistent patterns in the data as actual effects.

5. Conclusions

This analysis showed an elevated risk of cardiovascular mortality in Beijing from short-term exposure to particulate air pollution in the sub-micrometer range. Results especially point to a delayed association between particle NC and cardiovascular mortality. Results also indicate that locally produced ultrafine particles and regionally transported ACP may exhibit different effects in Beijing.

Disclosure statement

The authors declare they have no competing financial interests.

Acknowledgments

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Appendix A

Table A.1
Spearman rank correlation for daily means of air pollutants and meteorological parameters in Beijing, China, for the study period March 2004 to August 2005[a].

	Nucleation mode	Aitken mode	NC_1	SC 0.1–0.3 μm	SC 0.3–0.8 μm	SC_1	MC 0.1–0.3 μm	MC 0.3–0.8 μm	MC_1	temp_mean
Nucleation mode	1.00									
Aitken mode	0.17	1.00								
NC_1	0.57	0.80	1.00							
SC 0.1–0.3 μm	−0.55	0.45	0.21	1.00						
SC 0.3–0.8 μm	−0.65	0.22	0.01	0.91	1.00					
SC_1	−0.59	0.39	0.16	0.98	0.97	1.00				
MC 0.1–0.3 μm	−0.57	0.42	0.19	1.00	0.92	0.98	1.00			
MC 0.3–0.8 μm	−0.66	0.22	0.00	0.90	1.00	0.96	0.92	1.00		
MC_1	−0.64	0.29	0.06	0.94	0.99	0.99	0.96	0.99	1.00	
temp_mean	−0.25	−0.33	−0.47	−0.07	0.04	−0.03	−0.05	0.05	0.02	1.00
hum_mean	−0.67	−0.11	−0.41	0.40	0.56	0.47	0.42	0.57	0.53	0.37

[a]Correlation coefficients between 0.61 and 0.80 are highlighted in light gray and those between 0.81 and 1.00 are underlined and highlighted in light gray.

Table A.2
Sensitivity analyses. Percentage of change (95%-confidence interval) in cardiovascular (ICD-10 I00-I99) per an interquartile[a] increase in Aitken mode particles and NC_1 (<0.8 μm) in Beijing, from March 2004 to August 2005[b].

Type of sensitivity analysis	% Change (95% CI) for Aitken mode particles	% Change (95% CI) for NC_1 (<0.8 μm)
Original model	4.04 (1.18;6.98)	4.92 (1.50;8.45)
More DF (DF = 11) for smooth function of trend	3.74 (0.88;6.69) [c]	4.18 (0.70;7.77) [c]
More DF (DF = 5) for smooth functions of meteorological variables	4.32 (1.39;7.34)	5.76 (2.32;9.32)
Use of apparent temperature instead of mean air temperature	4.21 (1.35;7.16)	5.32 (1.90;8.86)
Excluding days with dust events	3.81 (0.90;6.80)	4.71 (1.26;8.27)

[a]Interquartile range for Aitken mode (0.03–0.1 μm): 6250 cm^{-3}; NC_1: 13,790 cm^{-3}.
[b]Models adjusted for trend, weekday, temperature (2-day average and 15-day average), and relative humidity (lag 0).
[c]The absolute value of the sum of the partial autocorrelation function (PACF) was around −0.78, so there was a large amount of overfitting in this model.

Fig. A.1. Map of Beijing administrative area (light gray) and Beijing urban area (dark gray).

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6 Size-fractioned particulate air pollution and cardiovascular emergency room visits in Beijing, China

Ready for submission

Size-fractioned particulate air pollution and cardiovascular emergency room visits in Beijing, China

Liqun Liu[1,2,3§], Susanne Breitner[1,2], Alexandra Schneider[1], Josef Cyrys[1,4], Irene Brüske[5], Ulrich Franck[6], Uwe Schlink[6], Arne Marian Leitte[6], Olf Herbarth [6,7], Alfred Wiedensohler [8], Birgit Wehner[8], Xiaochuan Pan[3], H-Erich Wichmann[2,5], Annette Peters[1,9]

[1]Helmholtz Zentrum München - German Research Center for Environmental Health, Institute of Epidemiology II, Neuherberg, Germany
[2]Ludwig-Maximilians-University Munich, IBE Chair of Epidemiology, Munich, Germany
[3]Peking University, Health Science Center, School of Public Health, Beijing, China
[4]University of Augsburg, Environmental Science Center, Augsburg, Germany
[5]Helmholtz Zentrum München - German Research Center for Environmental Health, Institute of Epidemiology I, Neuherberg, Germany
[6]Helmholtz Centre for Environmental Research – UFZ, Core Facility Studies, Leipzig, Germany
[7]University of Leipzig, Leipzig, Germany
[8]Leibniz Institute for Tropospheric Research (IfT), Physics Department, Leipzig, Germany
[9]Focus Network Nanoparticles and Health (NanoHealth), Helmholtz Zentrum München - German Research Center for Environmental Health, Neuherberg, Germany

[§]Corresponding author

Email addresses:

LL: liqun.liu@helmholtz-muenchen.de

SB: susanne.breitner@helmholtz-muenchen.de

AS: alexandra.schneider@helmholtz-muenchen.de

JC: cyrys@helmholtz-muenchen.de

IB: brueske@helmholtz-muenchen.de

UF: ulrich.franck@ufz.de

US: uwe.schlink@ufz.de

AML: arne.leitte@ufz.de

OH: olf.herbarth@medizin.uni-leipzig.de

AW: alfred.wiedensohler@tropos.de

BW: birgit@tropos.de

MH: minhu@pku.edu.cn

XP: xcpan@hsc.pku.edu.cn

HEW: wichmann@helmholtz-muenchen.de

AP: peters@helmholtz-muenchen.de

Abstract

Background

Although short-term exposure to ambient particulate matter has increasingly been linked with cardiovascular diseases, it is not quite clear how physical characteristics of particles, such as particle size may be responsible for the association. This study aimed at investigating whether daily changes in number or mass concentrations of accurately size-segregated particles in the range of 3nm to 10μm are associated with daily cardiovascular emergency room visits in Beijing, China.

Methods

Cardiovascular emergency room visit counts, particle size distribution data, and meteorological data were collected from Mar 2004 to Dec 2006. Particle size distribution data was used to calculate particle number concentrations (NC) in different size fractions, which were then converted to particle mass concentrations (MC) assuming spherical particles. We evaluated cumulative associations between cardiovascular emergency room visits (ERVT) and particle NC and MC using polynomial distributed lag (PDL) models and multi-day moving average (8-day, lags 0-7) of particle concentrations. Effects were considered linear and presented as relative risks (RR) of ERVT per interquartile range (IQR) increase in particle concentrations, together with 95% confidence intervals (CI).

Results

We observed delayed associations between NC of ultrafine particles (UFP) and ERVT, mostly contributed by particles in the size ranges of 10-30nm and 30-50nm. The RRs (95% CI) of ERVT associated with an IQR increase in 8-day moving average NC of UFP, 10-30nm particles and 30-50nm particles (9450cm^{-3}, 3248cm^{-3} and 2076cm^{-3}) were: 1.12 (1.05, 1.19), 1.13 (1.06, 1.20) and 1.09 (1.03, 1.15), respectively. The PDL curves for the effects of NC and MC of 100-300nm or 300-1000nm particles on ERVT showed to be similar.

Conclusions

Elevated sub-micrometer particles NC were associated with increased cardiovascular morbidity. UFP showed delayed associations, while the harmful effects of 100-1000nm particles were immediate. Using particle NC or MC didn't seem to affect the particle effects.

Background

Ambient particulate matter (PM) has increasingly been linked with cardiovascular diseases (CVD) during the last decades [1]. Observed effects of short-term fluctuations of ambient PM on the cardiovascular system include ischemia and arrhythmia in patients with coronary artery disease, altered heart rate and autonomic control, altered blood pressure, systemic inflammatory response, a pro-thrombotic state and endothelial dysfunction [2]. The exposure-response functions between short-term exposure to PM and cardiovascular mortality and morbidity are generally considered to be near-linear and without a threshold [3], indicating that even quite low concentrations of PM could result in adverse influence.

Different size fractions of PM are under investigation: PM with an aerodynamic diameter smaller than 10µm (PM_{10}) or 2.5µm ($PM_{2.5}$ or fine particles), PM with diameters between 2.5µm and 10µm (coarse particles), as well as particles smaller than 100nm (ultrafine particles, UFP) [1]. Both subcategories of PM_{10} (coarse and fine particles) showed short-term effects on cardiovascular mortality or morbidity [4]. Some findings suggested that the associations were stronger for finer than for coarser particles, or the effects of coarse particles on short-term total mortality no longer existed after adjusting for fine particles in a two-pollutant analysis [4-7]. A possible explanation for the stronger associations between fine particles and CVD is that they are deposited on the bronchial tree and alveoli; UFP are even able to cross over into the bloodstream [8]. The direct stimulation of blood vessels, as well as the particle-induced pulmonary reflexes and pulmonary inflammation, eventually leading to arrhythmia or myocardial ischemia, are all considered as possible biological mechanisms linking PM with CVD [1].

