



Long-term exposure to ambient fine particles associated with asthma: A cross-sectional study among older adults in six low- and middle-income countries

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ARTICLE INFO

Keywords:

Particulate matter
Asthma
Effect modification
Disease burden

ABSTRACT

Background: Ambient PM_{2.5} is considered harmful to the respiratory system. However, little has been shown about the long-term association between ambient PM_{2.5} and asthma.

Methods: A survey from 2007 to 2010 was conducted among adults over 50 years of age in six low- and middle-income countries (including China, India, Ghana, Mexico, Russia, and South Africa), which belonged to one part of a prospective cohort study - the Study on global AGEing and adult health. The yearly mean PM_{2.5} concentrations of the residential communities of participants were estimated from remote sensing data. A mixed effects model was applied to investigate the association between ambient PM_{2.5} and asthma.

Results: A total of 4553 asthma patients were identified among the 29,249 participants in this study, producing a prevalence of 15.57%. For each 10 µg/m³ increase in PM_{2.5}, the adjusted prevalence ratio of asthma was 1.05 (95% Confidence Interval: 1.01, 1.08) after controlling for the effects of sex, age, BMI, education attainment, smoking status, alcohol consumption, and occupational exposure. Further analyses showed that males and smokers might be particularly vulnerable populations. Additionally, it was estimated that about 5.12% of the asthma cases in the study population (95% Confidence Interval: 1.44%, 9.23%) could be attributed to long-term PM_{2.5} exposure.

Conclusion: Long-term exposure to PM_{2.5} might be an important risk factor of asthma. Effective air pollution reduction measures should be taken to reduce PM_{2.5} concentrations in order to reduce the associated asthma cases and disease burden.

1. Introduction

Asthma is a chronic pulmonary disease often accompanied by induced airway hyperresponsiveness, obstruction, and inflammation. It can seriously threaten an individual's life and health (Falcon-Rodriguez et al., 2016).

Numerous studies have shown that particulate matter (PM) may cause adverse health outcomes, both in the cardiovascular and respiratory systems (Bell et al., 2008; Belleudi et al., 2010). Fine particulate matter with an aerodynamic diameter ≤ 2.5 µm (PM_{2.5}) can enter the bronchioles and alveoli and deposit in the respiratory tract. This can result in airway hyperresponsiveness and oxidative stress, causing translation errorlung function impairment and decline (Guarnieri and Balmes, 2014; Stanek et al., 2011). Thus, PM_{2.5} exposure

has been considered a potential risk factor for some health outcomes, including asthma and chronic obstructive pulmonary disease (Zheng et al., 2015).

Previous studies have been mainly conducted in developed countries and focused on short-term associations between air pollution and respiratory diseases (Loftus et al., 2015; Pereira et al., 2010; Santus et al., 2012; Villeneuve et al., 2007). Limited evidence is available about the long-term effects of PM_{2.5} on asthma, especially in low-income countries. This is of particular importance as higher levels of air pollution usually exist in these regions. This study assessed the association between long-term exposure to PM_{2.5} and asthma among older adults in six countries, based on a large-scale survey. The effect modifiers of age, sex, smoking, and drinking status were further investigated. Lastly, the asthma burden attributable to PM_{2.5} was estimated.

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<https://doi.org/10.1016/j.envres.2018.09.028>

Received 4 May 2018; Received in revised form 30 August 2018; Accepted 22 September 2018

Available online 24 September 2018

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2. Methods

2.1. Study population

The data used in this study was obtained from an ongoing cohort study: the Study on global AGEing and adult health (SAGE). SAGE collected comprehensive, high quality data on the health and well-being of adults from the six countries of China, India, Ghana, Mexico, Russia, and South Africa (Kowal et al., 2012), aiming to provide an overview of aging and health status among adults over 50 years of age in low- and middle- income countries. The data from 2007 to 2010 (SAGE WAVE 1) was used for this study (Lin et al., 2017b). A multistage cluster sampling approach was used for participant selection. A household questionnaire interview was used to collect information on socio-demographic characteristics, behavioral factors, and health conditions. Detailed information about the SAGE survey can be found elsewhere (Kowal et al., 2012). In brief, the first sampling stage was carried out in different regions (e.g. provinces/municipalities), then in the city, county and community levels, and the last sampling units were household enumerations. For different countries, community was differently defined with different sampling numbers: in China, it is township/community (64); in India, it is a village/census enumeration block (350); in Mexico, it is the Basic Geo-Statistical Area (60); in Russia, it is an atenum (180); in Ghana and South Africa, it is an enumeration area, with a sampling number of 220 and 180, respectively.

