Chemosphere 216 (2019) 766–773

Contents lists available at ScienceDirect

Chemosphere

journal homepage: www.elsevier.com/locate/chemosphere

An urban-rural and sex differences in cancer incidence and mortality and the relationship with $PM_{2.5}$ exposure: An ecological study in the southeastern side of Hu line

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HIGHLIGHTS

- Increased risks for lung, ovarian, prostate cancers and leukemia are closely associated with increased $PM_{2.5}$ exposure (Short version: Lung/ovarian/prostate cancer and leukemia are closely related with increased $PM_{2.5}$).
- $PM_{2.5}$ significantly impacts the risks for lung cancer and leukemia in rural area.
- $PM_{2.5}$ significantly impacts the risks for prostate and ovarian cancers in urban area.
- Females are at higher risks for lung cancer and leukemia due to elevated $PM_{2.5}$

ARTICLE INFO

Article history:
Received 30 July 2018
Received in revised form
23 October 2018
Accepted 26 October 2018
Available online 26 October 2018

Handling Editor: R. Ebinghaus

Keywords:
Urban-rural difference
Sex difference
Relative risk
$PM_{2.5}$
Cancer incidence
Cancer mortality

ABSTRACT

This study investigates the urban-rural and sex differences in the increased risks of the ten most common cancers in China related to high $PM_{2.5}$ concentration in the southeastern side of Hu line. Pearson correlation coefficient is estimated to reveal how the cancers closely associated with $PM_{2.5}$ long-term exposure. Then linear regression is conducted to evaluate sex- and area-specific increased risks of those cancers from high level $PM_{2.5}$ long-term exposure. The major finding is with the increase of every 10 $\mu g/m^3$ of annual mean $PM_{2.5}$ concentration, the increase of relative risks for lung cancer incidence and mortality are 15% and 23% for males, and 22% and 24% for females in rural area. For urban area, the increase of relative risk for ovarian cancer incidence is 9% for females, while that for prostatic cancer increases 17% for males. For leukemia, the increase of relative risks for incidence and mortality are 22% and 19% for females in rural area, while in urban area the increase of relative risk for mortality is 9% for males and for incidence is 6% for females. It is also found that with increased $PM_{2.5}$ exposure, the risks for ovarian and prostatic cancer rise significantly in urban area, while risks for lung cancer and leukemia rise significantly in rural area. The results demonstrate the higher risks for lung cancer and leukemia with increased $PM_{2.5}$ exposure are more significant for female. This study also suggests that the carcinogenic effects of $PM_{2.5}$ have obvious sex and urban-rural differences.

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https://doi.org/10.1016/j.chemosphere.2018.10.183

1. Introduction

The threat to the public health caused by the exposure to fine particulate matter and air pollution has attracted more and more attentions from the public, governments and health organizations worldwide (Pope et al., 1995; Katsouyanni et al., 2001; Yim and Barrett, 2012). Recent studies show that air pollution has become a major global health risk factor (Gu et al., 2018; Forouzanfar et al., 2016; Cohen et al., 2004; Oliveri Conti et al., 2017), particulate matter with aerodynamic diameter less than 2.5 μm ($PM_{2.5}$) shortens life expectancy due to its health impact on morbidity and mortality (Mazzi et al., 2017; Dai et al., 2014; Samet et al., 2000), especially for lung cancer (Dehghani et al., 2017; MacNaughton et al., 2017) and cardiovascular diseases (Gurgueira et al., 2002; Zhang et al., 2018; Lee et al., 2014). Cohen et al. (2017) indicated that 4.2 million deaths in 2015 were caused by the exposure to $PM_{2.5}$, and more than 1.1 million deaths were in China. WHO issued a $PM_{2.5}$ guideline value of annual mean 10 μg/m^3, and interim targets (IT) level 1, 2 and 3 of 35, 25 and 15 μg/m^3. At IT-1 level, a 15% higher long-term mortality risk is reported relative to the guideline level (World Health Organization, 2006). However, IT-1 level is not achieved at most of the areas of China, and population-weighted mean of $PM_{2.5}$ concentration in Chinese cities were 61 μg/m^3 at the year of 2013 (Huang et al., 2014; Zhang and Cao, 2015). Therefore, the health impact caused by $PM_{2.5}$ exposure has become an urgent issue in China (Hu and Jiang, 2014; Li and Gao, 2014; Pui et al., 2014; Liu et al., 2016, 2017).

The studies in the developed areas revealed that air pollution caused by $PM_{2.5}$ was a serious threat to human health in various aspects, i.e. its enhancement of cardiopulmonary diseases (Yoshinaga et al., 2018; Ali et al., 2017; Wong et al., 2008; Pope et al., 2009; Oh et al., 2011; Madrigano et al., 2013; Cesaroni et al., 2014), premature birth and low birth weight (Han et al., 2018; Brauer et al., 2008; Aguilera et al., 2009; Kloog et al., 2012), and systemic diseases (O'Neill et al., 2005; Dubowsky et al., 2006; Zeka et al., 2006; Pope et al., 2016). In China, many studies showed that short-term exposure of $PM_{2.5}$ was also associated with the rise of hospital emergency-room visits, cardio-respiratory diseases and mortality in city areas (Chen et al., 2018; Guo et al., 2009; Li et al., 2010; Chen et al., 2011; Huang et al., 2012; Wang et al., 2013; Yang et al., 2012; Lu. et al., 2015; Qiao et al., 2014); while cohort studies show that ambient particulate matter can increase the risks of total, cardiovascular and respiratory mortality (Dong et al., 2012; Zhou et al., 2014; Zhang et al., 2014; Chen et al., 2016; Guo et al., 2016). There are two main causes of these health hazards: one is that the fine particles in $PM_{2.5}$ are small enough to arrive a large part of human organs (including the respiratory system, the circulatory system, and the reproductive system), and another is that there are numerous kinds of hazardous substances in the $PM_{2.5}$, i.e. carcinogenic polycyclic aromatic hydrocarbons (PAHs), heavy metals (such as lead, mercury, chromium and cadmium), and pathogenic microorganisms (such as bacteria, viruses and fungi) (Lee et al., 2007; Cao et al., 2014; Zhai et al., 2014). PAHs in $PM_{2.5}$ are suspected to be a predisposing factor of breast cancer because of its disruption of BRCA-1 gene expression in estrogen receptor (Jeffy et al., 2002). Parikh et al. (Parikh and Wei, 2016) also conclude that PAHs in $PM_{2.5}$ have a significant impact on the increased incidence of female breast cancer in urban areas. Further, BRCA-1 has been confirmed to be associated with ovarian cancer (Chen and Parmigiani, 2007). Therefore, it could be deduced that cancer is a manifestation of the health effects of $PM_{2.5}$ in the regions with large population density, since PAHs can almost always be detected in $PM_{2.5}$ in these regions (Yang et al., 2011).