UFP are most often measured by number per cubic centimetre [9]; their high particle number concentration and large active surface area (plus small size), thus high deposition efficiency in the pulmonary region, make them a great contributor to the observed cardiovascular effects [10, 11]. PM_{10}, $PM_{2.5}$ and coarse particles are typically measured by their mass per volume of air ($\mu g/m^3$) [9]. Meteorological conditions (such as air humidity) can modify the spectrum of the size fractions with consequences to health effects [12].

Due to the limited availability of appropriate measurement data, there are only few epidemiological studies on the short-term effects of more accurately size-segregated particles on daily cardiovascular mortality or morbidity [13-17]. Most studies about health effects of smaller particles have been conducted in North America or Europe; there is a relative lack of studies on Asian population. Different air pollution mixtures and levels in Asian areas might influence the associations between human health and air pollution.

This study aimed at investigating whether daily changes in ambient concentrations of particle size fractions in the range of 3nm to 10μm are associated with cardiovascular emergency room visits in Beijing, China. Moreover, we aimed to better delineate whether using particle number or mass concentration may affect the associations.

Material and methods

Study area and period

We conducted this study in Beijing, China, from 4 Mar 2004 to 31 Dec 2006 (1033 days). Beijing has an area of about 16,808km^2 consisting of eight urban and ten suburban districts (Figure 1), with a population size of approximately 15,380,000 in 2005 (http://baike.baidu.com/view/2621.htm). It is located in the North China Plain surrounded by mountains of 1000-1500m in altitude to the west, north, and northeast, and the Bohai Sea on the southeast side. Typical warm temperate semi-humid continental monsoon climate leads to hot, humid summers and cold, dry winters. Springs and autumns are both of relatively short duration.

Emergency room visit data

We obtained standard medical record forms from the Emergency Department of Peking University's Third Hospital, which is located in the Haidian District (Figure 1). Only the forms of patients who visited and left the emergency room within one day were available; the forms of patients with more severe problems who were transferred to the In-patient Department were not available for our database as their forms were transferred together with the patients. A database including diagnosis and date of visit based on information in the forms was built by medically trained students from Peking University – Health Science Center (School of Public Health). The diagnoses were coded according to the International Classification of Diseases 10th Revision (ICD-10), and comprised cases of ischemic heart diseases (I20-I25), arrhythmia (I47-I49), heart failure (I50), cerebrovascular diseases (I60-I69), and other diseases within the I00-I99 category as well as cause-unknown sudden death (R96). We combined all cases as "total circulatory emergency room visits (ERVT)". Moreover, we combined the first four sub-categories (cases of ischemic heart diseases, arrhythmia, heart failure, and cerebrovascular diseases), which are more severe or even fatal, as "severe cardiovascular emergency room visits (ERV)".

Meteorological data

We obtained meteorological data including daily mean temperature, relative humidity, and barometric pressure from the China Meteorological Data Sharing Service System (station

54511, located at N39°48' E116°28' in the south eastern part of Beijing within Daxing District, see Figure 1).

Particle concentration data

Particle size distribution data were sampled on top of a six-floor building inside the campus of Peking University, which is also located in the Haidian District (Figure 1). The setup of the measurement station is described in detail elsewhere [18, 19]. The measurement station is a few hundred meters away from major roads (no heavy traffic) and about 20m above ground. The campus is a primarily residential and commercial area without industrial sources or agricultural activities. Local emission sources within a radius of 1km could be vehicular traffic, fuel combustion for domestic cooking and heating, and construction. An earlier examination of the spatial variability of $PM_{2.5}$ mass and chemical composition in 1999 to 2002 showed only minor differences between the campus site and a downtown site [18-20]. Furthermore, average particle number size distributions at the Peking University measurement site and another regional measurement site, located around 50km to the south of the PKU, were shown to be similar in summer [21], confirming that the measurement site may be considered as an urban background station.

Aerosol number size distributions were continuously measured between 3nm to 10µm. Measurements were done by a Twin Differential Mobility Particle Sizer (TDMPS) which covered the size range from 3nm to 800nm (mobility diameter, D_p) [22], and an Aerodynamic Particle Sizer (APS, TSI model 3221) which covered the size range from 800nm to 10µm (aerodynamic diameter). The data were corrected for losses due to diffusion and sedimentation within the inlet line as described by Wehner et al. (2004) [19].

Data on number size distributions were used to calculate particle number concentrations (NC, cm^{-3}). These data were converted to particle mass concentrations (MC, $\mu g/m^3$) assuming spherical particles with a mean particle density of $1.5 g/cm^3$. The assumption of this density was based on previous measurements of chemical compositions of particles in Beijing [18, 20].

We calculated daily mean NC and MC for the size fractions (nm) 3-10, 10-30, 30-50, 50-100, 100-300, 300-1000, 1000-2500 and 2500-10000; also for 3-100 (ultrafine particles, UFP), 3-1000 (PM_1), 3-2500 ($PM_{2.5}$) and 3-10000 (PM_{10}). Because number and mass can better describe and are more common for sub-micrometer and larger particles' concentrations, also that in our study the NC of particles >1µm and the MC of particles <100nm were neglectable in comparison to other fractions (data not shown), we excluded those fractions from the analyses. So we excluded NC of $PM_{2.5}$ and PM_{10}, and MC of UFP as well.

Statistical analyses

We used generalized semi-parametric Poisson regression to model the natural logarithm of the expected daily emergency room visit counts as a function of the predictor variables. Penalized splines were used to allow for non-linear confounding. Data were analyzed using the package "mgcv" version 1.4-1.1 in the statistical software R version 2.7.2 (R Development Core Team, 2008).

In a first step, a base model was built for ERVT and ERV separately, without particle exposure (Supplemental table 1). To control for systematic variation over time, we considered long-term time trend as well as dummy variables for season (spring-April to May, summer-June to August, autumn-September to October, winter-November to March) (http://www.bast.net.cn/kjhd/kxpj/kprx/2005/11/7/47746.shtml), day of the week (DOW, Monday to Sunday), and public holidays (holiday versus non-holiday) as potential confounders. As potential meteorological confounders we considered daily mean temperature, relative humidity and barometric pressure. To ensure sufficient adjustment, trend, daily mean temperature and relative humidity were forced into all models. Season, DOW, public holidays, and barometric pressure were only included if they improved model fit. Meteorological confounders were included with the same lag pattern as the particle exposure term we used (see next paragraph), except that in the PDL models (see next paragraph), the meteorological confounders were always included with the 15-day moving average (MA) of lags 0 to 14. The minimization of the absolute value of the sum of the partial autocorrelation function (PACF) of the model's residuals for a fixed number of lags was used to guide the selection of degrees of freedom (DF) for trend [23]. Model selection for the other confounder variables was carried out by minimizing the Generalized Cross Validation (GCV) criterion [24].

We investigated the cumulative lagged effects of particles (also both NC and MC) of each size fraction up to 15 days, by applying polynomial distributed lag (PDL) models [25]. PDL models could avoid problems related to co-linearity among lagged exposure variables; we constrained the shape of the distributed lag curve to follow a polynomial of 5^{th}-order in order to get a flexible functional form. Furthermore, according to the PDL curves we obtained (showed in the results section) and a further study [14], we considered 8-day (lags 0 to 7) MA of NC and MC in different size fractions as exposure terms. We added all particle metrics separately to the base models and estimated associations linearly [3]. Effect estimates are presented as relative risks (RR) of ERVT or ERV together with 95% confidence intervals (CI)

based on an increase in NC or MC from the first to the third quartile (interquartile range [IQR]).

Sensitivity analyses

To explore the robustness of the models, we forced daily mean barometric pressure into the base models additionally (always with the MA of lags 0 to 14 in PDL models, or the same lag pattern as the particle exposure term in Poisson regression models) and then re-analyzed the particle effects. Moreover, for PDL models we varied the degree of the polynomial order; for Poisson regression models we changed smoothing parameter for the time trend functions. Furthermore, we explored the exposure-response functions between 8-day MA of NC or MC and ERVT or ERV to check the assumption of linearity by including these particle concentration terms as penalized splines in the models as well, as air pollution levels are much higher in Beijing (compared to other studies in the U.S. and Europe).

Results

Emergency room visit data and meteorological data

Table 1 presents the overall ERVT and ERV counts during the study period, as well as descriptive statistics for daily ERVT, ERV, temperature, relative humidity, and barometric pressure. ERV counts represented 67% of the ERVT counts. As shown in Supplementary figure 1, daily temperature, relative humidity and barometric pressure all followed seasonal patterns, but with different directions and magnitudes. We could not confidently detect a seasonal pattern within ERVT or ERV data; in contrast, daily cardiovascular death counts data of Beijing urban area was reported to follow a seasonal pattern [26].