2.2. Asthma and PM_{2.5}

In this study, asthma cases were defined as: participants who reported treatment for asthma within one year and/or those diagnosed with asthma by authoritative medical institutions. The self-reported patients were validated through professional medical testing to ensure the authenticity of the data (Kowal et al., 2012).

Aerosol Optical Depth (AOD) measurements were combined with the Global Chemical Transport Models (CTMs) method to estimate the yearly average concentrations of PM_{2.5} during 2007–2010 at 1 km * 1 km resolution. AOD observations were derived from both Multiangle Imaging Spectroradiometry and Moderate Resolution Imaging Spectroradiometry, which were obtained from NASA's Terra satellite. Original AOD data was refined from 10 km * 10 km resolution to 1 km * 1 km resolution, since the latter suggests a better description of the distribution of PM_{2.5} (Li et al., 2005). Then, the estimates of ambient PM_{2.5} concentrations were calculated using CTMs and validated by ground monitoring data with one-sigma uncertainty (Van Donkelaar et al., 2015). A few previous validation studies reported a high correlation between estimated PM_{2.5} concentrations and the ground monitored PM_{2.5} concentration (Van Donkelaar et al., 2015; Wong et al., 2015). The residential communities of participants were geocoded to match the estimated PM_{2.5} concentrations (Fleischer et al., 2014). The three-year average concentration of PM_{2.5} before the survey was used as the proxy for long-term PM_{2.5} exposure. This method has been used in previous similar studies (Lin et al., 2018).

2.3. Covariates

This analysis included socio-demographic factors and various behavioral risk factors. The following covariates were categorized into binary variables: sex (male or female), marital status (married or unmarried), residence location (urban or rural), educational attainment (primary school and lower, or middle school and higher), family income (low or high), smoking status (smoker or nonsmoker), alcohol consumption (drinker or nondrinker), occupational exposure condition (yes or no), domestic fuel type (liquid and gas fuel or solid fuel) and the use of ventilation (yes or no) (Lin et al., 2018; Wu et al., 2015). Body Mass Index (BMI) was calculated by way of dividing weight (in kg) by height (in meters) squared. Physical activity was categorized as low,

moderate, or high, according to the frequency and intensity of physical activity within the previous week (Wu et al., 2015).

2.4. Statistical analysis

The asthma cases from the same communities may be correlated with each other due the shared environment and facility, therefore violating the assumption of independence of regression model (Lin et al., 2017c). We thus performed a generalized estimation equation (GEE) models to account for the nested structure of the data when investigating the associations between ambient PM_{2.5} exposure and asthma (Zou, 2004). The selection criteria for these covariates were as follows: (1) they were potential risk factors for asthma; and/or (2) they changed the estimates for PM_{2.5} by at least 10% (Ritz et al., 2007). The associations were presented as prevalence ratio (PR) for each 10 µg/m³ increase in annual PM_{2.5} concentrations (Zou, 2004).

Stratified analyses were performed by sex (male versus female), age (< 65 versus ≥ 65), smoking status (smoker versus non-smoker), and alcohol consumption (drinker versus non-drinker) to detect possible effect modifiers of the PM_{2.5}-asthma relationship. The statistical difference of the associations between the strata of each potential effect modifier was examined by adding a productive term of PM_{2.5} and the potential effect modifier in the regression models (Schenker and Gentleman, 2001).

