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COMMENTARY

Ambient air pollution and lung disease in China: health effects, study design approaches and future research

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Abstract **Ambient air pollution in China has worsened following dramatic increases in industrialization, automobile use and energy consumption. Particularly bothersome is the increase in the $PM_{2.5}$ fraction of pollutants. This fraction has been associated with increasing rates of cardio-respiratory disease in China and elsewhere. Ambient pollutant levels have been described in many of China's cities and are comparable to previous levels in southern California. Lung cancer mortality in China has increased since the 1970s and has been higher in men and in urban areas, the exact explanation for which has not been determined. The estimation of individual risk for Chinese citizens living in areas of air pollution will require further research. Occupational cohort and case-control designs each have unique attributes that could make them helpful to use in this setting. Other important future research considerations include detailed exposure assessment and the possible use of biomarkers as a means to better understand and manage the threat posed by air pollution in China.**

Keywords air pollution; $PM_{2.5}$; lung disease; study design; epidemiology

Introduction

This paper provides a brief overview of ambient air pollution in China, discusses trends in China's lung disease mortality and comments on considerations for additional research to manage the health component of the issue.

Since the mid-1980s China has undergone dramatic increases in industrialization and urbanization. In 2007 China's total industrial production was 62% that of the United States, according to United Nations data. By 2011, China's industrial output was 120% that of the United States. This pace of industrialization is unparalleled in modern times and has involved dramatic changes in the use of energy. As examples, consider the following: coal has been the main source of energy in China and accounts for roughly 50% of the world's usage [1]. In 2000, China's energy consumption was 1.455 billion tons of standard coal equivalent (SCE) [2]. By 2011, consumption increased 123% to 3.48 billion tons of SCE. The industrial sector consumption, which accounts for approximately 70% of the country's total consumption, increased from 1.037 billion tons of SCE to 2.46 billion tons of SCE. Accompanying these changes has been deterioration in China's air quality, particularly in large metropolitan areas (Fig. 1).

Health problems that relate to air pollution have been consistently described in western countries since the mid-20th century. In 1948, air pollution in Donora, Pennsylvania resulted in 20 deaths. In 1952, the so-called "London Fog" resulted in pollution levels so high that visibility was extremely limited and resulted in around 4000 deaths. These two episodes also triggered legislation in their respective countries that ultimately led to lower pollutant levels and associated risks.

Internal combustion engines are main sources of SO_2, NO_x, lead and particulate matter (PM) pollutants, some of which can be reduced by using low sulfur and unleaded fuel, catalytic converters and diesel particulate filter. The increase in the number of vehicles can serve as an indicator for an increase in these pollutants, especially particulate matter of 2.5 μm or less in aerodynamic diameter ($PM_{2.5}$). In 2000, China had 16.08 million vehicles (8.53 million

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Fig. 1 Daytime air pollution, Xi'an, China (May, 2014).

passenger vehicles and 7.16 million trucks). By 2012 the number increased to 109.3 million vehicles (89.4 million passenger vehicles and 18.95 million trucks). The increase in new car sales corresponds to China's rising gross domestic product (GDP) [2]. Important to note is the increased truck use, especially heavy-duty trucks that use diesel fuel, most of them unequipped with diesel particulate filers.

The combination of increased coal and automobile use has resulted in noticeable effects on pollutants, including carbon dioxide levels [3,4]. In addition, China has experienced intermittent heavy haze over the last several years [5] with elevated PM_{10} and $PM_{2.5}$. The former measurement is analogous to some US cities in the 1970s. Estimates by the World Health Organization have indicated that thousands of individuals could die prematurely in China each year as a result of air pollution [6].

The major constituents of China's air pollution have been described [3,5,7]. Winter measurements have been consistently higher than those during summer, often by a factor of two or more. The sources of these pollutants have also been identified and consist of coal burning power plants, automobile use, bio-mass burning and other industrial sources. Vanadium and barium are fuel additives while lead, zinc, nickel and barium are produced by gasoline and diesel engines. Silica, aluminum, calcium and iron are also elements of diesel engine emissions [8]. The ratio of key constituents has been helpful in the identification of pollutant sources in 14 Chinese cities [7]. For example, NO_3/SO_4 ratios reflect coal burning, while automobile emissions are the major emitters of NO_x but contain little SO_2. As/Fe and Pb/Fe are both indicators of ash produced by uncontrolled coal combustion. Most of these values are noticeably higher in China compared with other locations (Table 1).

Air pollution varies from city to city, depending on such factors as the sources of the pollutants, geography, climate and the type and size of particles. Particularly concerning is the rapid increase in $PM_{2.5}$ that has occurred since 2000 [5]. $PM_{2.5}$ has known deleterious health effects including increased risk for cardiovascular and respiratory disease [5,10]. $PM_{2.5}$ levels have been recorded in major Chinese cities, with daily averages as high as 182 $\mu g/m^3$ in some locations [4,9,11–14]. From these data, it is clear that $PM_{2.5}$ levels are over four times higher than current daily standards in the United States, expressed as an annual or 24 h average of 15 and 35 $\mu g/m^3$ respectively.