The $PM_{2.5}$ concentration in China has been at the elevated level for a long time and the main hazardous substances in $PM_{2.5}$ such as PAHs and heavy metals have also been identified to have impacts on increased risks for some common disease (Martin et al., 2017; Leontief and Ford, 1971; Contoyannis and Jones, 2004; Huang et al., 2011). Thus, a screen on all most common disease is conducted in this study to understand the health effects of $PM_{2.5}$ exposure in China. Moreover, we need to consider the geographical and sex factors, because there are spatial differences in the $PM_{2.5}$ concentration and compositions (mainly between urban and rural area) as well as sex differences in the sensitivity to toxic substances. To assess the health effects caused by $PM_{2.5}$ in China, firstly, we need to find out which cancers closely associated with high $PM_{2.5}$ concentration; and then, we need to evaluate sex- and area-specific increased risks of those cancers from high level $PM_{2.5}$ long-term exposure.

In this study, we first investigated the association between the ten most common cancers in China (identified by the National Central Cancer Registry of China) incidence and mortality with $PM_{2.5}$ concentration to find out which cancers are closely relative to $PM_{2.5}$ by using the time series data of yearly incidence and mortality of the ten most common cancers and the annual mean $PM_{2.5}$ concentration in China from 2000 to 2011. Secondly, we estimated the sex- and area-specific increased cancer incidence/mortality risks from long-term exposure to high $PM_{2.5}$ concentration by using spatiotemporal series data of the southeastern side of Hu line from 2006 to 2009. Finally, we studied the urban-rural and sex differences in the increased risks of incidence and mortality for the ten most common cancers from long-term exposure to high $PM_{2.5}$ concentration. The southeastern side of Hu line (Hu, 1990) was selected as our research region, because this part of China has larger population density and more developed social economic level, which mean the air pollution caused by $PM_{2.5}$ is very serious and the data collected are also more consistent with the actual situation.

2. Materials and methods

The data collection method and statistical method were presented in section 2.1 and section 2.2, respectively.

2.1. Data

Cancer incidence and mortality data as well as gridded $PM_{2.5}$ concentrations and population data could be collected according to the following methods.

2.1.1. Cancer incidence and mortality data

The data used in this paper are:

1) Cancer statistics reported in the work of Chen et al. (Dong et al., 2012). This is a time series dataset spanning from 2000 to 2011. It consists of cancer incident and mortality of 22 registries covering 44.4 million population. This dataset was employed to conduct Pearson correlation coefficient analysis to investigate the relationship between cancer incidence and mortality and $PM_{2.5}$ exposure.
2) Chinese cancer registry annual report (2009–2012) issued by the National Central Cancer Registry of China (NCCR). Data collected from the report spanning from 2006 to 2009. This is a spatiotemporal series dataset containing cancer incident and mortality data reported from 34 local population-based cancer registries located in the area southeast of Hu line known as an area with greater population density and more developed economy (as presented in Fig. 1). The total 34 cancer registries including 16 and 18 sites for urban and rural areas respectively. This dataset was used to perform linear regression to estimate

the area-specific and sex-specific increased risks of cancer incidence and mortality from long-term exposure to high $PM_{2.5}$ concentration.

Both of the two datasets used in this study were validated by NCCR based on the Guidelines for Chinese Cancer Registration and International Agency for Research on Cancer/International Association of Cancer Registries (IARC/IACR) data-quality criteria.

2.1.2. Gridded $PM_{2.5}$ concentrations, population and per capita GDP data

The ambient $PM_{2.5}$ measurements in China were not available until 2012, thus $PM_{2.5}$ concentration was estimated from AOD as an alternative. The $0.1^\circ \times 0.1^\circ$ gridded annual mean $PM_{2.5}$ concentrations for the period of 2000–2011 were obtained from Atmospheric Composition Analysis Group (http://fizz.phys.dal.ca/~atmos/martin/?page_id=140). The area covered by each grid is approximately equal to the area covered by a cancer registration site. Therefore a corresponding gridded $PM_{2.5}$ concentration can be associated with each cancer registry.

The permanent resident population data for each cancer registry were obtained from the 5th and 6th national population census conducted in 2000 and 2010, respectively. The population were then linearly interpolated and extrapolated to the whole period of 2000–2011.

The annual per capita GDP data are obtained from National Bureau of Statistics of China (http://data.stats.gov.cn/easyquery.htm?cn=C01).

2.2. Statistical methods

2.2.1. The exposure level of $PM_{2.5}$

For each cancer registry, the population-weighted annual mean $PM_{2.5}$ exposure concentration could be calculated by Eq. (1):

$$\text{PWEL} = \sum(\text{Pi} \times \text{Ci}) \Big/ \sum \text{Pi} \tag{1}$$

where PWEL (population-weighted exposure level) is the population-weighted mean $PM_{2.5}$ exposure concentration ($\mu g/m^3$), and Pi and Ci are the population (10 thousands) and $PM_{2.5}$ concentration ($\mu g/m^3$) at each grid of the cancer registration site, respectively.

2.2.2. The association analysis of the time series dataset

In order to find out which cancers are closely associated with $PM_{2.5}$ long-term exposure, the correlation between cancers incidence (and mortality) and the population-weighted $PM_{2.5}$ exposure concentration were evaluated. As a comparison, the correlation between cancers incidence (and mortality) and per capita GDP were also calculated. Therefore, the Pearson correlation coefficients (R) between the time series of population-weighted annual mean $PM_{2.5}$ concentration (or per capita GDP) and incidence (or mortality) for the ten most common cancers were calculated and used to determine whether or not the two are related by comparing with the critical value of R when $p < 0.05$. R can be determined by Eq. (2):

$$R = \frac{\sum_{i=1}^{n}(X_i - \overline{X})(Y_i - \overline{Y})}{\sqrt{\sum_{i=1}^{n}(X_i - \overline{X})^2}\sqrt{\sum_{i=1}^{n}(Y_i - \overline{Y})^2}} \tag{2}$$

where R is the Pearson correlation coefficients, $n = 12$, is the number of the years. X_i and Y_i are the cancer incidence (or mortality) and the population-weighted $PM_{2.5}$ exposure concentration (or per capita GDP) of the ith year, respectively. $\overline{X} = \sum_{i=1}^{n} X_i \Big/ n$ and $\overline{Y} = \sum_{i=1}^{n} Y_i \Big/ n$, are the arithmetic average of X and Y, respectively.