2.5. Calculating attributable asthma burden

In addition to estimating the association between PM_{2.5} and asthma, the asthma burden attributable to PM_{2.5} exposure was also calculated. Attributable cases and population attributable fraction were used as indices to show attributable asthma burden. As an indicator with important public health significance, population attributable fraction can answer the question “what percent of cases could be prevented if one or more exposures were eliminated in a target population” by accounting for both the strength of association and the prevalence of exposure (Spiegelman et al., 2007). We used the PM_{2.5} concentration (25 µg/m³) set by WHO's Air Quality Guidelines as the reference. The formula for calculating the 2 indicators were shown below (Lin et al., 2017a):

$$\begin{aligned} \text{Attributable cases} &= \text{Baseline prevalence} * [\exp(\beta * \Delta BC - 1)] * \text{Risk population} \\ \text{Population attributable fraction} &= \text{Attributable cases} / \text{Overall cases} \end{aligned}$$

where baseline prevalence is the asthma prevalence among participants exposed to reference PM_{2.5} concentrations (25 µg/m³); β is the coefficient of PM_{2.5}-asthma relationship; ΔBC is the difference of actual concentration and reference concentration; Overall cases refer to all asthma cases.

2.6. Sensitivity analyses

A few sensitivity analyses were performed to test the robustness of the findings. For example, an exposure-response curve was plotted to graphically examine the linearity assumption of the PM_{2.5}-asthma relationship (Lin et al., 2017a). We also considered different exposure windows, one, two, four, and five year average PM_{2.5} concentrations, in the analyses. We also performed country-specific models for China and India, considering the two countries had wide range of PM_{2.5} concentrations and sufficient sample size to do the analysis. Additionally, we excluded the participants with chronic obstructive pulmonary disease (COPD), as these conditions are sometimes overlapped with asthma patients, and also significantly associated with ambient PM_{2.5} (Lin et al., 2018).

All analyses were conducted by R software, and a p-value of < 0.05 was defined as statistically significant.

Table 1
Characteristics of asthma and non-asthma participants.

Continuous Variables	Non-asthma (24,696) Mean (SD)	Asthma (4553) Mean (SD)	P value [#]
Age (years)	63 (9.6)	65 (9.6)	< 0.01
BMI (kg/m ²)	23.65 (7.08)	23.34 (7.53)	0.03
PM _{2.5} (μg/m ³)	34.33 (2.02)	37.33 (2.05)	0.12
Categorical Variables	Non-asthma (24,696) N (%)	Asthma (4553) N (%)	P value [#]
Sex			
Male	10229 (41.42)	1801 (39.56)	0.02
Female	14467 (58.58)	2752 (60.44)	
Marital status			
Married	16924 (68.53)	2972 (65.28)	< 0.01
Unmarried	7771 (31.47)	1581 (34.72)	
Residence			
Urban	12174 (49.30)	2324 (51.04)	0.03
Rural	12521 (50.70)	2229 (48.96)	
Education			
Primary school or lower	17086 (69.19)	3118 (68.48)	0.35
Middle school or higher	7610 (30.81)	1435 (31.52)	
Household income			
Low	12147 (49.19)	2424 (53.24)	< 0.01
High	12549 (50.81)	2129 (46.76)	
Smoking			
Nonsmoker	18229 (73.81)	3077 (67.58)	< 0.01
Smoker	6467 (26.19)	1476 (32.42)	
Drinking			
Nondrinker	16720 (67.70)	2886 (63.39)	< 0.01
Drinker	7976 (32.30)	1667 (36.61)	
Physical activity			
Low	8320 (33.69)	1487 (32.68)	< 0.01
Moderate	5351 (21.67)	1082 (23.76)	
High	11025 (44.64)	1984 (43.58)	
Occupational pollution exposure			
Yes	2107 (8.53)	468 (10.28)	< 0.01
No	22589 (91.47)	4085 (89.72)	
Indoor fuel type			
Liquid & gas	12884 (52.17)	2418 (53.11)	0.24
Solid	11812 (47.83)	2135 (46.89)	
Ventilation			
No	19395 (78.53)	3611 (79.31)	0.24
Yes	5301 (21.47)	942 (20.69)	

BMI: Body Mass Index; PM_{2.5}: Particulate matter with a diameter ≤ 2.5 μm; SD: standard deviation.

[#] P value represents the results of χ^2 tests for categorical variables and *t*-tests for continuous variables.

3. Results

A total of 29,249 participants were recruited in this study. The mean age of all subjects was 63 years, ranging from a mean of 62 in India to a mean of 68 in Mexico. The average PM_{2.5} concentration was 36.7 μg/m³. India had the highest mean concentration (49.7 μg/m³), which was only slightly higher than China's (47.0 μg/m³), while Mexico (13.3 μg/m³) had the lowest (Table s1).