The Air Quality Index, a composite index based on six major pollutants: SO_2, O_3, NO_x, CO, lead and particulate matter (PM), is used by government agencies worldwide to indicate the general pollution level in the atmosphere. Of these six, SO_2 and NO_x, under the right humidity and sunlight conditions, form submicron-sized aerosols and PM that affect visibility the most. Lead and PM are larger

Table 1 Comparison of $PM_{2.5}$ chemical component ratios for the 14 Chinese cities with ratios from selected cities in Europe, Canada, Mexico, and the United States [7]

Cities	SO_4/OC	SO_4/EC	NO_3/SO_4	As/Fe	Pb/Fe
14 Chinese cities	0.90±0.43	3.42±2.06	0.46±0.27	0.04±0.03	0.39±0.32
Europe	0.50	1.51	0.92	NA	NA
Toronto, Canada	0.62	4.93	0.81	0.007	0.062
Mexico City, Mexico	0.32	0.71	0.45	0.006	0.068
Seattle, WA	0.45	1.13	0.43	0.015	0.099

NA, not available; OC, organic carbon; EC, elemental carbon.

aerosol droplets or particles. Some of them are removed in the upper respiratory tract and some are inhaled into the lower regions of the lung where gas exchange occurs. Most of the inhaled aerosol is exhaled, with only a small fraction deposited inside the lung. Subsequent health effects are typically the result of long-term exposures unless the pollution level is extremely high.

Both Los Angeles and London have undergone significant improvement in air pollutant levels as a result of multi-faceted efforts that took place over several decades [15]. In these circumstances, steps were taken to ban open burning, control auto and industrial emissions and reduce power plant emissions. The results have demonstrated lowered NO_x, volatile hydrocarbons, ozone and carbon monoxide levels. It is important to note that the time to improvement was prolonged (decades) and the result of such factors as the development of required technology, development and implementation of legislative initiatives and overcoming social/political opposition. Nevertheless, dramatic changes have occurred in these cities.

In 2013, the Chinese government released its first National Action Plan on Air Pollution Prevention and Control. This requires aggressive reduction of air pollution particulates that, if successful, should help mitigate adverse health effects. However, to achieve this air quality improvement, a complex interaction of government, industry and academia will be needed and may take decades to lower pollutant levels, as was the case in southern California. These circumstances suggest further investigation of exposures and related health effects in hopes of developing more refined exposure guidelines and enhancing the ability to prevent further disease from occurring.

Disease from air pollution

Based upon reports in the western literature and English versions of reports from China, the focus of health research from air pollution has been on the lungs and heart, tissue with more direct exposure. Although the respiratory tract is the main site where the body absorbs air pollutants, health problems have been described in various ways. Adverse health effects include increased hospital visits [13,14], premature mortality [12,16], increased cardiovascular disease [9,12,18,19], increased asthma [20], lung cancer [21] and neurological conditions [22]. Many other disease categories may have important associations with air pollution (e.g., pregnancy, rheumatologic conditions, mental health) but have not been extensively evaluated.

Pope *et al.* conducted a meta-analysis of cardio-vascular mortality and exposure over a wide range of particulate inhalation doses and found a nonlinear dose-response relationship [19]. The dose-response curve had a sharply increasing trend at low doses followed by a much slower increase at higher doses. Insight from this nonlinear dose-response relationship suggests that a minor reduction in exposure may not lead to significant health benefits. Rather, a large reduction in exposures may be needed to obtain meaningful reductions in cardiovascular disease and mortality.

Many types of particulates may result in disease of the lungs. Toxicology studies have shown that the inflammatory responses in the lung as the result of inhaling low solubility, low-toxicity ultrafine particles and fine particles are proportional to deposited surface area [23–25]. Exposures to smaller particulates like $PM_{2.5}$ have been less studied but insights have been obtained. The United States EPA states that, “evidence is sufficient to conclude that a causal relationship is likely to exist between long-term exposure to $PM_{2.5}$ and respiratory effects” [10]. Others also suggest health effects occur from long-term exposure [26]. Decreased lung function, increased respiratory symptoms and asthma development are all findings in studies that assessed $PM_{2.5}$ exposure. Short-term exposures to high $PM_{2.5}$ levels in China, which are more common in urban areas, have been associated with increased hospitalizations and emergency department visits [4,11–14,27]. Studies of healthy volunteers that involved controlled exposures to ambient particles like diesel exhaust, suggest that pulmonary inflammation occurs as a result of oxidative stress on alveolar macrophages and bronchial epithelium [28]. Air pollutants may also trigger an obstructive airways abnormality, or chronic obstructive pulmonary disease (COPD) [12,29,30]. Because exposures are usually a mixture of different types and sizes of particulates, it is difficult to determine whether a specific $PM_{2.5}$ fraction is responsible for a unique health effect or whether the effect is from other fractions in combination. It has also been difficult to determine the specific role of smoking in air pollution studies. In countries, including China, high smoking rates undoubtedly play a role in disease formation. Information regarding $PM_{2.5}$ toxicity also stems from occupational environments where exposure measurements are more frequently gathered, often in response to government compliance needs. The aluminum industry is one example where ischemic heart disease has been associated with $PM_{2.5}$ exposure [31].