2.2.3. The regression analysis of the spatiotemporal series dataset

The spatiotemporal series data were derived from 34 cancer registries (including 16 urban sites and 18 rural sites) over a 4-year period, and a sample of 136 (including 64 for urban sites and 72 for rural sites) $PM_{2.5}$-cancer incidence (and $PM_{2.5}$-cancer mortality) data were obtained. All the annual data at each of sites were firstly categorized at a bin of 5 $\mu g/m^3$ population-weighted annual mean $PM_{2.5}$ concentration, and then bin-averaged incidence, mortality and population-weighted annual mean $PM_{2.5}$ concentration were calculated. With the bin-averaged data, linear regression was performed to reveal the relation between incidence/mortality of the ten most common cancers and population-weighted annual mean $PM_{2.5}$ concentration, then to obtain the increased risks of cancers incidence and mortality with every 10 $\mu g/m^3$ increment of population-weighted annual mean $PM_{2.5}$ concentration. Accordingly, the errors can be reduced and the regression precision can be improved by using the average values of $PM_{2.5}$ exposure level, cancer incidence and mortality in each bin instead of original ones.

3. Results and discussion

The results of this study were firstly presented in this section, then, the results were discussed in details.

3.1. The association between the time series of $PM_{2.5}$ and incidence (and mortality) of the ten most common cancers during 2000–2011

The correlation coefficients between the time series of population-weighted annual mean $PM_{2.5}$ concentration and incidence (and mortality) of the ten most common cancers for both males and females were presented in Fig. 2. The parameter-per capita GDP was added as a contrast, because economy is an important interference factor which can not only contribute to

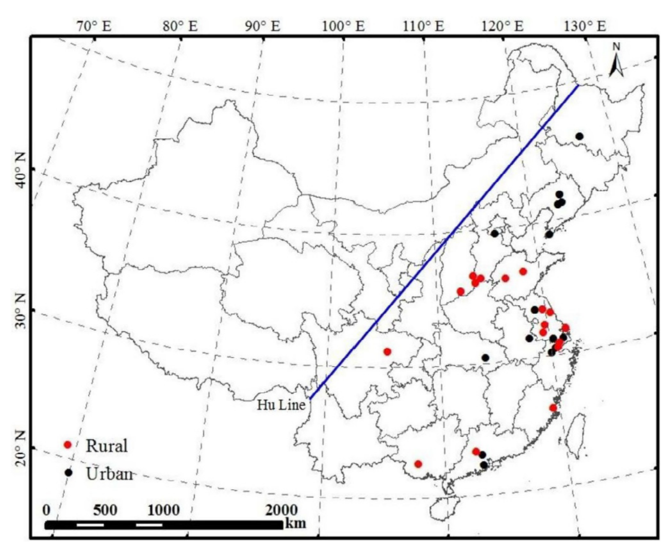

Fig. 1. Maps of the contributing cancer registries and geographic regions in China from the Chinese cancer registry annual report (2009–2012). The blue line indicates the Hu line, which marks a drastic difference in the distribution of China's population. The southeast of Hu line is known as an area with greater population density and more developed economy.

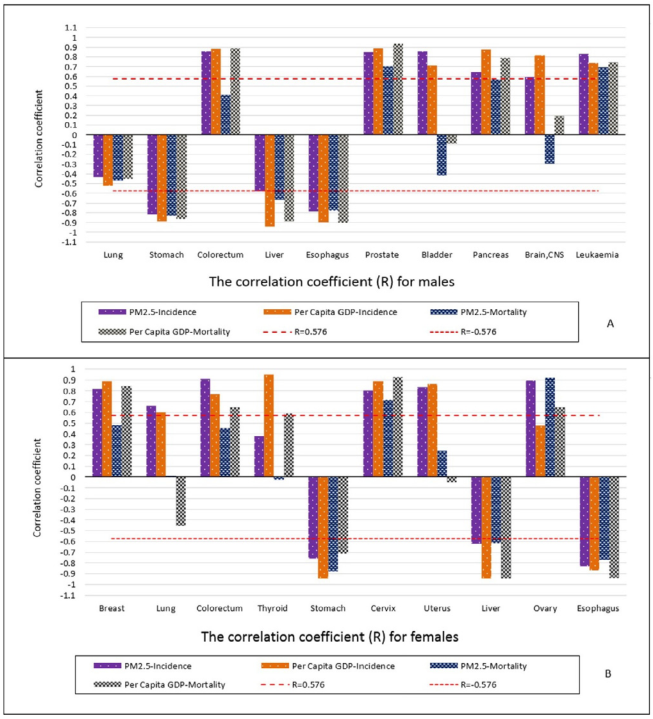

Fig. 2. The correlation coefficient (R) between population-weighted annual mean $PM_{2.5}$ concentrations (and per capita GDP) and cancer incidence, between population-weighted annual mean $PM_{2.5}$ concentrations (and per capita GDP) and cancer mortality for males and females. The $R = \pm$ 0.576 lines are also shown in the figure as orange dashed lines (when $|R| > 0.576$, $P < 0.05$, and the correlation is significant). The cancer with a larger incidence is at a more left position on X-axis. $R_{PM2.5\text{-per capita GDP}}$ is 0.594.

environmental deterioration but also the public health condition. In fact, studies have reported that some high cancers incidence were stimulated by the economic development (Lee et al., 2007), and two main reasons were speculated: firstly, environmental degradation usually follows with economic development (Cao et al., 2014), the results in this study also validated this ($R_{PM2.5\text{-per capita GDP}}$ is 0.594, means the population-weighted annual mean $PM_{2.5}$ concentration is positively related with per capita GDP between 2000 and 2011); secondly, more mature cancer screening methods were applied with economic development, and advanced methods can diagnose cancers earlier to reduce the missed diagnosis cases, and finally result in increased incidence (Zhai et al., 2014). For example, the incidence of female thyroid cancer increased year by year may be a false alarm due to the improvement of medical technology (Jeffy et al., 2002).