Particle concentration data

Table 2 presents the descriptive statistics for daily NC and MC in different size fractions. According to time-series plots (data not shown), particle concentrations of all size fractions were higher in colder periods and lower in warmer periods. Clear seasonal patterns (peak in winter and trough in summer) could be seen for NC of 3-10nm, 50-100nm and 100-300nm particles, as well as for MC of 100-30 nm particles. There was a decline from 2004 to 2006 in NC of 3-10nm, 10-30nm and 30-50nm particles, as well as in NC of UFP and PM_1. Spearman rank correlations among NC/MC of all size fractions are shown in Supplemental table 2. As expected, NC of size fractions within the Nucleation mode range (<30nm), within the Aitken mode range (30-100nm) and within the accumulation mode range (100-1000nm), respectively, were highly correlated with each other. Particle NC within different mode range fractions were not substantially correlated. Modest negative correlation has also been seen between the smallest size fraction of 3-10nm and the size fraction 300-1000nm. Again as

expected, MC of size fractions within the accumulation mode range were highly correlated with each other. And modest correlations were seen between MC of 1000-2500nm and 100-300nm as well as 300-1000nm particles. The NC and MC of the two size fractions within the accumulation mode range were also highly cross-correlated with each other. Modest correlation could be seen between NC of 3-10nm and MC of 300-1000nm particles (negative), and between NC of 50-100nm and MC of 100-300nm particles, in agreement with what mentioned for NC of 100-300nm and 300-1000nm particles above. Modest correlation could also be seen between NC of 300-1000nm and MC of 1000-2500nm particles.

Regression results

Figure 2, Figure 3, Supplementary figure 2 and Supplementary figure 3 present the PDL curves of ERVT and ERV for the IQR-increases of NC or MC of each particle size fraction. The shapes of the curves for ERVT and ERV with the same particle metrics and particle size fraction were very similar, with the ones of ERV having broader 95% CI, probably due to fewer ERV cases compared with ERVT.

The increase of NC of the four size fractions smaller than 100nm showed delayed harmful effects on ERVT and ERV, among which the effects of 10-30nm particles were strongest and longest, from lag4 to lag10, while the effect of 50-100nm particles did not reach statistical significance. The increase of NC of the four size fractions within the range 30-1000nm may also point to current-day immediate effects on ERVT and ERV. Delayed and current-day immediate effects could also be seen with the increase of NC of UFP and PM_1. Note, however, that the effects with these two larger size fractions here actually referred especially the two size fractions 10-30nm and 30-50nm.

The rises of MC of all size fractions, together with the rises of NC of 100-300nm and 300-1000nm particles, showed a similar shape with delayed “protective” effects on ERVT and ERV, mainly from lag10 to lag13. However, we would rather refer them as morbidity displacements (harvesting) after harmful effects of particulate air pollution. The harmful effects of the increase of MC mostly appeared at lag0 and lasted until lag2, although all without statistical significance.

Table 3 and Supplementary table 3 present the quantitative RRs (95% CI) of ERVT and ERV associated with 8-day MA of NC or MC. Significant effects ranged between 4 and 13% increase in RR. For most size fractions, the magnitude of the harmful effect on ERVT was higher than the one on ERV; the only exception was the size fraction 3-10nm.

Sensitivity analyses

Forcing daily mean barometric pressure additionally into the base models did not substantially change the shapes of the PDL curves or the RRs (95% CI) (data not shown). After varying the degree of polynomial order of the PDL models from 5 to 4, 3 or 6, the PDL curves kept similar trends, but became smoother or rougher; the curves of MC were more affected than the curves of NC (data not shown). Changing the smoothness for the function of time trend in the Poisson regression models to a smaller value induced changes on some particle effects' magnitudes but not on directions; changing the smoothness to a bigger value made almost no change in particle effects (data not shown). Figure 4 and 5 present the exposure-response functions for ERVT associated with the 8-day MA of NC or MC of each particle size fraction. Looking at the fragment with most of the NC or MC data of each exposure-response function plot, only the function associated with the 8-day MA of NC of 3-10 nm particles seemed to show a J-shape; the other functions did not substantially deviate from linearity. The exposure-response functions for ERV were similar (data not shown).

Discussion

Summary

In our study UFP NC as well as NC in the four UFP size fractions showed delayed associations on ERVT and ERV. Strongest effects were seen for the size class 10-30nm. The harmful effects of the rises of MC mostly appeared at lag0 and lasted until lag2. Regarding each size fraction, the harmful effect of particles on ERVT was in most cases higher than the effect on ERV, except for the NC of 3-10nm particles.

Effects of sub-micrometer (<1000nm) ambient particles

Using particle data from the same measurement station, Breitner et al. (2011) [26] reported 2-days delayed associations between daily cardiovascular mortality in the Beijing urban area and NC of Aitken mode particles and particles smaller than 800nm. In a study conducted in London by Atkinson et al. (2010) [13], the associations between particle NC and cardiovascular death and emergency hospital admissions were observed at lag 1 and lag 2, respectively. In studies conducted in Erfurt, Germany, an increase in NC of 10-30nm particles, 30-50nm particles and UFP at lag 4 were associated with the most increased risk for daily mortality [16-17]. In our study on cardiovascular ERV, the "best single-day lag" appeared to be lag 7, suggesting that the effects of sub-micrometer particles (measured in NC) on hospital admission may (although not always) appear later (with more lag days) than the effects on death.

Branis et al. (2010) [14] reported that in Prague, Czech Republic, the 7-days moving average of NC of Aitken mode, accumulation mode and total submicron particles all elevated

the number of cardiovascular hospital admissions. The RRs associated with an increase of 1000 particles/cm^3 were 1.018 (95%CI: 1.007-1.029), 1.164 (95%CI: 1.052-1.287) and 1.011 (95%CI: 1.004-1.018), respectively. They also reported significant associations between cardiovascular hospital admissions and NC of Aitken mode, accumulation mode and total submicron particles at lag 0, comparable to what we found. When re-calculating our data on the base of 1000 particles/cm^3 increase in 8-day MA of NC, the RRs for ERVT associated with 30-50nm, 50-100nm, 100-300nm, 300-1000nm as well as 3-1000nm particles were 1.043 (95% CI: 1.014-1.072), 1.018 (95% CI: 1.000-1.036), 1.004 (95% CI: 0.989-1.019), 0.978 (95% CI: 0.913-1.044) and 1.010 (95% CI: 1.004-1.017), respectively. Halonen et al. (2009) [15] investigated the associations between NC of Nucleation mode, Aitken mode and accumulation mode particles and acute hospital admissions of a population aged 65 years or older due to coronary heart disease (CHD), stroke and arrhythmia in Helsinki, Finland. They found that only the 5-day average NC of Aitken mode particles was significantly associated with arrhythmia admission with a RR of 1.041 (95% CI: 1.003-1.080) per an increase of 2467 particles/cm^3. Arrhythmia admission accounted for 20% ERV in our study; we found an increase in ERV admissions of 1.07 (95% CI: 1.00-1.14) per 2076/cm^3 increase in 8-days MA of NC of 30-50nm particles. On the other hand, Andersen et al. (2008) [27] failed in finding any significant associations between NC of 6-700nm particles or UFP and cardiovascular admissions of elderly people (≥65 years) in Copenhagen, Denmark.

Only very few studies have used MC of accumulation mode or sub-micrometer particles, mainly focusing on cardiovascular mortality rather than cardiovascular hospital admission. Breitner et al. (2011) [26] reported an increased ischemic heart disease mortality associated with increases in lag 2 MC of 100-300nm, 300-800nm and <800nm particles in Beijing, China. Perez et al. (2009) [28] found increases in cardiovascular and cerebrovascular mortality associated with an increase in lag 1 MC of PM_1 in a study conducted in Barcelona. In a study conducted in Spokane, Washington, cardiac emergency room visits and hospital admissions were considered, but no consistent associations between them and MC of PM_1 were found [29]. In our study, the increased cardiovascular morbidity were mainly associated with the increases in lag 0 to 1 MC of particles <1000nm.

Effects of 1000-2500nm ambient particles and fine particles

A number of epidemiologic studies have examined the adverse effect of fine particles on cardiovascular morbidity [30-33]. Guo et al. (2010) [30] explored the risk of hypertension emergency hospital visits in Beijing, China associated with fine particles. They reported an odds ratio (overall effect of five days) of 1.084 (95% CI: 1.028-1.139) associated with a

10μg/m^3 increase in $PM_{2.5}$. Jalaludin et al. (2006) [31] found in Sydney, Australia, the percentage changes of all CVD attendances associated with an increase of 4.8μg/m^3 in lag 0 or lag 0-1 average $PM_{2.5}$ were 1.26% (95% CI: 0.56-1.96%) and 0.85% (95% CI: 0.18-1.52%), respectively. According to Figure 3, the percentage change of ERVT associated with an IQR increase in lag 0 or lag 1 MC of $PM_{2.5}$ in our study was about 1.00%; however, our IQR value was 94.5μg/m^3. This largely different IQR in fine particle MC versus the observed similar changes in cardiovascular emergency visit counts might give a hint on possible population adaptation to air pollution in Beijing (although the linearity of effects doesn't point towards an adaptation). There is a lack of time-series study exactly examining the adverse effect of 1000-2500nm particles ($PM_{2.5-1}$) on cardiovascular hospital admission. But two panel studies [34, 35] have shown that increased $PM_{2.5-1}$ (MC) could raise the risk of arterial stiffness and heart rate variability (HRV) reduction. Moreover, morbidity displacement of $PM_{2.5}$ was also reported by Belleudi et al. (2010) [36], but for chronic obstructive pulmonary disease (COPD) hospital admission.