An important mechanism by which air pollution causes lung injury is through the inflammatory response. Immunoglobulin levels, T cell regulation and neutrophil counts have all been impacted by air pollution [32]. Children may be particularly vulnerable to pollutants as their lungs are still growing and may be more subject to abnormal development, function and infection [20,32]. Asthma and increased hospital admissions in children are related to air pollution [32,33]. An increased rate for cardiovascular mortality in China [27] and elsewhere [16], a likely reflection of pollution effects on the elderly.

The pathogenesis of lung cancer and fine particulate exposure has been linked to DNA adducts and DNA damage [34–36]. An extensive review has identified DNA adducts, chromosomal aberrations, 1-hydroxypyrene, nucleobase oxidative damage and methylation as suspected markers of lung cancer associated with particulate exposure [37].

There are early biomarkers of disease that could be helpful in identifying individuals at risk for these particle-related lung diseases. Biomarkers may play an important role in the prevention of disease progression if they can be identified early enough in the presence of exposure and prior to the occurrence of disease. A number of biomarkers are under investigation currently for this purpose and include C-reactive protein, fibrinogen, leukocyte counts and platelet counts [3]. There is a lung-specific biomarker that has been used in research involving the prediction of COPD mortality. This is known as CCSP (club-cell specific protein) and represents the degree of injury to the bronchial epithelial lining [30]. This could be another candidate that could be helpful in biomarker research, although it requires the collection of bronchial washings obtained by bronchoscopy, thus limiting its utility in larger studies.

Epidemiologic designs in the study of air pollution

There are multiple types of air pollution epidemiology studies that are potentially available to better understand the associated health problems. The best study approach depends on which questions are asked, which populations are available for study, what health data resources are available, and the quality and accessibility of exposure/pollutant information. The goal is to understand health endpoints as a function of air pollutant exposure. This exposure-disease relationship, once defined, can theoretically be utilized to predict and prevent diseases from occurring and to refine exposure guidelines.

Most epidemiologic studies of air pollution and health effects to date have taken place at the population level with the use of ambient air pollution levels as the exposure of interest. These have focused on cardiovascular disease, asthma and lung cancer, although recent studies have included cognition [22]. Some have included a hierarchal approach using population and individual data to get at confounding issues. For example, a component of the MESA study assessed various air contaminants in six cities across the United States and evaluated cardiovascular disease in these same cities [17]. A small number of individuals also participated in personal monitoring. Although some studies have used geocoded ambient measurements with monitoring stations this approach assumes that all members of a geocode have similar exposures and may be prone to exposure misclassification.

An alternative design approach is to study the effect of air pollution using the individual as the unit of study. This approach may occur in several different designs, each with its own strengths and weaknesses [29,39,40]. In these designs, individual disease measurement and individual exposure measurement are used to assess the exposure-disease association. Studies of this type potentially allow increased accuracy and precision in measurement, as there is a greater opportunity to control for factors (e.g., smoking) that may influence outcomes and conclusions. Two important designs that utilize individual exposure and health information are the cohort and case-control studies.

In the cohort design, a group of individuals is often identified because of a common exposure environment. In the United States and Western Europe, the workplace has been a focal point for this design. The work group (cohort) may be followed into the future (prospective cohort approach) or can be identified at a point in the past and followed to the present (retrospective cohort approach). Each individual in the cohort has an estimate made of exposure(s) during the time of the study. In workplace studies, exposure measurements are often available through the employer, where the measurement of air contaminants may have been obtained for government compliance reasons. These measurements may include sampling of the air in which an individual works and/or measurements of the immediate breathing zone of a worker. Occupational cohort studies are excellent ways to assess common diseases in terms of morbidity and mortality rates since there is typically a way to completely enumerate the number of cases (numerator of the rate) as well as the total number of workers (denominator). However, they are not particularly good at evaluating more uncommon conditions. Also, if the cohort is too large, it is not practical to have detailed exposure information on each worker [29,39,40]. However, they may lack information on important confounding variables like smoking, making them less helpful.