According to Fig. 2, it could be concluded that the incidence of six cancers in the ten most common cancers are significantly positive associated with population-weighted annual mean $PM_{2.5}$ concentration and per capita GDP both for male (including prostatic cancer, leukemia, brain/central nervous system (CNS) cancer, pancreatic cancer, bladder cancer, and colorectal cancer) and female (including lung cancer, breast cancer, colorectal cancer, uterine cancer, ovarian cancer and cervical cancer). On the Contrary, there are only two cancers whose mortality are significantly positive associated with population-weighted annual mean $PM_{2.5}$ concentration and per capita GDP, both for male (including leukemia and prostatic cancer) and female (ovarian cancer and cervical cancer).

Consequently, the negative correlation of cancer-$PM_{2.5}$/GDP presented in Fig. 2 can be attributed to the health effects of economic development, while the positive correlation was associated with the environmental deterioration ($PM_{2.5}$ is one of the most dangerous pathogenic contaminants) or/and more mature cancer screening methods.

More concretely, significant positive association between cancer incidence and per capital GDP reveals that there is an increased risk from environmental deterioration (mainly from $PM_{2.5}$) and/or more mature cancer screening methods, while significant positive association between cancer mortality and per capital GDP was irrelevant to the screening methods. Meanwhile, negative association shows that there is a decreased risk because of some healthy factors along with a higher per capital GDP such as a lower smoking rate. Therefore, the negative association between cancer and $PM_{2.5}$ should be attributed to the health effects of GDP and the positive correlation between $PM_{2.5}$ and GDP. And the positive association between cancer incidence and $PM_{2.5}$ were caused by two reasons: one is that $PM_{2.5}$ pollution increases the risk of cancer incidence, and another is that more mature cancer screening methods increase the cancer incidence. Meanwhile, there is only one reason for the positive association between cancer mortality and $PM_{2.5}$, and it is that $PM_{2.5}$ pollution can increase the risk of cancer mortality.

A lower smoking rate was one of the most important protector of health (Chen et al., 2015). According to the work of Research on National Health Services in Global Adult Tobacco Survey between 1993 and 2010, smoking rates in China are declining (see Table 1), which is the possible cause of the decreasing incidence of lung cancer, esophagus cancer, liver cancer and stomach cancer. Meanwhile, Fig. 2 also shows that the incidence and mortality of male lung cancer were not correlated with $PM_{2.5}$ concentration, and the results was inconsistent with literature (Zhang et al., 2014; Li and Gao, 2014) due to the smoke rate data. The positive correlation between female lung cancer incidence and population-weighted annual mean $PM_{2.5}$ concentration demonstrates the effect of $PM_{2.5}$ exposure on lung, while the hazards by $PM_{2.5}$ exposure to lung for male have been papered over. A possible explanation is that the effect of $PM_{2.5}$ on lung is not noticeable on people with high smoking rate (male) but significant on those with low smoking rates (female), because smoking is much more harmful compared with $PM_{2.5}$ (Yoshinaga et al., 2018).

To summarize, for the ten most common cancers, the incidence of six cancers and the mortality of two cancers are closely related with $PM_{2.5}$ exposure. The involved organs include cardiovascular system, respiratory system, reproductive system, digestive system and hematopoietic system.

3.2. The association between the spatiotemporal series of $PM_{2.5}$ and incidence/mortality of the ten most common cancers during 2006–2009

In order to investigate the urban-rural and sex differences of the health effects of $PM_{2.5}$ exposure, the association between the spatiotemporal series of $PM_{2.5}$ and incidence (and mortality) of the ten most common cancers during 2006–2009 were analyzed. According to results in section 3.1, cancer incidence was increased both by $PM_{2.5}$ pollution and mature screening methods, while cancer mortality was only increased by $PM_{2.5}$ pollution, therefore,

Table 1
Smoking rates for residents over 15 years old (%).

Year	Male			Female		
	Total	Urban	Rural	Total	Urban	Rural
2010	52.9	49.2	56.1	2.4	2.6	2.2
1993	59.3	56.8	60.3	5.0	6.2	4.5

in order to exclude the impact of mature screening methods, we select the cancers whose mortality are significantly positive related with $PM_{2.5}$ as our study subjects in this section. As a special case, lung cancer was also analyzed in this section because it is fully demonstrated to be affected by $PM_{2.5}$ exposure (Dehghani et al., 2017).

Table 2 shows the numbers of urban or rural sites that fall into each of the 5 $\mu g/m^3$ bins. The annual mean of $PM_{2.5}$ concentration at most of the sites falls into the range of 36–60 $\mu g/m^3$, and only 9% are below 35 $\mu g/m^3$ (IT-1 level), 92% of which are from rural area. Furthermore, there are about 20% of urban areas and 35% of rural areas with $PM_{2.5}$ concentration more than 60 $\mu g/m^3$ respectively, which means more rural population were exposed to high levels $PM_{2.5}$ concentration. It is worth pointing out that the annual mean $PM_{2.5}$ concentration was not weighted by population because the area of $0.1° \times 0.1°$ grid is almost equal to the area covering by a cancer registry.

For each kind of cancer, the regression of cancer with urban male, rural male, urban female and rural female were carried out. The regression formula was presented in Eq. (3):

$$y = Bx + b_0 \tag{3}$$

Where y is cancer incidence or mortality, x is annual mean $PM_{2.5}$ concentration. All the data need to be preprocessed with the method stated in section 2.2.3.

According to Table 3, there is not always a linear relationship between the incidence and mortality of the selected five cancers and $PM_{2.5}$ concentration. For the same cancer, there are significant sex and urban-rural differences in the health effects of $PM_{2.5}$. And for different cancers, $PM_{2.5}$ has different hazards in urban and rural areas. The regression relationships were employed to identify the trends and patterns, as presented Fig. 3.