Effects of coarse particles and PM_{10}

A large number of epidemiologic studies have examined the adverse effect of PM_{10} on cardiovascular health outcomes [37]. The short-term (time lag: 0-5 days) effects of PM_{10} were seen on cardiovascular diseases hospital admission of people of every age group; however, the effect size varied a lot (even within each age group) [38]. The percentage changes in the admission associated with per 10μg/m^3 increase in PM_{10} ranged from 0.50% to 4.80% [38]. With regard to coarse particles and cardiovascular morbidity, Peng et al. (2008) [6] reported an association between a 10μg/m^3 increase in $PM_{10-2.5}$ in the United States and a 0.36% (95% CI: 0.05-0.68%) increase in cardiovascular disease admission on the same day. Host et al. (2008) [39] reported an association between a 10μg/m^3 increases in $PM_{10-2.5}$ in six French cities and increases in ischemic heart disease hospitalization of elderly people (6.4% (95% CI: 1.6-11.4%). Besides, two studies [40, 41] conducted on the base of repeatedly measured data of certain group of subjects also reported that increase in coarse particles concentration was associated with increased risk of systemic inflammation and decreased HRV. In contrast, Kan et al. (2007) [5] did not find a significant effect of coarse particles on CVD mortality in Shanghai, China. According to Figure 2, the percentage changes of ERVT associated with the IQR increases in lag 0 MC of PM_{10} and $PM_{10-2.5}$ in our study were about 1.20% and 1.10%, respectively (IQR: PM_{10} 116.1μg/m^3 and $PM_{10-2.5}$ 21.6μg/m^3, respectively).

Strengths and limitations

This study was conducted in a highly polluted city and based on data of accurately size-segregated particles. The emergency room visit data was collected from Peking University's Third Hospital, located in the Haidian district, where patients within 10 km of the measurement site were likely to be treated (personal communication with hospital doctors) [20]. As the urban area of Beijing is 1,368km^2 with about 7,072,000 registered permanent residents in 2005 [42], this area about 314km^2 then contained approximately 1,623,251 permanent residents. The daily ERVT count reached 13, ensuring the statistical power of the analysis. About 20% (randomly chosen 4-5 days per month) of the emergency room visit information were double entered; the identity of the numeric content between the two entries was higher than 90%. Assignments of the diagnoses to ICD-10 disease categories (done by the investigators) were quality assured by a nosological expert from the Third Hospital (percentage of misclassification was about 4%). These two steps assured good quality of emergency room visit data.

Nevertheless, this study also has some limitations. We collected particle data from only one measurement site; therefore, measurement error due to greater spatial variability of Beijing could be present in this study, especially for numbers of traffic-associated particles. Nevertheless, the average particle number size distributions at the Peking University measurement site and another regional measurement site located around 50km to the south of the University were shown to be comparable [20]. Moreover, the Peking University measurement site and the Third Hospital were quite near to each other (see Figure 1); so the measurement site is assumed to have measured the average exposure of the district. On the other hand, we collected emergency room visit data also from only one hospital, and only patients within a certain area of Beijing (patients within 10km of the measurement site, as mentioned above) were likely to be treated there. This area is an urban area, has no substantial difference from other areas of the urban part of Beijing, except that many universities are located there. Therefore, it can be speculated that the education level and socioeconomic status (SES) of the population of this area might be higher than the average level of the whole Beijing urban area. Moreover, due to too many missing records in age and gender, we were not able to investigate particle effects by age or gender subgroups.

Conclusions

The results from our study add to the evidence that elevated concentrations of sub-micrometer particles are associated with increased cardiovascular morbidity. UFP showed delayed associations, while the harmful effects of 100-1000nm particles were rather immediate. This might indicate that particles of different size ranges play their effects through

different pathways. The different lags by which the effects of certain particle size fractions appear should be considered when taking preventive measures to improve public health.

List of abbreviations used

PM: particulate matter; CVD: cardiovascular diseases; PM_{10}: PM with an aerodynamic diameter smaller than 10μm; $PM_{2.5}$: PM with an aerodynamic diameter smaller than 2.5μm; UFP: ultrafine particles, PM with an aerodynamic diameter smaller than 0.1μm; ICD-10: International Classification of Diseases 10th Revision; ERVT: total circulatory emergency room visits; ERV: severe cardiovascular emergency room visits; PKU: Peking University; TDMPS: Twin Differential Mobility Particle Sizer; APS: Aerodynamic Particle Sizer; NC: number concentration; MC: mass concentration; PM_1: PM with an aerodynamic diameter smaller than 1μm; PDL model: polynomial distributed lag model; DOW: day of the week; MA: moving average; PACF: partial autocorrelation function; DF: degrees of freedom; GCV: Generalized Cross Validation; RR: relative risk; 95% CI: 95% confidence intervals; IQR: interquartile range; $PM_{2.5\text{-}10}$: PM with an aerodynamic diameter of 2.5-10μm; CHD: coronary heart disease; HRV: heart rate variability; BP: blood pressure; HR: heart rate; $PM_{2.5\text{-}1}$: PM with an aerodynamic diameter of 1-2.5μm; COPD: chronic obstructive pulmonary disease; AS: Atherosclerosis; EC: endothelial cell; SES: socioeconomic status.

Competing interests

The authors declare that they have no competing interests.

Author contributions

LL performed the statistical analyses and drafted the manuscript. SB and AS guided the statistical analyses and the interpretation of the results, and revised the manuscript critically. JC, AW and BW performed air pollution data collection and data processing, and revised the manuscript critically. IB was involved in the study design and revised the manuscript critically. UF, US, AML and OH were involved in the study design and in air pollution data processing, and revised the manuscript critically. XP obtained emergency room visit data and meteorological data, and revised the manuscript critically. HEW was substantially involved in the study design and revised the manuscript critically. AP was

substantially involved in the study design, guided the interpretation of the results, and revised the manuscript critically.

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Table 1. Descriptive statistics of daily emergency room visit counts, daily mean temperature, relative humidity, and barometric pressure

	Total	Mean ± SD	Min	Median	Max
ERVT [a]	13026	13 ± 5	1	12	30
ERV [b]	8698	8 ± 4	1	8	24
Temperature (°C)		14.2 ± 10.7	-10.1	16.4	32.1
Relative humidity (%)		53 ± 20	8	54	93
Barometric pressure (hPa)		1012 ± 10	988	1012	1043

a. ERVT = Cardiovascular diseases (I00-I99) + Cause-unknown sudden death (R96)

b. ERV = Ischemic heart diseases (I20-I25) + Arrhythmia (I47-I49) + Heart failure (I50) + Cerebrovascular diseases (I60-I69)

Table 2. Descriptive statistics of daily mean particle number concentrations (NC) and mass concentrations (MC)

Size fraction (nm)	Missing (%)	NC (cm^{-3})				MC ($\mu g\ m^{-3}$)			
		Mean±SD	Min	Median	Max	Mean±SD	Min	Median	Max
3-10	7.0	3367 ± 4250	85	1804	40703		a		
10-30	7.0	6732 ± 3736	1182	5862	29914		a		
30-50	7.0	4890 ± 1839	893	4691	13608		a		
50-100	7.0	6792 ± 2881	634	6454	19393		a		
100-300	7.0	6430 ± 3583	337	5904	21169	29.3 ± 18.3	1.4	26.2	105.1
300-1000	18.8	882 ± 725	28	712	4775	62.0 ± 52.6	2.2	49.4	323.9
1000-2500	18.8		a			16.4 ± 15.0	0.3	12.7	139.4
2500-10000	18.8		a			23.7 ± 21.4	0.4	18.4	222.0
3-100	7.0	21781 ± 9616	5612	19622	76283		a		
3-1000	18.8	29297 ± 10226	7441	27624	86864	93.4 ± 68.6	3.8	80.0	412.5
3-2500	18.8		a			109.8 ± 77.9	7.8	92.9	451.5
3-10000	18.8		a			136.4 ± 93.3	11.4	117.0	539.0

a. Neglectable, therefore excluded from analyses

Table 3. Relative risks (RR) (together with 95% confidence intervals (CI)) for ERVT per interquartile range (IQR) increase in 8-days MA of NC or MC. NC or MC of each size fraction and each lag term was added individually to the base models linearly.

