The attributable risk of chronic obstructive pulmonary disease due to ambient fine particulate pollution among older adults

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\textbf{A B S T R A C T}

\textbf{Background:} The linkage between ambient fine particle pollution (PM\textsubscript{2.5}) and chronic obstructive pulmonary disease (COPD) and the attributable risk remained largely unknown. This study determined the cross-sectional association between ambient PM\textsubscript{2.5} and prevalence of COPD among adults ≥50 years of age.

\textbf{Methods:} We surveyed 29,290 participants aged 50 years and above in this study. The annual average concentrations of PM\textsubscript{2.5} derived from satellite data were used as the exposure indicator. A mixed effect model was applied to determine the associations and the burden of COPD attributable to PM\textsubscript{2.5}.

\textbf{Results:} Among the participants, 1872 (6.39\%) were classified as COPD cases. Our analysis observed a threshold concentration of 30 μg/m\textsuperscript{3} in the PM\textsubscript{2.5}-COPD association, above which we found a linear positive exposure-response association between ambient PM\textsubscript{2.5} and COPD. The odds ratio (OR) for each 10 μg/m\textsuperscript{3} increase in ambient PM\textsubscript{2.5} was 1.21 (95\% CI: 1.13, 1.30). Stratified analyses suggested that males, older subjects (65 years and older) and those with lower education attainment might be the vulnerable subpopulations. We further estimated that about 13.79\% (95\% CI: 7.82\%, 21.62\%) of the COPD cases could be attributable to PM\textsubscript{2.5} levels higher than 30 μg/m\textsuperscript{3} in the study population.

\textbf{Conclusion:} Our analysis indicates that ambient PM\textsubscript{2.5} exposure could increase the risk of COPD and accounts for a substantial fraction of COPD among the study population.

1. Introduction

Chronic obstructive pulmonary diseases (COPD) have been an increasingly important global public health problem. It is estimated that there are about 70 million COPD patients worldwide (Bazargani et al., 2014). It is particularly a problem in low and middle-income countries, where about 90\% of COPD deaths occur and effective prevention and control measures are usually lacking (Ferkol and Schraufnagel, 2014). Despite the widespread concern, the relationship between COPD and some important risk factors, especially environmental factors, has not been adequately studied (Zhao et al., 2017).

Ambient air pollution is one potential environmental factor for COPD. While compelling evidence has shown an etiology association between tobacco smoking, indoor air pollution and COPD (Kurmi et al., 2010; Salvi, 2014), the relationship between COPD and outdoor air pollution, such as PM\textsubscript{2.5}, has only been evaluated in a few studies with mixed results. A significant association was observed in two longitudinal studies (Naess et al., 2007; Pinault et al., 2016) and one cross-sectional study in China (Liu et al., 2016). Conversely, non-significant associations were reported in one Canadian cohort study (Gan et al., 2013), an English cohort (Atkinson et al., 2014), and some other studies (Atkinson et al., 2014; Wong et al., 2015). These inconsistent findings indicated the necessity to conduct more studies.

Furthermore, it would be of great importance to estimate the...
attributable risk of COPD due to air pollution exposure. This could provide more important information by showing how much of the disease is preventable if we have effective public health and prevention measures (Burnett et al., 2014).

Additionally, most existing evidence was obtained from developed countries. Very few studies have been available in low- and middle-income countries, where high air pollution generally exists. Here we reported the results on the cross-sectional effects of ambient PM$_{2.5}$ on the risk of COPD among older adults in six low- and middle-income countries. We further estimated the COPD burden attributable to ambient PM$_{2.5}$ using a health risk assessment framework.

2. Methods

2.1. Study participants

We used the baseline survey data of the World Health Organization (WHO) Study on global AGEing and adult health (SAGE), the details of the survey have been introduced elsewhere (Wu et al., 2015). Briefly, SAGE is a longitudinal study in six low- and middle-income countries: China, Ghana, India, Mexico, Russia and South Africa. The participants were selected using a multi-stage stratified cluster sampling approach. The relevant information was collected from each participant by trained investigators using a standardized questionnaire during 2007–2010.

2.2. COPD

Participants were recognized as COPD cases if they met one of the following criteria: 1) Participants who have been diagnosed with COPD by a clinician; 2) who self-reported receiving treatment for COPD during the past 12 months. This diagnosis approach has previously produced a comparable prevalence rate with a large population-based survey in China (Zhong et al., 2007).