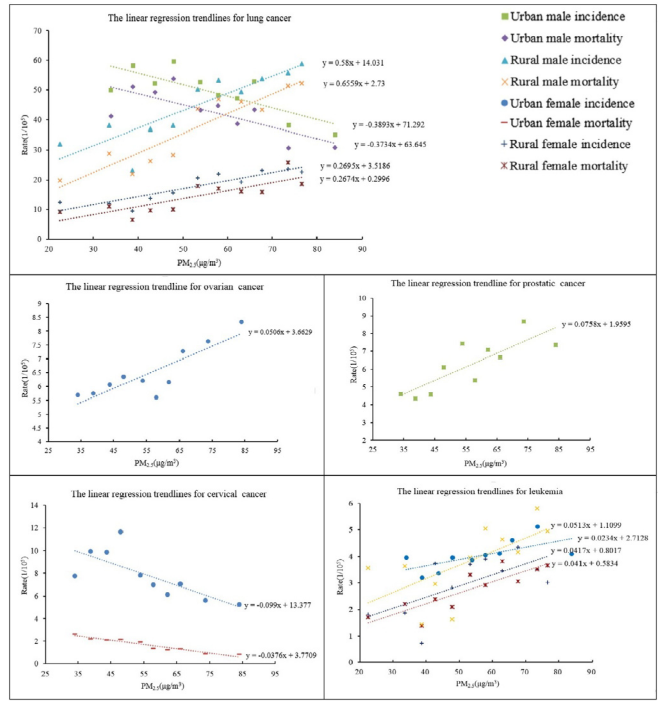

Fig. 3. The linear regression trendlines for the five cancers. The formulas in the chart are the regression formulas of the corresponding regression trendlines.

Accordingly, it could be estimated that the increased relative risks (RRs) of the five cancers incidence and mortality for every 10 $\mu g/m^3$ increment of annual mean $PM_{2.5}$ concentration, compared with which is at 35 $\mu g/m^3$ can be determined according to Eqs. (4) and (5).

$$RR_I = 10B/I_0 \tag{4}$$

$$RR_M = 10B/M_0 \tag{5}$$

Where RR_I and RR_M are the increased relative risk for incidence and mortality respectively, and I_0 and M_0 are incidence and mortality when annual mean $PM_{2.5}$ concentration is at 35 $\mu g/m^3$ (IT-1 proposed by WHO) respectively,. B is the coefficient of the corresponding formula.

Table 4 shows that, there are obvious urban-rural and male-female distinctions for the health impact of $PM_{2.5}$ exposure. More specifically, the risks of $PM_{2.5}$ exposure are higher in urban area for ovarian cancer and prostatic cancer; while for lung cancer and leukemia, the risks are higher in rural area. Moreover, the risks of male lung cancer and cervical cancer in urban decrease along with every 10 $\mu g/m^3$ increment of annual mean $PM_{2.5}$ concentration, and

Table 2
The number of data in each $PM_{2.5}$ concentration range.

Bins of $PM_{2.5}$ concentration ($\mu g/m^3$)	Urban area (numbers of data)	Rural area (numbers of data)
21–25	0	4
26–30	0	0
31–35	1	7
36–40	5	3
41–45	9	8
46–50	15	6
51–55	6	10
56–60	15	9
61–65	7	16
66–70	2	4
71–75	3	2
76–80	0	3
81–85	1	0
Total	64	72

Table 3
The R^2 and significance of regression model for cancer incidence and mortality.

Site	Urban				Rural			
	Male		Female		Male		Female	
	Incidence	Mortality	Incidence	Mortality	Incidence	Mortality	Incidence	Mortality
Lung	0.616*	0.576*	0.307	0.387	0.766*	0.861*	0.805*	0.671*
Ovary	/	/	0.747*	0.015	/	/	0.291	0.009
Prostate	0.668*	0.009	/	/	0.048	0.279	/	/
Cervix	/	/	0.561*	0.924*	/	/	0.162	0.087
Leukemia	0.021	0.269	0.454*	0.236	0.198	0.415*	0.429*	0.742*

* Indicates $P < 0.05$ and the regression is significant.

Table 4
The RRs of cancer incidence and mortality for every 10 μg/m^3 increment of annual mean $PM_{2.5}$ concentration, compared with which is at 35 μg/m^3.

Site	Urban				Rural			
	Male		Female		Male		Female	
	Incidence	Mortality	Incidence	Mortality	Incidence	Mortality	Incidence	Mortality
Lung	−8%	−9%	Non	Non	15%	23%	22%	24%
Ovary	/	/	9%	Non	/	/	Non	Non
Prostate	17%	Non	/	/	Non	Non	/	/
Cervix	/	/	−13%	−14%	/	/	Non	Non
Leukemia	Non	Non	6%	Non	Non	9%	22%	19%

'Non' represents there is no significant risk.

this should be an erroneous conclusion, since that recent years in developed areas when annual mean $PM_{2.5}$ concentration kept growing, and the declined smoking rate was a dominant factor for diminished lung cancer; and more advanced medical techniques inhibited cervical cancer.

More concretely, compared to the situation of 35 μg/m^3 annual mean $PM_{2.5}$ concentration (IT-1), RRs of lung cancer mortality for males and females in rural area increases 23% and 24% respectively with every 10 μg/m^3 increase of annual mean $PM_{2.5}$ concentration, which is consistent with Turner et al. (2011), and there is almost no sex difference in lung cancer mortality in rural area. Different from rural area, the risks of incidence and mortality for male (female) lung cancer decline (change insignificantly) with $PM_{2.5}$ respectively in urban area, which again suggests that smoking rate decline could be the dominant factor for lung cancer. The urban and rural differences of RRs of incidence and mortality for other cancers are as following: with every 10 μg/m^3 increment of annual mean $PM_{2.5}$ concentration, the RR of ovarian cancer incidence increases 9% in urban area, which changes insignificantly in rural area; the RR of prostatic cancer incidence increases 17%, which also changes insignificantly in rural area; for male leukemia, only the RR of mortality in rural increase 9%, but for female leukemia, the RRs of incidence and mortality increase 22% and 19% in rural area respectively, and in urban area, only the RR of incidence increases 6%, which suggests that the RR of leukemia from $PM_{2.5}$ exposure is more significant in rural area than urban area, and it is more significant for females than males.