Size fraction (nm)	NC (cm^{-3})		MC ($\mu g\ m^{-3}$)	
	IQR	RR (95%CI) for ERVT	IQR	RR (95%CI) for ERVT
3-10	2800	1.04 (1.00, 1.09) *		
10-30	3248	1.13 (1.06, 1.20) *		
30-50	2076	1.09 (1.03, 1.15) *		
50-100	2777	1.05 (1.00, 1.10) *		
100-300	2694	1.01 (0.97, 1.05)	12.5	1.00 (0.96, 1.04)
300-1000	458	0.99 (0.96, 1.02)	33.4	0.99 (0.96, 1.02)
1000-2500			10.2	1.01 (0.99, 1.04)
2500-10000			16.1	1.02 (0.98, 1.05)
3-100	9450	1.12 (1.05, 1.19) *		
3-1000	11270	1.11 (1.04, 1.19) *	46.6	0.99 (0.96, 1.02)
3-2500			51.4	1.00 (0.96, 1.03)
3-10000			64.7	1.00 (0.97, 1.03)

Figure 1. Beijing (shaded area is the urban area) and the locations of data sources.

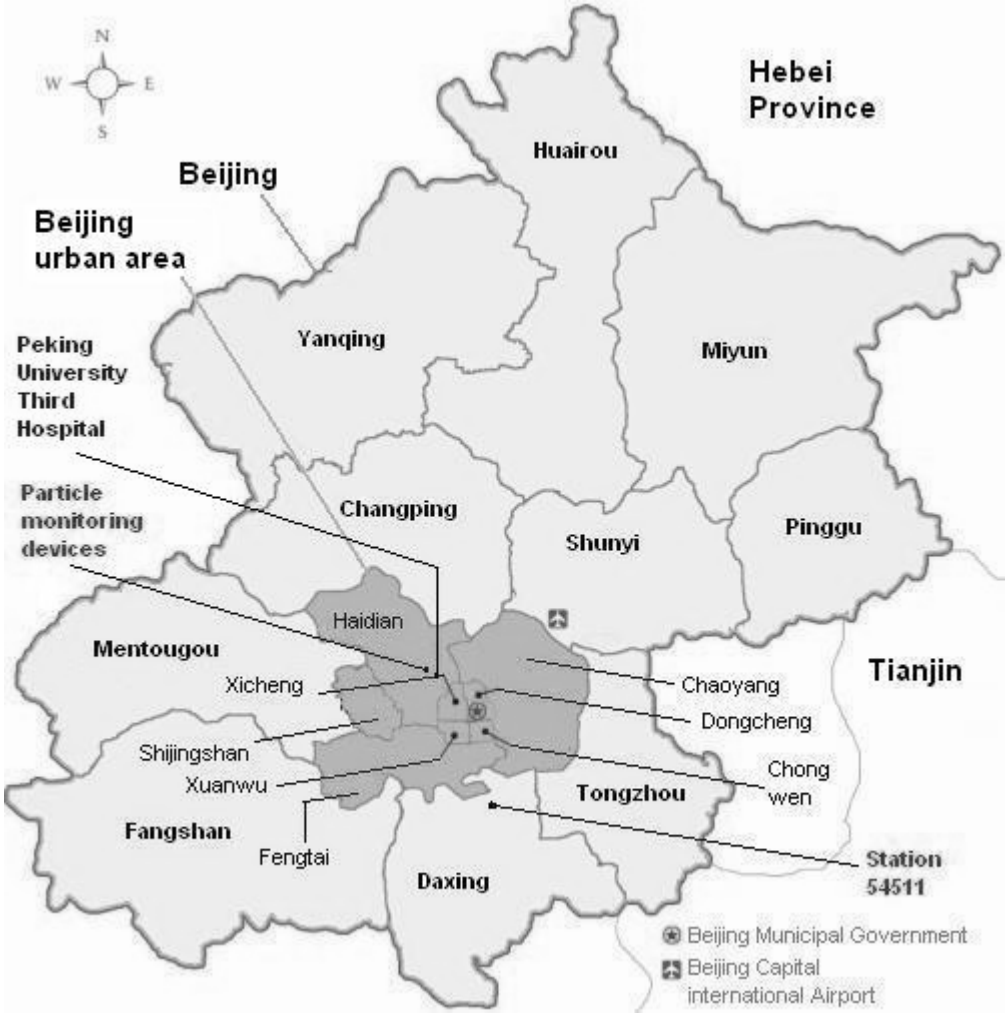


Figure 2. Relative risks (RR, together with 95% confidence intervals (CI)) for ERVT in association with an interquartile range (IQR) increase in NC or MC of each particle size fraction, excluding UFP, PM_1, $PM_{2.5}$ and PM_{10}, obtained with polynomial distributed lag models. Models were estimated with lags up to 15 days using a fifth degree polynomial. Indicated in each plot are the overall 15-day relative risks.

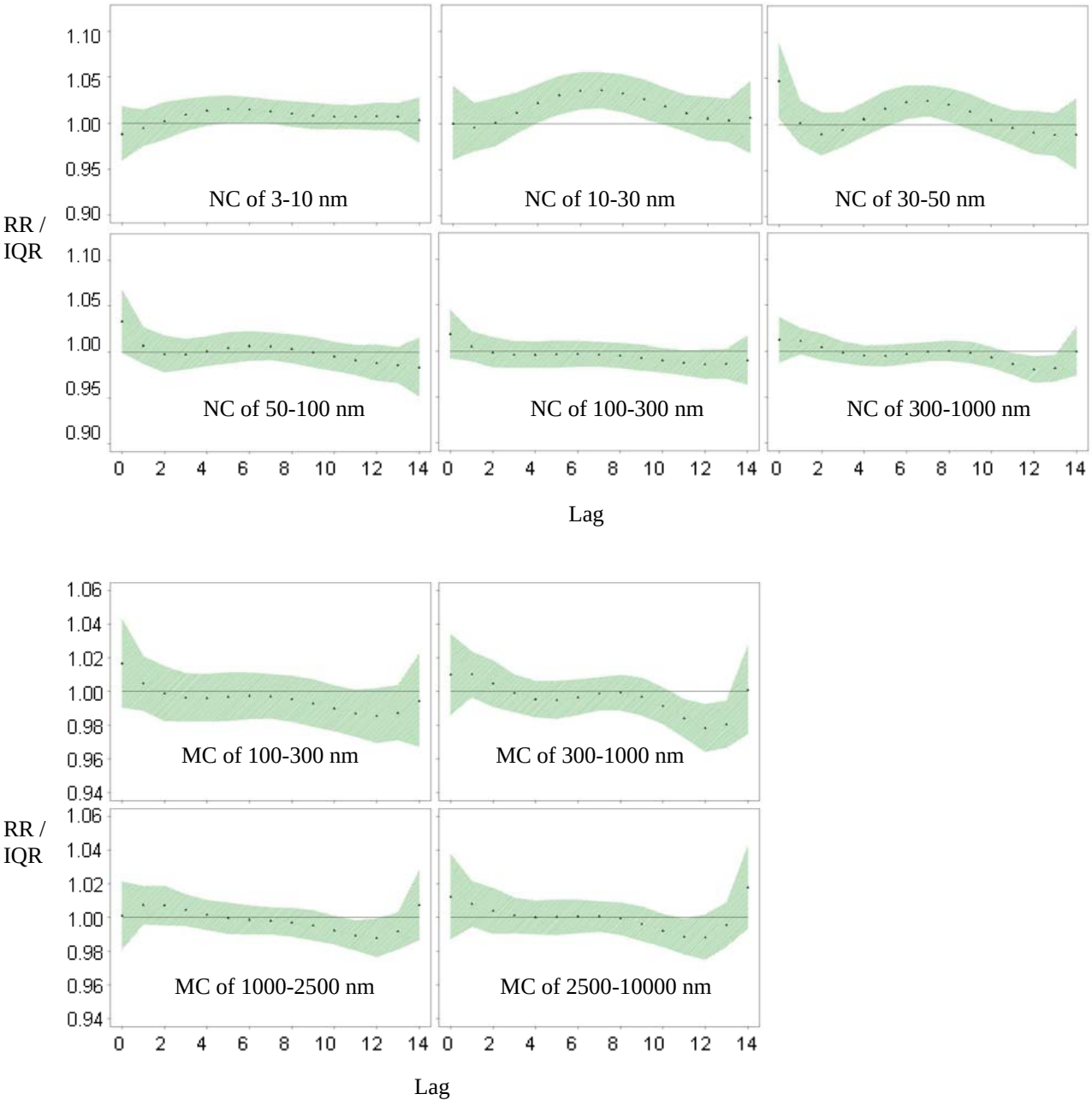


Figure 3. Relative risks (RR, together with 95% confidence intervals (CI)) for ERVT in association with an interquartile range (IQR) increase in NC or MC of UFP, PM_1, $PM_{2.5}$ and PM_{10} obtained with polynomial distributed lag models. Models were estimated with lags up to 15 days using a fifth degree polynomial. Indicated in each plot are the overall 15-day relative risks.