There were 4553 participants diagnosed with asthma, producing a prevalence of 15.57%. Asthma participants were significantly older than those without asthma (65 versus 63 years) and were more likely to be females, smokers, drinkers, unmarried, living in urban areas, and exposed to a higher occupational pollution level. Non-asthma participants were more likely to have a higher BMI (23.65 versus 23.34 kg/m²), household income, and physical activity level. No significant difference was observed in education level, indoor fuel type, or ventilation (Table 1).

The exposure-response curve between exposure to PM_{2.5} and asthma suggested an approximately linear relationship (Fig. 1.), so linear associations were reported in subsequent analyses. The crude PR was 1.03 (95% Confidence Interval [CI]: 1.00, 1.06) and remained significant after adjusting for potential confounders in the multivariate model (adjusted PR = 1.05; 95% CI: 1.01, 1.08) (Table 2). Further

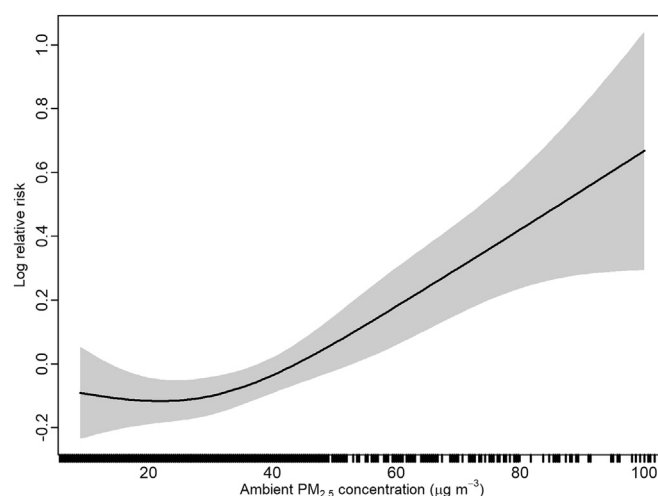


Fig. 1. The concentration-response curve of the association between ambient PM_{2.5} and prevalence of asthma among older adults in six low- and middle-income countries.

Table 2

Crude and adjusted PRs and 95% CIs for asthma associated with each 10 μg/m³ increase in PM_{2.5}.

	Crude PR (95% CI)	Adjusted PR (95% CI) [*]	P value [#]
Overall	1.03 (1.00, 1.06)	1.05 (1.01, 1.08)	
Sex			
Female	1.02 (0.98, 1.06)	1.01 (0.97, 1.06)	0.01
Male	1.07 (1.02, 1.11)	1.09 (1.04, 1.14)	
Age group			
< 65 years	1.04 (1.00, 1.08)	1.04 (1.00, 1.09)	0.16
≥ 65 years	1.01 (0.96, 1.06)	1.01 (0.96, 1.05)	
Smoking			
Nonsmoker	1.00 (0.97, 1.04)	1.01 (0.97, 1.05)	0.03
Smoker	1.05 (0.99, 1.10)	1.07 (1.02, 1.13)	
Drinking			
Nondrinker	1.03 (1.00, 1.07)	1.05 (1.01, 1.09)	0.21
Drinker	1.01 (0.95, 1.07)	1.03 (0.97, 1.08)	

^{*} Adjusted for sex, age, BMI, education, smoking status, alcohol consumption, and occupational pollution exposure.

[#] P value represents the difference between strata.

analyses indicated that sex and smoking status might be important effect modifiers. The association between PM_{2.5} and asthma was stronger among males (PR = 1.09; 95% CI: 1.04, 1.14) than females (PR = 1.01; 95% CI: 0.97, 1.06) and was stronger among smokers (PR = 1.07; 95% CI: 1.02, 1.13) than for non-smokers (PR = 1.01; 95% CI: 0.97, 1.05). However, no significant effect modifications were found by age and alcohol consumption.

The estimated asthma burden attributable to PM_{2.5} is displayed in Table 3. The population attributable risk for all participants owing to ambient PM_{2.5} was 5.12% (95% CI: 1.44%, 9.23%), which corresponded to 233 asthma cases (95% CI: 66, 421). In addition, a larger burden was observed among males (11.87%; 95% CI: 5.47%, 19.85%).