4. Conclusions

Particulate matter pollution has become an urgent issue in most areas in China because that the annual mean $PM_{2.5}$ concentration has remained at a high level greater than 35 μg/m^3 for a long period. In this paper we used the data of cancer incidence/mortality and $PM_{2.5}$ concentration to carry out a preliminary exploration of the sex and urban-rural differences in the health effects of $PM_{2.5}$ pollution in densely populated areas located in the southeastern side of Hu line of China. Pearson correlation coefficient and linear regression were performed to analyze the association between $PM_{2.5}$ and the incidence (and mortality) of the ten most common cancers. For the ten most common cancers, the incidence of six cancers and the mortality of two cancers are closely related with $PM_{2.5}$ exposure. The mainly involved organs include cardiovascular system, respiratory system, reproductive system, digestive system and hematopoietic system. For the same cancer, there is a big gap in RRs of $PM_{2.5}$ long term exposure between urban and rural area, and between male and female. For different cancers, the hazards of $PM_{2.5}$ vary in urban and rural areas. Our results are demonstrated reliable because of the consistency with Turner et al. (2011).

All in all, $PM_{2.5}$ long term and high concentration exposure sharply raises the risks of some cancers in China, meanwhile, the responses of cancers to $PM_{2.5}$ are inconsistent in urban and rural areas, and in different sex. Specifically, the responses of lung cancer and leukemia to $PM_{2.5}$ are more significant in rural area, while the responses of ovarian cancer and prostatic cancer are more significant in urban area. In addition, the hazards of $PM_{2.5}$ on female are more significant. Therefore, urban and rural differences and sex differences should be taken into account in the management of the air pollution and the associated health problem.

Our research is the first step of differential study of the health risks of $PM_{2.5}$ long term and high concentration exposure in urban-rural areas and different sex, so the interference of some other factors is not completely excluded and leads to some abnormal results. A case in point is that the RRs of male lung cancer and cervical cancer in urban area decrease along with $PM_{2.5}$ concentration increment, which suggests that there may be other influencing factors leading to the result, such as the declined smoking rate and more advanced medical techniques. In order to get more accurate exposure-response relationship between cancers and long-term $PM_{2.5}$ exposure, it is necessary to choose typical areas to carry on large-scale prospective cohort study.

Data sharing statement

The data used in this study all come from published articles, yearbooks and publicly-accessible websites, therefore, all the data are open to everyone. No additional data available.

Author contributions

H.W. contributed to all aspects of this study; Z.G. and Y.L. conducted data analysis. J. R. led this manuscript; L.C., K.C., and Y.L. gave some useful comments and suggestions to this work. All the authors reviewed the manuscript.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgments

This work was supported by the National Key Research and Development Program of China (No. 2016YFC0203300), the National Natural Science Foundation of China (No. 41601550) and the Open Project Program (No. KLME1508) of the Key Laboratory of Meteorological Disaster of Ministry of Education at Nanjing University of Information Science and Technology.

References

Aguilera, I., Guxens, M., Garcia-Esteban, R., Corbella, T., Nieuwenhuijsen, M.J., Foradada, C.M., Sunyer, J., 2009. Association between GIS-based exposure to urban air pollution during pregnancy and birth weight in the INMA Sabadell