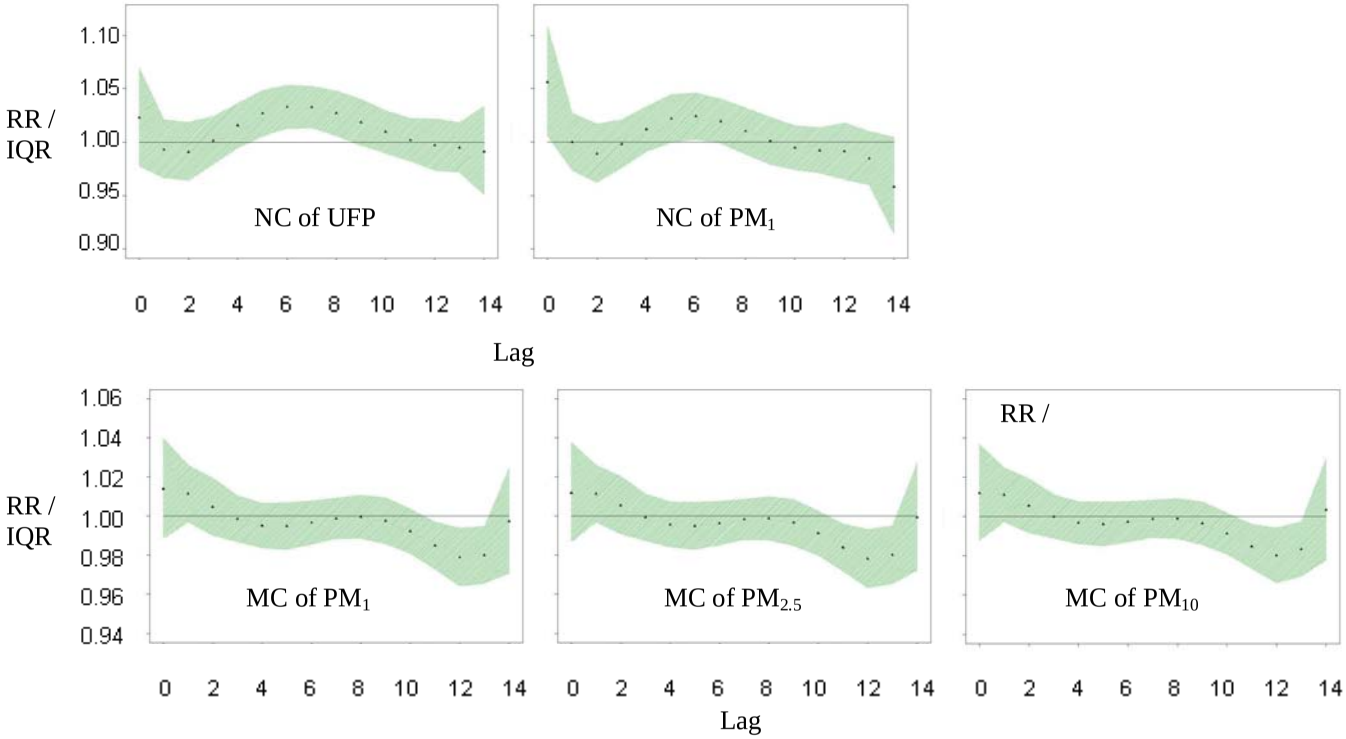
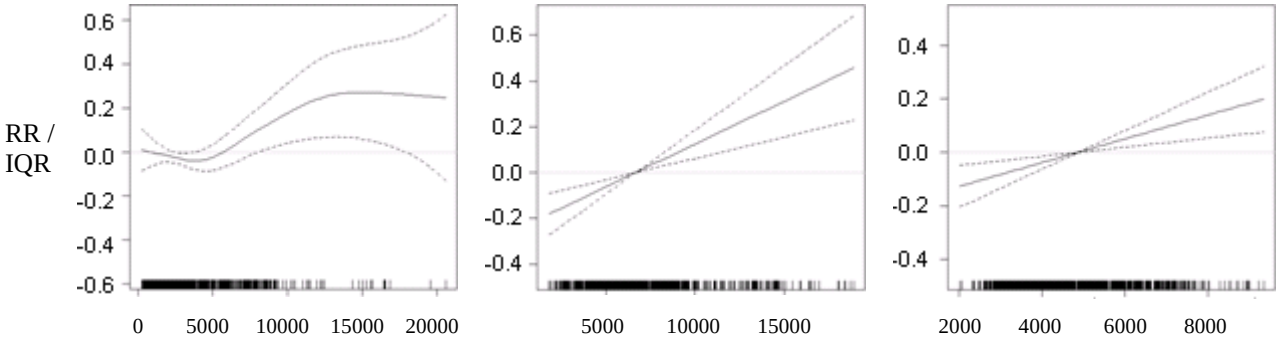
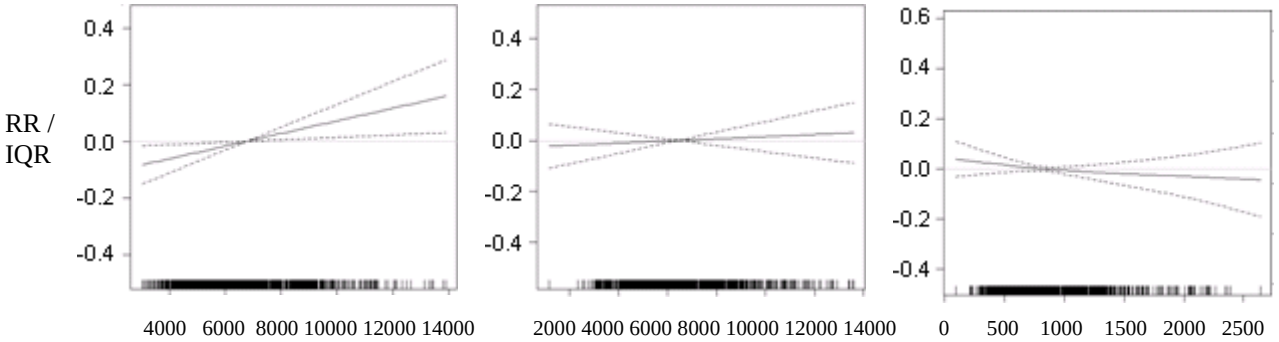


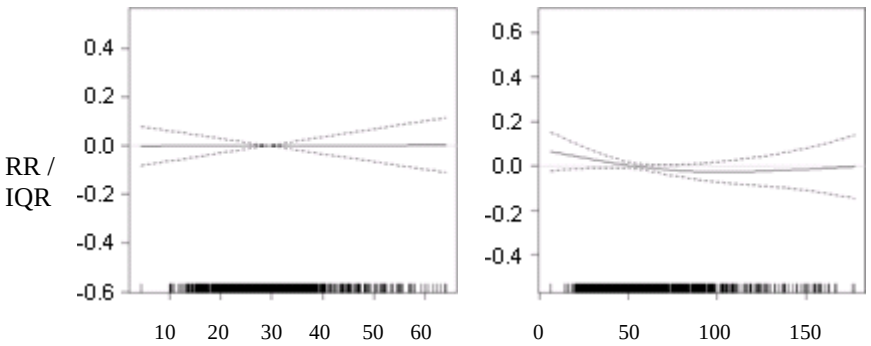
Figure 4. Exposure-response functions (together with 95% confidence intervals) for daily ERVT associated with 8-day MA of NC or MC of each particle size fraction, excluding UFP, PM_1, $PM_{2.5}$ and PM_{10}.