2.3. Ambient PM$_{2.5}$

We retrieved the annual concentrations of ambient PM$_{2.5}$ which were estimated based on the aerosol optical depth (AOD) information in the remote sensing data of NASA (Van Donkelaar et al., 2015). The AOD is an indicator to reflect the transparency for electro-magnetic radiation and particulate matter concentration in the troposphere (NASA (National Aeronautics and Space Administration), 2013). The PM$_{2.5}$ concentrations were firstly estimated in a 10*10 km resolution in consideration of local weather conditions; and they were then refined into a 1 * 1 km resolution (Van Donkelaar et al., 2015). Previous studies have observed that the estimated PM$_{2.5}$ concentrations were highly correlated with the actual monitored concentrations (Wong et al., 2015). The estimation served as a proxy of exposure level of ambient PM$_{2.5}$. The participants’ residential community centroid was geo-coded and used to match the estimated PM$_{2.5}$ concentrations. The mean concentrations of the prior three years before the survey were used as the exposure in the main model (Filleul et al., 2005; Lin et al., 2017b).

2.4. Covariates

A series of covariates were considered in the analysis, including demographic factors [sex, age, marital status, and body mass index (BMI)], socioeconomic factors (education attainment, and annual household income), and lifestyle factors (smoking, alcohol consumption, occupational pollution exposure, physical activity, and domestic cooking-related air pollution). We categorized marital status into three groups: married, unmarried and widowed. Those who were never married, separated, or divorced were classified as unmarried. Household income was grouped into low and high categories using median as the cut point. Assessment of lifetime tobacco smoking has been described elsewhere (Wu et al., 2015). Three smoking variables were used for this study: status of smoking (never or ever), duration of smoking (never, and less or > 20 years), and amount (never, fewer or > 10 cigarettes/day).

Two variables were used to assess indoor air pollution, namely fuel type and ventilation in cooking spaces. Fuel type was classified into two categories: solid fuels and liquid and gas fuels. The former included coal, wood, dung and agricultural residues; the latter included electricity, liquefied petroleum gas and natural gas. Ventilation was defined as whether there was any ventilation apparatus in the cooking area, such as chimney, extraction hood, or fan. Occupations were classified as air pollution related occupations, including mining, construction, cleaning, renovation, mechanic-related work; and others without occupational air pollution exposure, such as administrative, office work, service, academic, sales, fishery, unemployed, etc. (Neupane et al., 2010). Physical activity was classified into three levels: low, moderate, and high according to the time spent on each activity and its total energy consumption (Wu et al., 2015).

2.5. Statistical analysis

Since the participants residing in the same community may not be independent from each other due to the shared environment, and facilities, violating the independence assumption of regression models (Fleischer et al., 2014), we applied a mixed effect model with the PM$_{2.5}$ exposure and other covariates at the participant level as a fixed effect term, and community as a random effect term (Lin et al., 2017a).

We first examined the dose-response relationship between PM$_{2.5}$ and COPD using a natural spline smoothing function (Tian et al., 2016). Our initial analysis observed the existence of a threshold concentration, above which there was a linear effect. We then identified the threshold based on the Akaike Information Criterion (AIC), a method described previously by Zhang et al. (Zhang et al., 2016). In brief, we examined several potential thresholds. For example, a visual inspection of the concentration–response curve may suggest that the potential threshold might be 25 and 35 μg/m$^3$. We thus fitted two models with the cut-off varying within the concentrations (by each 1 μg/m$^3$). The model that minimizes the sum of the AICs will be selected as the threshold (Zhang et al., 2016).

We then investigated the linear association between ambient PM$_{2.5}$ and COPD above the identified threshold concentration. Multivariate models were conducted to control for some important covariates in the models, which were selected according to two criteria: 1) variables that are potential risk factors for COPD; and/or (2) variables that changed the association between PM$_{2.5}$ and COPD by > 10% when added to the model. Using these criteria, the variables included in the final model were sex, age, BMI, education, smoking, alcohol drinking and occupational exposure.

2.6. Stratified analysis

To identify the potential effect modifiers, stratified analyses were conducted by a few potential variables: sex (males and females), age group (< 65 years and ≥65 years), smoking (ever-smokers and never-smokers), education (low and high levels) and season of the survey (warm and cold seasons, with warm season defined as April to September, and cold season as January to March and October to December). The statistical significance of the difference between the stratum was tested by using the 95% confidence interval: $(\beta_1 - \beta_2) \pm 1.96 \times (SE_1)^2 + (SE_2)^2$. $\beta_1$ and $\beta_2$ represented the regression coefficients in each stratum, and SE$_1$ and SE$_2$ were the corresponding standard errors (Wu et al., 2014).
2.7. Estimating attributable COPD burden

Based on the PM$_{2.5}$-COPD association, we estimated the COPD burden due to ambient PM$_{2.5}$ (Lin et al., 2016). Two indicators were used to reflect the attributable burden, attributable cases and population attributable fraction. The threshold concentration of ambient PM$_{2.5}$ (30 μg/m$^3$) was used as the reference concentration. The methods to calculate the two variables have been described elsewhere (Lin et al., 2017b).