Cohort. Environ. Health Perspect. 117, 1322.
Ali, M.U., Liu, G.U., Yousaf, B., et al., 2017. Pollution characteristics and human health risks of potentially (eco) toxic elements (PTEs) in road dust from metropolitan area of Hefei, China. Chemosphere 181, 111–121.
Brauer, M., Lencar, C., Tamburic, L., Koehoorn, M., Demers, P., Karr, C., 2008. A cohort study of traffic-related air pollution impacts on birth outcomes. Environ. Health Perspect. 116, 680–686.
Cao, C., Jiang, W.J., Wang, B.Y., Fang, J.H., Lang, J.D., Tian, G., Jiang, J.K., Zhu, T.F., 2014. Inhalable microorganisms in Beijing's $Pm_{2.5}$ and Pm_{10} pollutants during a severe smog event. Environ. Sci. Technol. 48, 1499–1507.
Cesaroni, G., Forastiere, F., Stafoggia, M., Andersen, Z.J., Badaloni, C., Beelen, R., Fratiglioni, L., 2014. Long term exposure to ambient air pollution and incidence of acute coronary events: prospective cohort study and meta-analysis in 11 European cohorts from the ESCAPE Project. Br. Med. J. 348, f7412.
Chen, S., Parmigiani, G., 2007. Meta-analysis of BRCA1 and BRCA2 penetrance. J. Clin. Oncol. 25, 1329–1333.
Chen, R., Pan, G., Zhang, Y., Xu, Q., Zeng, G., Xu, X., et al., 2011. Ambient carbon monoxide and daily mortality in three Chinese cities: the China Air Pollution and Health Effects Study CAPES. Sci. Total Environ. 409, 4923–4928.
Chen, Z.M., Peto, R., Iona, A., et al., 2015. Emerging tobacco-related cancer risks in China: a nationwide, prospective study of 0.5 million adults. Cancer 121, 3097–3106.
Chen, W.Q., Zheng, R.S., Baade, P.D., Zhang, S.W., Zeng, H.M., Bray, F., Jemal, A., Yu, X.Q., He, J., 2016. Cancer statistics in China, 2015. CA-A Cancer J. Clin. 66, 115–132.
Chen, X.C., Ward, T.J., Cao, J.J., Lee, S.C., Chow, J.C., Lau, G.N.C., Yim, S.H.L., Ho, K.F., 2018. Determinants of personal exposure to fine particulate matter ($PM_{2.5}$) in adult subjects in Hong Kong. Sci. *Total Environ* 628 (629), 1165–1177.
Cohen, A., et al., 2004. Mortality impacts of urban air pollution. In: Ezzati, M., et al. (Eds.), Comparative Quantification of Health Risks: Global and Regional Burden of Disease Attributable to Selected Major Risk Factors. World Health Organization, Geneva, pp. 1353–1434.
Cohen, A.J., Brauer, M., Burnett, R., Anderson, H.R., Frostad, J., et al., 2017. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. Lancet 389 (10082), 1907–1918.
Contoyannis, P., Jones, A.M., 2004. Socio-economic status, health and lifestyle. J. Health Econ. 23, 965–995.
Dai, L., Zanobetti, A., Koutrakis, P., Schwartz, J.D., 2014. Associations of fine particulate matter species with mortality in the United States: a multicity time-series analysis. Environ. Health Perspect. 122, 837–842.
Dehghani, M., Keshtgar, L., Javaheri, M.R., et al., 2017. The effects of air pollutants on the mortality rate of lung cancer and leukemia. Mol. Med. Rep. 15, 3390–3397.
Dong, G.H., Zhang, P., Sun, B., Zhang, L., et al., 2012. Long-term exposure to ambient air pollution and respiratory disease mortality in Shenyang; China: a 12-year population-based retrospective cohort study. Respiration 84, 360–368.
Dubowsky, S.D., Suh, H., Schwartz, J., Coull, B.A., Gold, D.R., 2006. Diabetes, obesity, and hypertension may enhance associations between air pollution and markers of systemic inflammation. Environ. Health Perspect. 114, 992.
Forouzanfar, M.H., Afshin, A., Alexander, L.T., Anderson, H.R., Bhutta, Z.A., Biryukov, S., et al., 2016. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 388 (10053), 1659–1724.
Gu, Y.F., Wong, T.W., Law, S.C.K., Dong, G.H., Ho, K.F., Yang, Y.J., Yim, S.H.L., 2018. Impacts of sectoral emissions in China and the implications: air quality, public health, crop production, and economic costs. Environ. Res. Lett. https://doi.org/10.1088/1748-9326/aad138.
Guo, Y., Jia, Y., Pan, X., Liu, L., Wichmann, H.E., 2009. The association between fine particulate air pollution and hospital emergency room visits for cardiovascular diseases in Beijing; China. Sci. Total Environ. 407, 4826–4830.
Guo, Y., Zeng, H., Zheng, R., Li, S., Barnett, A.G., et al., 2016. The association between lung cancer incidence and ambient air pollution in China: a spatiotemporal analysis. Environ. Res. 144, 60–65.
Gurgueira, S.A., Lawrence, J., Coull, B., Murthy, G.G.K., González-Flecha, B., 2002. Rapid increases in the steady-state concentration of reactive oxygen species in the lungs and heart after particulate air pollution inhalation. Environ. Health Perspect. 110, 749–755.
Han, W., Gao, G., Geng, J., Li, Y., Wang, Y., 2018. Ecological and health risks assessment and spatial distribution of residual heavy metals in the soil of an e-waste circular economy park in Tianjin, China. Chemosphere 197, 325–335.
Hu, H.Y., 1990. The distribution, division and Prospect of China's population. J. Geol. 2, 139–145.
Hu, D., Jiang, J., 2014. $PM_{2.5}$ pollution and risk for lung cancer: a rising issue in China. J. Environ. Protect. 5, 731.
Huang, O., Wu, W.L., Wang, O.C., et al., 2011. Sentinel lymph node biopsy is unsuitable for routine practice in younger female patients with unilateral low-risk papillary thyroid carcinoma. BMC Canc. 11, 386.
Huang, W., Cao, J., Tao, Y., Dai, L., Lu, S.E., Hou, B., et al., 2012. Seasonal variation of chemical species associated with short-term mortality effects of $PM_{2.5}$ in Xi'an; a central city in China. Am. J. Epidemiol. 175, 556–566.
Huang, R.J., Zhang, Y., Bozzetti, C., et al., 2014. High secondary aerosol contribution to particulate pollution during haze events in China. Nature 514 (7521), 218–222.
Jeffy, B.D., Chirnomas, R.B., Romagnolo, D.F., 2002. Epigenetics of breast cancer: polycyclic aromatic hydrocarbons as risk factors. Environ. Mol. Mutagen. 39, 235–244.
Katsouyanni, K., Touloumi, G., Samoli, E., Gryparis, A., Le Tertre, A., Monopolis, Y., Rossi, G., Zmirou, D., Ballester, F., Boumghar, A., Anderson, H.R., 2001. Confounding and effect modification in the short-term effects of ambient particles on total mortality: results from 29 European cities within the APHEA2 project. Epidemiology 12, 521–531.
Kloog, I., Melly, S.J., Ridgway, W.L., Coull, B.A., Schwartz, J., 2012. Using new satellite based exposure methods to study the association between pregnancy PM2.5 exposure; premature birth and birth weight in Massachusetts. Environ. Health 11, 40.
Lee, C.S.L., Li, X.D., Zhang, G., Li, J., Ding, A.J., Wang, T., 2007. Heavy metals and Pb isotopic composition of aerosols in urban and suburban areas of Hong Kong and Guangzhou; South China. Evidence of the long-range transport of air contaminants. Atmos. Environ. 41, 432–447.
Lee, B.J., Kim, B., Lee, K., 2014. Air pollution exposure and cardiovascular disease. Toxicol. Res. 30, 71.
Leontief, W.W., Ford, D., 1971. Air Pollution and the Economic Structure: Empirical Results of Input-output Computations [M]. Harvard University.
Li, Y.G., Gao, X., 2014. Epidemiologic studies of particulate matter and lung cancer. Chin. J. Canc. 33, 376.
Li, Y., Wang, W., Kan, H., Xu, X., Chen, B., 2010. Air quality and outpatient visits for asthma in adults during the 2008 Summer Olympic Games in Beijing. Sci. Total Environ. 408, 1226–1227.
Liu, J., Han, Y., Tang, X., Zhu, J., Zhu, T., 2016. Estimating adult mortality attributable to $PM_{2.5}$ exposure in China with assimilated $PM_{2.5}$ concentrations based on a ground monitoring network. Sci. Total Environ. 568, 1253–1262.
Liu, M., Huang, Y., Ma, Z., Jin, Z., Liu, X., et al., 2017. Spatial and temporal trends in the mortality burden of air pollution in China: 2004–2012. Environ. Int. 98, 75–81.
Lu, F., Xu, D., Cheng, Y., Dong, S., Guo, C., et al., 2015. Systematic review and meta-analysis of the adverse health effects of ambient $PM_{2.5}$ and PM_{10} pollution in the Chinese population. Environ. Res. 136, 196–204.
MacNaughton, P., Eitland, Erika, Kloog, I., Schwartz, J., Allen, J., 2017. Impact of particulate matter exposure and surrounding "Greenness" on chronic absenteeism in Massachusetts public schools. Int. J. Environ. Res. Publ. Health 14, 207.
Madrigano, J., Kloog, I., Goldberg, R., Coull, B.A., Mittleman, M.A., Schwartz, J., 2013. Long-term exposure to $PM_{2.5}$ and incidence of acute myocardial infarction. Environ. Health Perspect. 121, 192.
Martin, C.S., Wong, J.Y., Jiang, J., et al., 2017. Global temporal patterns of pancreatic cancer and association with socioeconomic development. Sci. Rep. 7, 3165.
Mazzi, A., Toniolo, S., Catto, S., De Lorenzi, V., Scipioni, A., 2017. The combination of an environmental management system and life cycle assessment at the territorial level. Environ. Impact Assess. Rev. 63, 59–71.
O'Neill, M.S., Veves, A., Zanobetti, A., Sarnat, J.A., Gold, D.R., Economides, P.A., Horton, E.S., Schwartz, J., 2005. Diabetes enhances vulnerability to particulate air pollution-associated impairment in vascular reactivity and endothelial function. Circulation 111, 2913–2920.
Oh, S.M., Kim, H.R., Park, Y.J., Lee, S.Y., Chung, K.H., 2011. Organic extracts of urban air pollution particulate matter $PM_{2.5}$-induced genotoxicity and oxidative stress in human lung bronchial epithelial cells BEAS-2B cells. Mutat. Res. 723, 142–151.
Oliveri Conti, G., et al., 2017. A review of AirQ Models and their applications for forecasting the air pollution health outcomes. Environ. Sci. Pollut. Res. Int. 24, 6426–6445.
Parikh, P.V., Wei, Y., 2016. PAHs and $PM_{2.5}$ emissions and female breast cancer incidence in metro Atlanta and rural Georgia. Int. J. Environ. Health Res. 26, 458–466.
Pope III, C.A., Thun, M.J., Namboodiri, M.M., Dockery, D.W., Evans, J.S., Speizer, F.E., Heath, C.W., 1995. Particulate air pollution as a predictor of mortality in a prospective study of U.S. adults. Am. J. Resp. Crit. Care 151, 669–674.
Pope, C.A., Burnett, R.T., Krewski, D., Jerrett, M., Shi, Y., Calle, E.E., Thun, M.J., 2009. Cardiovascular mortality and exposure to airborne fine particulate matter and cigarette smoke. Circulation 120, 941–948.
Pope, C.A., Bhatnagar, A., McCracken, J.P., Abplanalp, W., Conklin, D.J., O'Toole, T., 2016. Exposure to fine particulate air pollution is associated with endothelial injury and systemic inflammation novelty and significance. Circ. Res. 119, 1204–1214.
Pui, D.Y., Chen, S.C., Zuo, Z., 2014. $PM_{2.5}$ in China: measurements; sources; visibility and health effects; and mitigation. Particuology 13, 1–26.
Qiao, L., Cai, J., Wang, H., Wang, W., et al., 2014. $PM_{2.5}$ constituents and hospital emergency-room visits in Shanghai; China. Environ. Sci. Technol. 48, 10406–10414.
Samet, J.M., Zeger, S.L., Dominici, F., Curriero, F., Coursac, I., Dockery, D.W., 2000. The national morbidity, mortality and air pollution study. Part ii: morbidity and mortality from air pollution in the United States. Res. Rep. Health Eff. Inst. 94, 5–70.
Turner, M.C., Krewski, D., Pope III, C.A., et al., 2011. Long-term ambient fine particulate matter air pollution and lung cancer in a large cohort of never-smokers. Am. J. Respir. Crit. Care Med. 184, 1374–1381.
Wang, Z., Liu, Y., Hu, M., Pan, X., et al., 2013. Acute health impacts of airborne particles estimated from satellite remote sensing. Environ. Int. 51, 150–159.
Wong, C.M., Ou, C.Q., Chan, K.P., Chau, Y.K., Thach, T.Q., Yang, L., Hedley, A.J., 2008. The effects of air pollution on mortality in socially deprived urban areas in Hong Kong, China. Environ. Health Perspect. 116, 1189–1194.