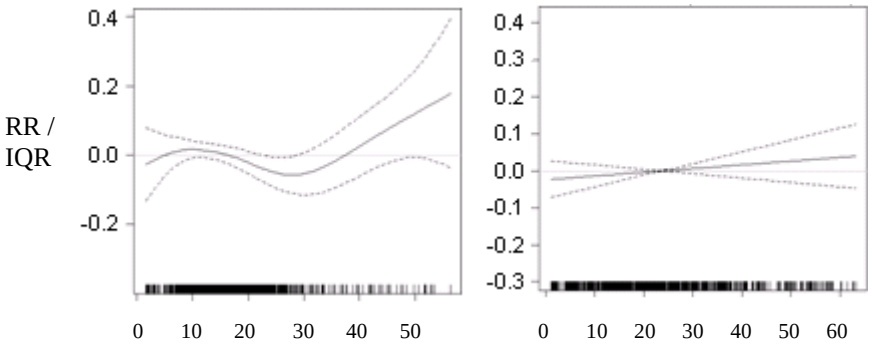
8-day MA of NC of 3-10 nm, 10-30 nm and 30-50 nm particles (from left to right)



8-day MA of NC of 50-100 nm, 100-300 nm and 300-1000 nm particles (from left to right)

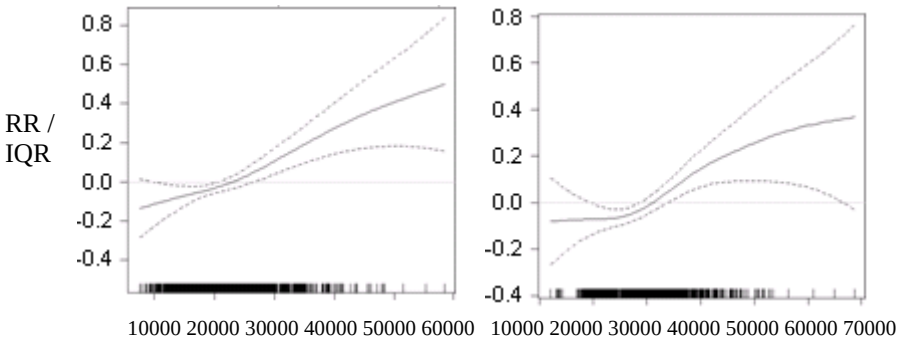


8-day MA of MC of 100-300 nm (left) and 300-1000 nm (right) particles

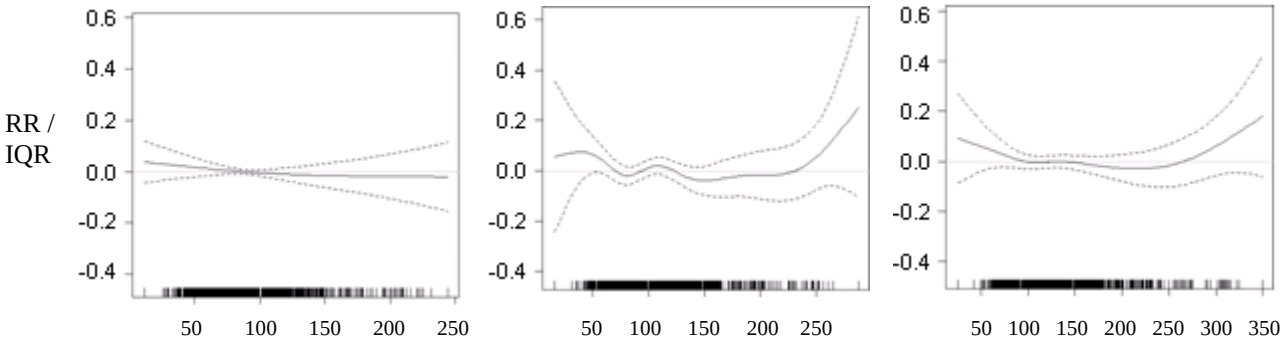


8-day MA of MC of 1000-2500 nm (left) and 2500-10000 nm (right) particles

Figure 5. Exposure-response functions (together with 95% confidence intervals) for daily ERVT associated with 8-day MA of NC or MC of UFP, PM_1, $PM_{2.5}$ and PM_{10}.



8-day MA of NC of UFP (left) and PM_1 (right)



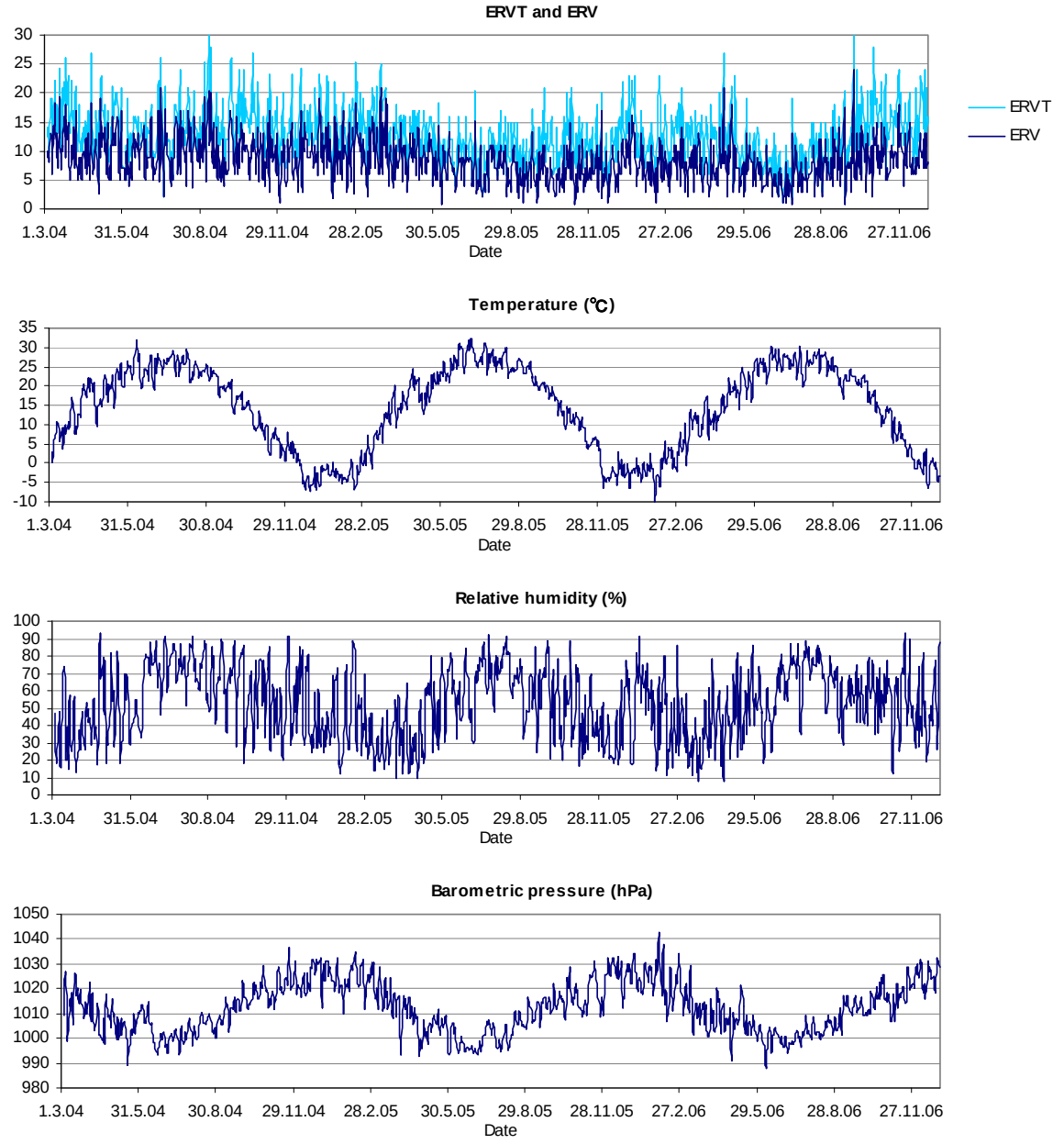
8-day MA of MC of PM_1, $PM_{2.5}$ and PM_{10} (from left to right)

Supplementary table 1. Confounders included in each base model *

ERVT or ERV	Confounders					
	trend	**season**	**day of the week (DOW)**	**public holidays**	**temperature**	**relative humidity**
ERVT	penalized spline	dummy variable	dummy variable	dummy variable	penalized spline	penalized spline
ERV	penalized spline	dummy variable	dummy variable	dummy variable	penalized spline	penalized spline

***** As one sensitivity analysis, we forced barometric pressure into the base models by penalized spline additionally.

Supplementary figure 1. Daily ERVT, ERV, temperature, relative humidity and barometric pressure