The sensitivity analyses showed that the estimates in the models did not change greatly when the time window for measuring PM_{2.5} was shortened or lengthened (Table s2). For instance, when using the

Table 3

Estimated asthma burden attributable to PM_{2.5} (95% CIs in parentheses).

	Attributable cases	Population attributable fraction (%)
Overall	233 (66, 421)	5.12 (1.44, 9.23)
Females	27 (0, 160)	0.96 (0.00, 5.81)
Males	214 (94, 358)	11.87 (5.47, 19.85)

average concentrations of two years before the survey, the PR for each $10 \mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ was 1.06 (95% CI: 1.03, 1.09). And the analyses in China and India also yielded a similar association with that from the six countries with an adjusted PR of 1.08 (95% CI: 1.04, 1.12). And when excluding the COPD cases (877 were COPD cases among the 4553 asthma cases), we also obtained a consistent association (PR = 1.05; 95% CI: 1.01, 1.08).

4. Discussion

In this study, it was observed that long-term exposure to $\text{PM}_{2.5}$ was positively associated with an increased asthma patients, and it was estimated that about 5.12% of the asthma cases in this study could be ascribed to $\text{PM}_{2.5}$ exposure in the six countries included.

The findings from this study were generally in line with several previous studies. For example, a cohort study in Toronto, Canada reported a positive association between long-term $\text{PM}_{2.5}$ exposure and asthma in adults after adjusting for individual and neighborhood level covariates (Weichenthal et al., 2017). A birth cohort study in the Netherlands reported that long-term $\text{PM}_{2.5}$ exposure was linked with an increased asthma risk, with a relatively larger effect than found in this current study (OR = 1.28, 95% CI: 1.10–1.49) (Gehring et al., 2010). A cross-sectional study in the U.S. showed that exposure to PM pollution from both indoor and outdoor sources could result in lower lung function and aggravated respiratory symptoms in adult asthmatic patients (Balmes et al., 2014). While a cohort study conducted among American women did not find any significant association between $\text{PM}_{2.5}$ exposure and asthma incidence, it did observe a significant effect of NO_2 exposure (Young et al., 2014).

Although the exact mechanism by which $\text{PM}_{2.5}$ might induce asthma remained unknown, some possible hypotheses may include airway inflammation and oxidative stress (Mirabelli et al., 2016). $\text{PM}_{2.5}$ can deposit in the lungs and respiratory tract, especially in the alveoli, which leads to oxidative stress and many biochemical changes associated with asthma. The organic components of $\text{PM}_{2.5}$ can induce macrophages and bronchial epithelial cells in the lungs to generate reactive oxygen species, which may be involved in activating protein-1 and nuclear factor- κB signaling pathways to cause and/or aggravate an allergic reaction in the respiratory tract. Moreover, organic diesel exhaust particles may cause apoptosis and necrosis of bronchial epithelial cells through the mitochondrial pathway. This may be the cause of airway hyperresponsiveness that could result in asthma aggravation (Nel et al., 2001). Other immunogenic substances contained in $\text{PM}_{2.5}$, such as pollen, spores, etc., could also aggravate asthma symptoms (Guarnieri and Balmes, 2014).

The analysis in this study suggested a higher effect of $\text{PM}_{2.5}$ on asthma among males, which was in agreement with previous studies. For instance, Alhanti et al. found a stronger association between asthma and $\text{PM}_{2.5}$ among males compared to females (Alhanti et al., 2016). A plausible explanation for the higher association among males may be that men were more likely to participate in outdoor activities than women, thus leading to a higher level of pollution exposure and then inducing the possibility of asthma occurrence.