World Health Organization, 2006. WHO Air Quality Guidelines for Particulate Matter, Ozone, Nitrogen Dioxide and Sulfur Dioxide: Global Update 2005: Summary of Risk Assessment.

Yang, F., Tan, J., Zhao, Q., et al., 2011. Characteristics of $PM_{2.5}$ speciation in representative megacities and across China. Atmos. Chem. Phys. 11, 5207–5219.

Yang, C., Peng, X., Huang, W., Chen, R., Xu, Z., et al., 2012. A time-stratified case-crossover study of fine particulate matter air pollution and mortality in Guangzhou; China. Int. Arch. Occup. Environ. Health 85, 579–585.

Yim, S.H.L., Barrett, S.R.H., 2012. Public health impacts of combustion emissions in the United Kingdom. Environ. Sci. Technol. 46, 4291–4296.

Yoshinaga, M., et al., 2018. A comprehensive study including monitoring, assessment of health effects and development of a remediation method for chromium pollution. Chemosphere 201, 667–675.

Zeka, A., Sullivan, J.R., Vokonas, P.S., Sparrow, D., Schwartz, J., 2006. Inflammatory markers and particulate air pollution: characterizing the pathway to disease. Int. J. Epidemiol. 35, 1347–1354.

Zhai, Y.B., Liu, X.T., Chen, H.M., Xu, B.B., Zhu, L., Li, C.T., Zeng, G.M., 2014. Source identification and potential ecological risk assessment of heavy metals in $PM_{2.5}$ from Changsha. Sci. Total Environ. 493, 109–115.

Zhang, Y.L., Cao, F., 2015. Fine particulate matter $PM_{2.5}$ in China at a city level. Sci. Rep. 5, 14884.

Zhang, Xin, Chen, Xi, Zhang, Xiaobo, 2018. The impact of exposure to air pollution on cognitive performance. Proc. Natl. Acad. Sci. U.S.A. 115 (37), 9193–9197.

Zhang, L.W., Chen, X., Xue, X.D., Sun, M., Han, B., et al., 2014. Long-term exposure to high particulate matter pollution and cardiovascular mortality: a 12-year cohort study in four cities in northern China. Environ. Int. 62, 41–47.

Zhou, M., Liu, Y., Wang, L., Kuang, X., Xu, X., Kan, H., 2014. Particulate air pollution and mortality in a cohort of Chinese men. Environ. Pollut. 186, 1–6.