In the case-control design, exposures of interest are compared to a group of cases and a “control” group, which is similar in as many ways to the “case” group, except for not having the disease of interest [40]. This approach has more efficiency than cohort studies, since the cases are already in existence and may be identified from data sources like cancer registries. Case-control studies are generally suited for the study of rare diseases, where the cohort study may not be practical. In some instances, a case-control study may be complicated by cases occurring after a worker leaves the work setting. In other cases, exposure information may be limited or absent in the workplace, creating the possibility of exposure misclassification. Both case-control and cohort designs are used to study occupational groups, where the complete enumeration of workers is possible, the length of employment is available, and the job and exposure information has often been gathered. Population-based case-control studies are more complicated to conduct, as the exposure of interest may be difficult to quantify and where comparable control groups may be difficult to find. Case-control studies may also be limited by information on confounding. This is particularly true when the disease in question is highly fatal, and the information on confounding is not directly available from the cases.

In the cross-sectional design, individual data on disease status and exposure are captured at one point in time. This is the simplest, but also the weakest design in terms of assessing an exposure-disease relationship [40]. Typically, in a screening study, a group of participating individuals fills out a questionnaire that provides occupational, medical and smoking information and undergoes clinical testing (chest X-rays, laboratory tests, etc.). Cross sectional studies have inherent limitations due to collecting data at just one point in time. They are prone to participation bias, meaning either the healthiest or the sickest individuals may be more likely to participate. It may be possible to overcome this shortcoming by collecting information at multiple points in time to create an interval where events may be captured.

The time-series approach may be used as a way to study population mortality or morbidity outcomes over specified time intervals in combination with ambient exposure levels over the same intervals. This design is useful for understanding whether a change in disease frequency is related to changes in ambient exposures [29]. When exposures measurements are not limited to the individual studied, there may be a potential for exposure misclassification since there is typically individual variation in how exposures occur. The tendency is for this type of error to be random (non-differential misclassification) but it is possible for error in this setting to occur in a systematic way, concentrating an effect (differential misclassification).

Exposure assessment issues in air pollution studies

The indoor residential and work microenvironments are maybe important contributors to an individual's personal exposure to airborne contaminants. Although the relationship between exposure and disease might be better investigated using personal exposures that account for individual exposures in various micro-environments, this is rarely done. Study designs that account for personal exposures (e.g., case-control or cohort studies) typically are occupational in nature and may be considerably more time and resource intensive, particularly if multiple exposures are involved. The ideal approach requires the assessment of exposures in indoor residential and workplace exposures in addition to outdoor exposures and each of these micro-environments presents its own challenges in assessing exposures.

Another important consideration is selection of the metric used to assess exposure. While the gravimetric measure of $PM_{2.5}$ has been used most commonly for regulatory and population-based epidemiological purposes, several other metrics have been proposed. Since the three main PM sources in China, vehicular exhaust, power plant emissions and biomass burning are combustion-related, we would expect particles less than 1 μm in aerodynamic diameter to predominate. Using $PM_{1.0}$ as a metric would exclude some of the non-combustion related aerosols and would be a more source-specific metric. Pui hypothesized that $PM_{1.0}$ may give a more realistic indication of air pollution, may be better correlated with health effects and may be better used for targeted pollution reduction methods that focus on automobile and industrial emissions [5].

The above exposure metrics are all time-averaged over 24 or 48 h. However, PM levels are known to exhibit significant short-term variability and a systematic assessment of short-term variability in indoor and outdoor values requires suitable real-time PM monitors, both mass-based and surface area or number-based. These short-term variations may be relevant to health. Michaels has hypothesized that short-term excursions may potentially explain some of the excess mortality and morbidity attributed to ambient PM [41,42].

Epidemiologic data from China

In China, general rates of overall cancer incidence and mortality and specifically lung cancer incidence and mortality in urban and rural areas have been reported from 2006 to 2010 (Tables 2 and 3) [43–47]. New cancer cases have been increasing since 2006, corresponding to the increase in number of registries reporting. Four of these five years of reports also suggest an increase in lung cancer incidence and mortality in men vs. women and in urban vs. rural areas. The fifth year (2010) is lower than the others but is somewhat difficult to use in comparison, as the covered lives are substantially larger. Although consistent with urban areas having greater degrees of pollution, the exact explanation for this finding is not known. It is known that different parts of China have different configurations of air contaminants. Lung cancer mortality appears to have increased. In the 1970s, mortality from lung cancer was reported to be 5.7/100 000, changing to 17.2/100 000 in the 1990s [48]. Today's rates are increased from the 1990s. Exposure to cigarette smoke and indoor air contaminants

Table 2 Cancer incidence and mortality in China, 2006–2010

Year	Population size[a]	Crude incidence	Total incidence	Total mortality[b]
2006 [43]	59 567 322	273/100 000	163 013	104 662
2007 [44]	59 809 313	276/100 000	165 171	105 416
2008 [45]	66 138 784	299/100 000	197 838	122 136
2009 [46]	85 470 522	285/100 000	214 366	137 462
2010 [47]	158 403 248	235/100 000	3 293 029	1 956 622[c]

[a]Cancer registries covered lives; size is a reflection of urban and rural-based cancer registries reporting.
[b]Refers to deaths from all cancers.
[c]Estimated number projected to entire country.