No significant effect modification by age and drinking was found in this study, which was unexpected (Bentayeb et al., 2012; Canova et al., 2012; Cockcroft, 2018). Most studies investigating health effects of air pollutants targeted on adults or children, while studies conducted among the elderly are scarce. Limited studies have shown a higher odds ratio or relative risk among the old people, although the statistical difference of different age group have not been tested (Bentayeb et al., 2012). Our results did not find the effect modification of age, and only a significant association with a higher PR was found among adults < 65 years. One possible underlying reason might be that the two age group of populations (50–65 years vs ≥ 65 years) varies little in susceptibility to $\text{PM}_{2.5}$ exposure due to similar living environment and physiological condition. Besides, important confounding factors like environmental

tobacco smoking should also be included if the availability of related information could be achieved. Previous studies have shown that alcohol consumption may be involved in the process of immune function that relates to individual allergic response (Vally and Thompson, 2003). It has also been shown that the dose of consumption could play an important role: low to moderate intake may improve lung function, while high intake could induce harmful health effects (Sisson et al., 2005; Tabak et al., 2001). Therefore, it may be more informative to classify alcohol consumption by intake levels rather than as a dichotomous variable. This will be examined in future studies.

Most previous studies have mainly examined the association between air pollutants and respiratory disease. One advantage of the current study is the estimation of attributable burden, which indicated prominent public health significance would be achieved if appropriate interventions could be carried out to reduce air pollution exposure. Similar methods have been applied in a few other recent studies. For instance, one such study revealed that about 7% of stroke cases could be attributed to $\text{PM}_{2.5}$ exposure in the same six countries examined here (Lin et al., 2017a). Li et al. reported that 10.91%, 12.71%, and 13.38% of COPD cases studied could be attributable to exposures of PM_{10} , SO_2 , and NO_2 in Guangzhou, China (Li et al., 2016).

Some limitations of this study should be noted. First, as a cross-sectional study, it could not ascertain the causal relationship between $\text{PM}_{2.5}$ and asthma. Further studies exploring the biological mechanism of the relationship may be helpful to fill this gap. Second, the satellite-derived three-year average concentrations of $\text{PM}_{2.5}$ were used as surrogates for the actual $\text{PM}_{2.5}$ exposure of each participants, this could have introduced exposure misclassification, especially, we did not have the information of the residential changes of the participants, which could also affect the exposure assessment in this study. Finally, all possible confounders could not be controlled for due to lack of information of some important variables, such as family history of allergy, ownership of pets, dietary factors, environmental tobacco smoking and so on (McConnell et al., 2006).

In summary, this analysis indicates that $\text{PM}_{2.5}$ exposure may be a critical risk factor for asthma and may be responsible for a substantial percentage of asthma cases. In particular, males may be more vulnerable to the effects of $\text{PM}_{2.5}$ exposure. Governments should recognize the apparent severity of air pollution, based on the estimated attributable burden of this study, and take practical measures to improve the environmental conditions of public health.

Acknowledgments

We are very grateful to the funding provided by World Health Organization (Grant Nos: OGH404034785 and YA1323-08-CN-0020).

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.envres.2018.09.028.

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Supplemental materials

Table s1. Description of population and air pollution characteristics, by country, WHO SAGE Wave 1.

Country	Participants	Age [years (Mean±SD)]	PM _{2.5} (µg/m ³)			
			Min	Mean	Medium	Max
China	11504	63±9.2	22.3	47.0	44.3	95.0
Ghana	3568	64±10.7	21.0	29.0	28.7	36.0
India	6020	62±8.9	19.7	49.7	43.0	106.7
Mexico	1613	68±9.1	5.0	13.3	12.3	27.7
Russia	3358	65±10.2	5.3	16.8	16.0	35.7
South Africa	3186	63±9.7	3.3	16.9	14.7	37.3
Overall	29249	63±9.6	3.3	36.7	34.7	106.7

SD: standard deviation; Min: minimum; Max: maximum.

Table s2. Adjusted prevalence ratio and 95% CI for asthma associated with each 10 µg/m³ increase in ambient PM_{2.5} in the sensitivity analyses

Models	Prevalence ratio (PR)	95% CI
Per 10 ug/m ³ increase*		
With 1 year PM _{2.5}	1.06	1.03, 1.09
With 2 year PM _{2.5}	1.06	1.03, 1.09
With 4 year PM _{2.5}	1.05	1.02, 1.08

With 5 year PM _{2.5}	1.05	1.02, 1.08
In China and India	1.08	1.04, 1.12
Excluding COPD cases	1.05	1.01, 1.08

* Adjusted for sex, age, BMI, education, smoking, alcohol drinking and occupational pollution exposure.

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