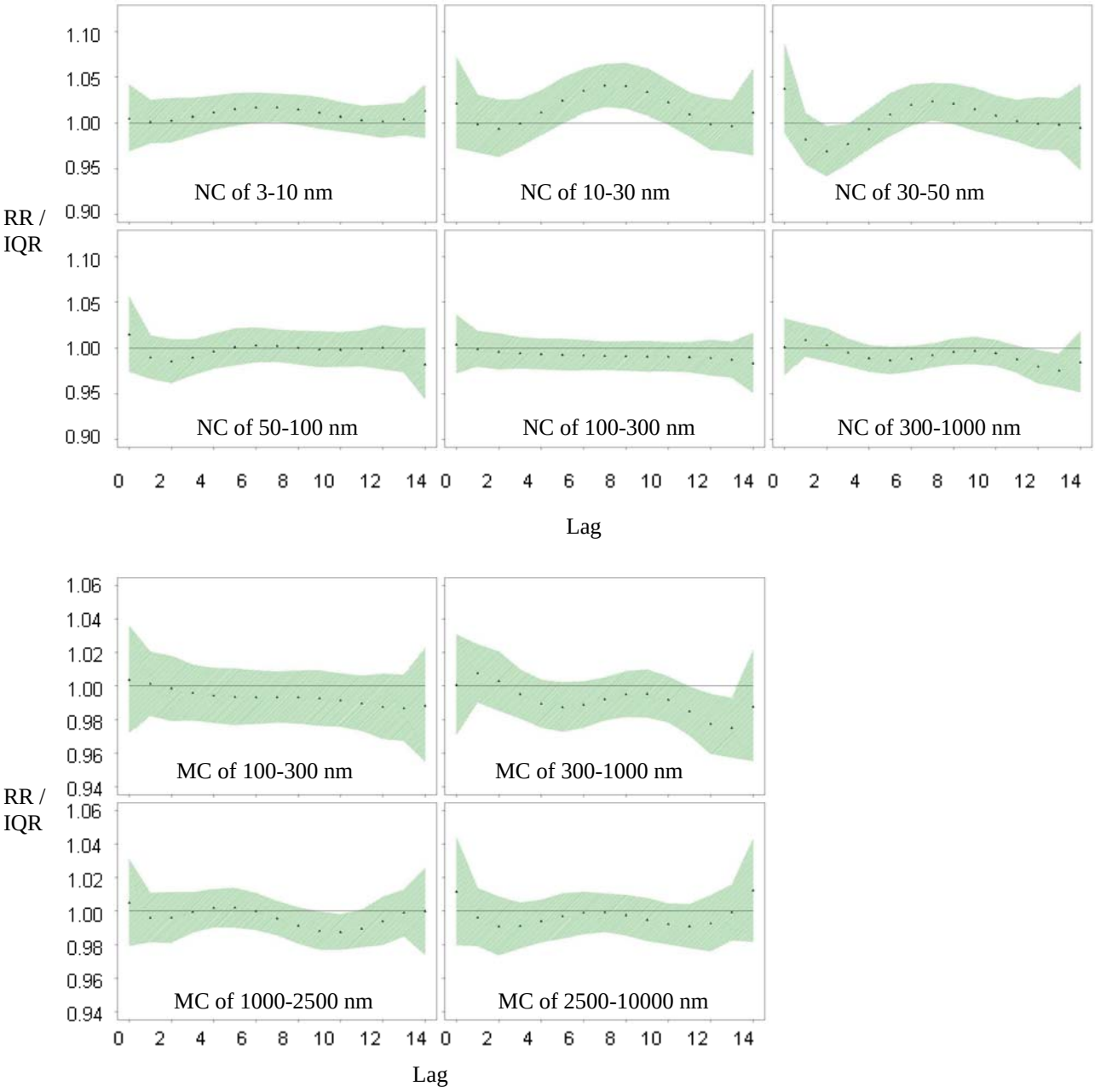


Supplementary table 2. Spearman rank correlations [a]

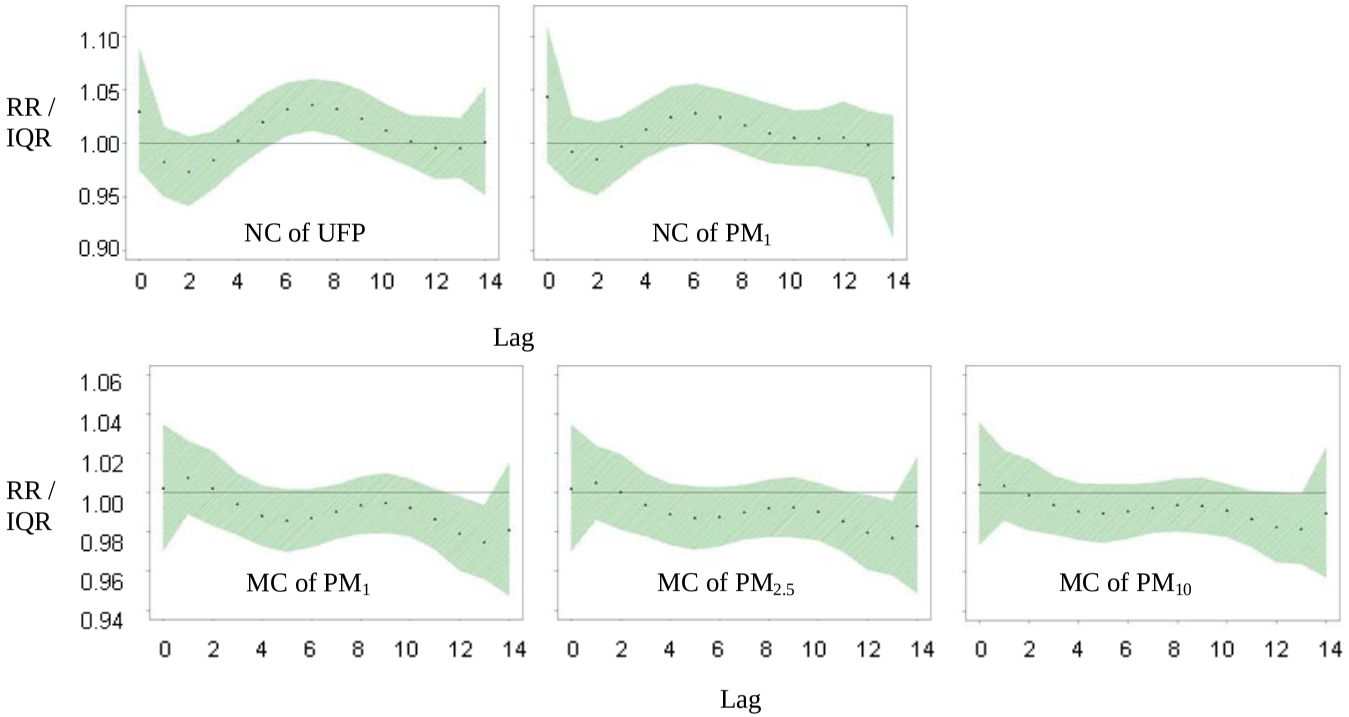
		NC (cm^{-3})						MC ($\mu g\ m^{-3}$)			
		3-10	10-30	30-50	50-100	100-300	300-1000	100-300	300-1000	1000-2500	2500-10000
NC (cm^{-3})	3-10	1									
	10-30	0.87	1								
	30-50	0.34	0.63	1							
	50-100	-0.09	0.19	0.81	1						
	100-300	-0.51	-0.28	0.33	0.74	1					
	300-1000	-0.67	-0.48	0.05	0.43	0.87	1				
MC ($\mu g\ m^{-3}$)	100-300	-0.57	-0.35	0.23	0.63	0.98	0.93	1			
	300-1000	-0.66	-0.48	0.04	0.42	0.84	0.99	0.91	1		
	1000-2500	-0.43	-0.32	-0.04	0.23	0.58	0.71	0.63	0.74	1	
	2500-10000	-0.14	-0.06	0.16	0.31	0.49	0.51	0.51	0.52	0.79	1

a. Correlation coefficients between 0.61 and 0.80 are highlighted in light grey and those between 0.81 and 1.00 are underlined and highlighted in dark grey.

Supplementary figure 2. Relative risks (RR, together with 95% confidence intervals (CI)) for ERV in association with an interquartile range (IQR) increase in NC or MC of each particle size fraction, excluding UFP, PM_1, $PM_{2.5}$ and PM_{10}, obtained with polynomial distributed lag models. Models were estimated with lags up to 15 days using a fifth degree polynomial. Indicated in each plot are the overall 15-day relative risks.



Supplementary figure 3. Relative risks (RR, together with 95% confidence intervals (CI)) for ERV in association with an interquartile range (IQR) increase in NC or MC of UFP, PM_1, $PM_{2.5}$ and PM_{10} obtained with polynomial distributed lag models. Models were estimated with lags up to 15 days using a fifth degree polynomial. Indicated in each plot are the overall 15-day relative risks.



Supplementary table 3. Relative risks (RR) (together with 95% confidence intervals (CI)) for ERV per interquartile range (IQR) increase in 8-days or 15-days MA of NC or MC. NC or MC of each size fraction and each lag term was added individually to the base models linearly.

Size fraction (nm)	NC (cm^{-3})		MC ($\mu g\ m^{-3}$)	
	IQR	RR (95%CI) for ERVT	IQR	RR (95%CI) for ERVT
3-10	2800	1.06 (1.01, 1.12) *		
10-30	3248	1.10 (1.02, 1.18) *		
30-50	2076	1.07 (1.00, 1.14) *		
50-100	2777	1.03 (0.98, 1.09)		
100-300	2694	0.99 (0.95, 1.04)	12.5	0.99 (0.95, 1.03)
300-1000	458	0.97 (0.93, 1.01)	33.4	0.98 (0.94, 1.02)
1000-2500			10.2	1.01 (0.97, 1.04)
2500-10000			16.1	0.99 (0.95, 1.04)
3-100	9450	1.10 (1.03, 1.18) *		
3-1000	11270	1.10 (1.02, 1.19) *	46.6	0.97 (0.93, 1.02)
3-2500			51.4	0.98 (0.94, 1.02)
3-10000			64.7	0.99 (0.94, 1.03)

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