Table 3 Lung cancer mortality by gender in urban and rural areas[a]

Year	Overall[b]	Urban men[b]	Urban women[b]	Rural men[b]	Rural women[b]
2006 [43]	44.15	63.44	30.84	46.19	19.59
2007 [44]	45.50	65.71	33.05	46.51	NA
2008 [45]	46.07	65.62	31.66	50.79	20.18
2009 [46]	45.57	67.61	28.39	48.58	22.56
2010 [47]	37.00	56.72 41.04[c]	27.04 17.31[c]	43.26 38.09[c]	19.56 15.64[c]

[a]Rates are a reflection of urban and rural-based cancer registries reporting.
[b]Crude cancer mortality is presented as an unadjusted rate (cases/100 000).
[c]Top number represents non-age adjusted rate; bottom number represents age-adjusted rate standardized to China population in 2000.

may play a role in these findings, but no definitive explanation is available at this time.

Knowledge gaps and direction for additional research

To better understand the health risks of $PM_{2.5}$ and other atmospheric pollutants we need to better understand which individuals are at highest risk. If this were known, efforts could be focused on minimizing future exposure in these individuals, with hopes of preventing further disease incidence and progression. The type of information required to enhance our understanding of individual risk begins with the use of the most appropriate study design. Although the population-based studies have identified the putative diseases of interest, individual-based exposure and health end point studies are required to refine the estimates of individual risk. Cohort and case-control studies are the best studies by which to obtain this information. They offer a key advantage in being able to assess disease after an exposure has occurred, compared to a cross-sectional study where this may be obscured. The study of mortality and morbidity as the endpoint of interest, along with individual exposure in these studies, could be a helpful step to further understanding air pollution in China. Studies have been conducted in other settings looking at individual health end points [49] or individual exposure monitoring [50]. But, ambient exposure estimates have predominated the air pollution literature.

The investigation of an occupational cohort may be helpful, providing that exposure measurements are available within the workforce and these exposures parallel those in the general population. The more similar the workplace exposure to the ambient environment, the more easily inference can be made to the general population. A major advantage in studying the workforce is that, at least in western countries, it is usually possible to track each employee as they enter and leave the workforce, making it possible to obtain a complete enumeration of the workforce along with the amount of time worked. The resulting disease rate can then be readily determined. This is in opposition to the more complicated task of assessing communities where people are routinely moving in and out, with subsequent uncertain estimates in disease rates. In some circumstances, understanding exposure may be obtained through the use of on-site personal and area exposure measurements. If a workplace process has been stable, it may be possible to use these measures to estimate past exposure. This requires information on what job tasks workers performed and for how long. The subsequent exposure estimate is expressed as a cumulative exposure. The cumulative exposure metric is an accepted technique often used in epidemiologic investigations of dust-related lung disease, because of its biological relevance. Within the occupational setting it is typical to have a range of exposures and durations, making internal comparisons possible.

There may also be disadvantages of studying workers. Individuals who work are typically healthier than those not working. The latter group also contributes to rates of disease in the comparison population. This may result in lower rates of disease in working groups, an occurrence known as the "healthy worker effect." If present, it may provide the false assurance that workers are unaffected by exposures that they encounter. Exposures in some work settings may be dramatic. This could overwhelm the ability to detect additional work-related diseases, which could be masked by a large exposure. This is an unusual problem in community exposure assessment. Studies of workers do not address the exposure-disease relationships in non-working ages, the very young and the elderly, groups that could be more vulnerable to pollutants. The length of time a cohort works will vary by the type of job and industry. The exposure time will likewise vary. The follow-up of cohorts with short work durations is complicated as these individuals could have multiple exposures in multiple industries over time, complicating the exposure-disease relationship.

In addition to the proper design and exposure metric, the use of biomarkers and traditional measures of disease identification will be required to better understand exposure-related diseases. The use of biomarkers is limited by their relative novelty in air pollution research. The ideal biomarker for air pollutants has not been clarified as of yet. As genetic information becomes more available, gene-environment interaction studies will have potential future use in China and elsewhere, in combination with biomarkers and other disease endpoints.

Conclusions

China's air pollution has been increasing and has been associated with population-based disease. It is likely that this problem does not have a short-term solution and will require further study of exposed individuals. Existing data suggest higher disease rates in men and in urban areas, the exact explanation for which is lacking. Cohort and case-control investigations have unique attributes that could make them desirable to use in this setting. Other important considerations include detailed exposure assessment and the use of biomarkers as a means to better understand and manage the threat posed by air pollution in China.

Compliance with ethics guidelines

Jeffrey H. Mandel, Christine Wendt, Charles Lo, Guangbiao Zhou, Marshall Hertz, and Gurumurthy Ramachandran declare no conflicts of interest. This article does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

References

1. Chen Z, Wang JN, Ma GX, Zhang YS. China tackles the health effects of air pollution. Lancet 2013; 382(9909): 1959–1960
2. China Statistical Yearbook at http://www.stats.gov.cn/tjsj/ndsj/2013/indexeh.htm
3. Cheng S, Yang L, Zhou X, Wang Z, Zhou Y, Gao X, Nie W, Wang X, Xu P, Wang W. Evaluating $PM_{2.5}$ ionic components and source apportionment in Jinan, China from 2004 to 2008 using trajectory statistical methods. J Environ Monit 2011; 13(6): 1662–1671
4. Guo Y, Jia Y, Pan X, Liu L, Wichmann HE. The association between fine particulate air pollution and hospital emergency room visits for cardiovascular diseases in Beijing, China. Sci Total Environ 2009; 407(17): 4826–4830
5. Pui DYH, Chen SC, Zuo Z. $PM_{2.5}$ in China: Measurements, sources, visibility and health effects, and mitigation. Particuology 2014; 13: 1–26
6. WHO Country profile of environmental burden of disease: China. World Health Organization 2009 at: http://www.who.int/entity/quantifying_ehimpacts/national/countryprofiles/china.pdf
7. Cao JJ, Shen ZX, Chow JC, Watson JG, Lee SC, Tie XX, Ho KF, Wang GH, Han YM. Winter and summer $PM_{2.5}$ chemical compositions in fourteen Chinese cities. J Air Waste Manag Assoc 2012; 62(10): 1214–1226
8. Chen SC, Tsai CJ, Huang CY, Chen HD, Chen SJ, Lin CC, Tsai JH, Chou CCK, Lung SCC, Huang WR, Roam GD, Wu WY, Smolik J, Dzumbova L. Chemical mass closure and chemical characteristics of ambient ultrafine particles and other PM fractions. Aerosol Sci Technol 2010; 44(9): 713–723
9. Cao J, Xu H, Xu Q, Chen B, Kan H. Fine particulate matter constituents and cardiopulmonary mortality in a heavily polluted Chinese city. Environ Health Perspect 2012; 120(3): 373–378
10. U. S. EPA. Integrated science assessment for particulate matter (final report). Washington, D.C.: US EPA 2009
11. Guo Y, Tong S, Zhang Y, Barnett AG, Jia Y, Pan X. The relationship between particulate air pollution and emergency hospital visits for hypertension in Beijing, China. Sci Total Environ 2010; 408(20): 4446–4450
12. Li P, Xin J, Wang Y, Wang S, Li G, Pan X, Liu Z, Wang L. The acute effects of fine particles on respiratory mortality and morbidity in Beijing, 2004–2009. Environ Sci Pollut Res Int 2013; 20(9): 6433–6444
13. Wang X, Chen R, Meng X, Geng F, Wang C, Kan H. Associations between fine particle, coarse particle, black carbon and hospital visits in a Chinese city. Sci Total Environ 2013; 458–460: 1–6
14. Qiao L, Cai J, Wang H, Wang W, Zhou M, Lou S, Chen R, Dai H, Chen C, Kan H. $PM_{2.5}$ constituents and hospital emergency-room visits in Shanghai, China. Environ Sci Technol 2014; 48(17): 10406–10414
15. Parrish DP. Air Pollution in Developing Mega Cities-Something Old, Something New—Lessons from Los Angeles. Cooperative Institute for Research in Environmental Sciences, University of

Colorado Presentation: Bolder Colorado on August 7, 2014
16. Franklin M, Zeka A, Schwartz J. Association between $PM_{2.5}$ and all-cause and specific-cause mortality in 27 US communities. J Expo Sci Environ Epidemiol 2007; 17(3): 279–287
17. Kaufman JD, Adar SD, Allen RW, Barr RG, Budoff MJ, Burke GL, Casillas AM, Cohen MA, Curl CL, Daviglus ML, Diez Roux AV, Jacobs DR Jr, Kronmal RA, Larson TV, Liu SL, Lumley T, Navas-Acien A, O'Leary DH, Rotter JI, Sampson PD, Sheppard L, Siscovick DS, Stein JH, Szpiro AA, Tracy RP. Prospective study of particulate air pollution exposures, subclinical atherosclerosis, and clinical cardiovascular disease: the Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESA Air). Am J Epidemiol 2012; 176 (9): 825–837
18. Yorifuji T, Suzuki E, Kashima S. Outdoor air pollution and out-of-hospital cardiac arrest in Okayama, Japan. J Occup Environ Med 2014; 56(10): 1019–1023
19. Pope CA 3rd, Burnett RT, Krewski D, Jerrett M, Shi Y, Calle EE, Thun MJ. Cardiovascular mortality and exposure to airborne fine particulate matter and cigarette smoke: shape of the exposure-response relationship. Circulation 2009; 120(11): 941–948
20. Lee SL, Wong WH, Lau YL. Association between air pollution and asthma admission among children in Hong Kong. Clin Exp Allergy 2006; 36(9): 1138–1146
21. Raaschou-Nielsen O, Andersen ZJ, Beelen R, Samoli E, Stafoggia M, Weinmayr G, Hoffmann B, Fischer P, Nieuwenhuijsen MJ, Brunekreef B, Xun WW, Katsouyanni K, Dimakopoulou K, Sommar J, Forsberg B, Modig L, Oudin A, Oftedal B, Schwarze PE, Nafstad P, De Faire U, Pedersen NL, Östenson CG, Fratiglioni L, Penell J, Korek M, Pershagen G, Eriksen KT, Sørensen M, Tjønneland A, Ellermann T, Eeftens M, Peeters PH, Meliefste K, Wang M, Bueno-de-Mesquita B, Key TJ, de Hoogh K, Concin H, Nagel G, Vilier A, Grioni S, Krogh V, Tsai MY, Ricceri F, Sacerdote C, Galassi C, Migliore E, Ranzi A, Cesaroni G, Badaloni C, Forastiere F, Tamayo I, Amiano P, Dorronsoro M, Trichopoulou A, Bamia C, Vineis P, Hoek G. Air pollution and lung cancer incidence in 17 European cohorts: prospective analyses from the European Study of Cohorts for Air Pollution Effects (ESCAPE). Lancet Oncol 2013; 14(9): 813–822
22. Ailshire JA, Crimmins EM. Fine particulate matter air pollution and cognitive function among older US adults. Am J Epidemiol 2014; 180(4): 359–366
23. Brown DM, Wilson MR, MacNee W, Stone V, Donaldson K. Size-dependent proinflammatory effects of ultrafine polystyrene particles: a role for surface area and oxidative stress in the enhanced activity of ultrafines. Toxicol Appl Pharmacol 2001; 175(3): 191–199
24. Tran CL, Buchanan D, Cullen RT, Searl A, Jones AD, Donaldson K. Inhalation of poorly soluble particles. II. Influence Of particle surface area on inflammation and clearance. Inhal Toxicol 2000; 12 (12): 1113–1126
25. Maynard RL, Maynard RL. A derived association between ambient aerosol surface area and excess mortality using historic time series data. Atmos Environ 2002; 36(36–37): 5561–5567
26. Beelen R, Stafoggia M, Raaschou-Nielsen O, Andersen ZJ, Xun WW, Katsouyanni K, Dimakopoulou K, Brunekreef B, Weinmayr G, Hoffmann B, Wolf K, Samoli E, Houthuijs D, Nieuwenhuijsen M, Oudin A, Forsberg B, Olsson D, Salomaa V, Lanki T, Yli-Tuomi T, Oftedal B, Aamodt G, Nafstad P, De Faire U, Pedersen NL, Östenson CG, Fratiglioni L, Penell J, Korek M, Pyko A, Eriksen KT, Tjønneland A, Becker T, Eeftens M, Bots M, Meliefste K, Wang M, Bueno-de-Mesquita B, Sugiri D, Krämer U, Heinrich J, de Hoogh K, Key T, Peters A, Cyrys J, Concin H, Nagel G, Ineichen A, Schaffner E, Probst-Hensch N, Dratva J, Ducret-Stich R, Vilier A, Clavel-Chapelon F, Stempfelet M, Grioni S, Krogh V, Tsai MY, Marcon A, Ricceri F, Sacerdote C, Galassi C, Migliore E, Ranzi A, Cesaroni G, Badaloni C, Forastiere F, Tamayo I, Amiano P, Dorronsoro M, Katsoulis M, Trichopoulou A, Vineis P, Hoek G. Long-term exposure to air pollution and cardiovascular mortality: an analysis of 22 European cohorts. Epidemiology 2014; 25(3): 368–378
27. Shang Y, Sun Z, Cao J, Wang X, Zhong L, Bi X, Li H, Liu W, Zhu T, Huang W. Systematic review of Chinese studies of short-term exposure to air pollution and daily mortality. Environ Int 2013; 54: 100–111
28. Vedal S, Sullivan J. Particulate matter. In: Rom WN, Markowitz S. Environmental and Occupational Medicine. 4th ed. Philadelphia, PA: Wolters Kluwer/Lippincott, Williams and Wilkins, 2007: 1487–1506
29. Samet JM, Bell ML. Air polution: epidemiology. In: Rom WN, Markowitz S. Environmental and Occupational Medicine. 4th ed. Philadelphia, PA: Wolters Kluwer/Lippincott, Williams and Wilkins, 2007: 1400–1420
30. Kelly E, Owen CA, Pinto-Plata V, Celli BR. The role of systemic inflammatory biomarkers to predict mortality in chronic obstructive pulmonary disease. Expert Rev Respir Med 2013; 7(1): 57–64
31. Neophytou AM, Costello S, Brown DM, Picciotto S, Noth EM, Hammond SK, Cullen MR, Eisen EA. Marginal structural models in occupational epidemiology: application in a study of ischemic heart disease incidence and $PM_{2.5}$ in the US aluminum industry. Am J Epidemiol 2014; 180(6): 608–615
32. Esposito S, Tenconi R, Lelii M, Preti V, Nazzari E, Consolo S, Patria MF. Possible molecular mechanisms linking air pollution and asthma in children. BMC Pulm Med 2014; 14(1): 31
33. Barnett AG, Williams GM, Schwartz J, Neller AH, Best TL, Petroeschevsky AL, Simpson RW. Air pollution and child respiratory health: a case-crossover study in Australia and New Zealand. Am J Respir Crit Care Med 2005; 171(11): 1272–1278
34. Vineis P, Husgafvel-Pursiainen K. Air pollution and cancer: biomarker studies in human populations. Carcinogenesis 2005; 26 (11): 1846–1855
35. Palli D, Russo A, Masala G, Saieva C, Guarrera S, Carturan S, Munnia A, Matullo G, Peluso M. DNA adduct levels and DNA repair polymorphisms in traffic-exposed workers and a general population sample. Int J Cancer 2001; 94(1): 121–127
36. Ruchirawa M, Mahidol C, Tangjarukij C, Pui-ock S, Jensen O, Kampeerawipakorn O, Tuntaviroon J, Aramphongphan A, Autrup H. Exposure to genotoxins present in ambient air in Bangkok, Thailand—particle associated polycylic aromatic hydrocarbons and biomarkers. Sci Total Environ 2002; 287(1-2): 121–132
37. Demetriou CA, Raaschou-Nielsen O, Loft S, Møller P, Vermeulen R, Palli D, Chadeau-Hyam M, Xun WW, Vineis P. Biomarkers of ambient air pollution and lung cancer: a systematic review. Occup Environ Med 2012; 69(9): 619–627
38. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein

and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med 2000; 342(12): 836–843
39. Rothman KJ, Greenland S, Lash TL. Modern Epidemiology. Chapters 6–12 (Study Design and Conduct). Philadelphia, PA: Wolters-Kluwer/Lippincott, Williams and Wilkins, 2008: 87–209
40. Elwood M. Study designs which can demonstrate and test causation. In: Elwood M. Critical Appraisal of Epidemiological Studies and Clinical Trials. 3rd ed. New York, NY: Oxford University Press, 2007: 19–52
41. Michaels RA. Airborne particle excursions contributing to daily average particle levels may be managed via a 1- hour standard, with possible public health benefits. Aerosol Sci Technol 1996; 25(4): 437–444
42. Michaels RA. Permissible daily airborne particle mass levels encompass brief excursions to the “London Fog” range, which may contribute to daily mortality and morbidity in communities. Appl Occup Environ Hyg 1998; 13(6): 385–394
43. Chen WQ, Zhang SW, Zou XN, Zhao P. Cancer incidence and mortality in China, 2006. Chin J Cancer Res 2011; 23(1): 3–9
44. Chen WQ, Zeng HM, Zheng RS, Zhang SW, He J. Cancer incidence and mortality in China, 2007. Chin J Cancer Res 2012; 24(1): 1–8
45. Chen WQ, Zheng RS, Zhang SW, Li N, Zhao P, Li GL, Wu LY, He J. Report of incidence and mortality in China cancer registries, 2008. Chin J Cancer Res 2012; 24(3): 171–180
46. Chen W, Zheng R, Zhang S, Zhao P, Li G, Wu L, He J. Report of incidence and mortality in China cancer registries, 2009. Chin J Cancer Res 2013; 25(1): 10–21
47. Chen W, Zheng R, Zhang S, Zhao P, Zeng H, Zou X, He J. Annual report on status of cancer in China, 2010. Chin J Cancer Res 2014; 26(1): 48–58
48. Chen W, Zheng R, Zeng H, Zhang S. The epidemiology of lung cancer in China. J Cancer Biol Res 2014; 2(1): 1043
49. Dockery DW, Pope CA, Xu X, Spengler JD, Ware JH, Fay ME, Ferris BG Jr, Speizer FEN. An association between air pollution and mortality in six U.S. cities. N Engl J Med 1993; 329 (24): 1753–1759
50. Jerrett M, Shankardass K, Berhane K, Gauderman WJ, Künzli N, Avol E, Gilliland F, Lurmann F, Molitor JN, Molitor JT, Thomas DC, Peters J, McConnell R. Traffic-related air pollution and asthma onset in children: a prospective cohort study with individual exposure measurement. Environ Health Perspect 2008; 116(10): 1433–1438