Several sensitivity analyses were conducted. Different PM$_{2.5}$ exposure definitions were applied: one, two, four and five-year averaged concentrations prior to the survey. We excluded other respiratory diseases (asthma) and cardiovascular diseases (stroke) due to their association with PM$_{2.5}$ (Anderson et al., 2013; Lin et al., 2017a).

We conducted all the analyses using R software, and p-values < 0.05 were considered statistically significant.

3. Results

A total of 36,742 participants aged 50 years and older were initially recruited in the SAGE survey, among whom, 7452 participants were excluded due to missing information for COPD, age, sex or other important covariates. Our analyses were based on the remaining 29,290 participants (Table 1). The participants included and excluded had comparable characteristics, including similar prevalence of COPD (6.39% among included participants, and 6.21% among those excluded), and exposure to PM$_{2.5}$ (37.0 μg/m$^3$ and 36.7 μg/m$^3$), indicating a representative sample of the participants included in this analysis. The three-year mean PM$_{2.5}$ concentration was 37.0 μg/m$^3$ across the six countries (Table s1). The highest concentrations occurred in China and India (47.0 and 50.0 μg/m$^3$), respectively, and the lowest level was in Mexico (13.0 μg/m$^3$). The mean age was 63 years.

Among the participants, 1872 (6.39%) were classified as COPD. The participants with COPD were older than the referent group, had higher BMI, were more likely to be males, lived in urban areas, had higher tobacco consumption.

The smoothing curve showed a U-shaped exposure-response relationship between ambient PM$_{2.5}$ and COPD with an exposure threshold (Fig. 1). Our analysis suggests that the threshold concentration was 30 μg/m$^3$. Above the threshold, we observed significant associations of COPD prevalence with ambient PM$_{2.5}$ (Table 2). The crude odds ratio (OR) for each 10 μg/m$^3$ increase in PM$_{2.5}$ was 1.19 (95% CI: 1.11, 1.27), and the association remained significant after adjusting for potential confounders (adjusted OR = 1.21, 95% CI: 1.13, 1.30).

The stratified analyses suggested that sex, age, and education might be important modifiers of the associations (Table 2). We observed higher effects among males (adjusted OR = 1.23 (95% CI: 1.14, 1.33) for males, and 1.09 (95% CI: 1.00, 1.19) for females), older adults (adjusted OR = 1.17 (95% CI: 1.08, 1.27) for older participants, and 1.09 (95% CI: 1.01, 1.18) for younger participants), and those with lower education levels (adjusted OR = 1.13 (95% CI: 1.05, 1.21) for those with lower education level, and 0.94 (95% CI: 0.83, 1.06) for those with higher education level). We did not find significant differences between smokers and never-smokers, or between warm and cold seasons.

Table 3 presents the COPD burden attributable to PM$_{2.5}$ in the six countries. We estimated that about 259 (95% CI: 147, 405) COPD cases could be attributable to ambient PM$_{2.5}$ higher than 30 μg/m$^3$ in the study population, corresponding to a population attributable fraction of 13.79% (95% CI: 7.82%, 21.62%). The stratified analyses by sex and age showed a larger burden among males and the older population.

Our sensitivity analyses yielded similar effect estimates with those in the main models, suggesting a robust model (Table s2). For example, comparable results were observed when using one, two, four and five-year averaged PM$_{2.5}$ concentrations as the exposure variable. When excluding other respiratory and cardiovascular diseases, we also observed a significant effect. For example, the OR for each 10 μg/m$^3$ increase in PM$_{2.5}$ was 1.24 (95% CI: 1.16, 1.33) when excluding other respiratory cases.

4. Discussion

This study provided evidence that long-term PM$_{2.5}$ exposure was associated with increased risk of COPD. We estimated that about 14% of the COPD cases could be attributable to PM$_{2.5}$ in the study.
population. We further observed a higher effect among males, older participants, never-smokers and those with lower education levels.

The observed association between PM$_{2.5}$ and COPD was consistent with some previous literature. The European Studies on Chronic Air Pollution Effects cohort study observed significant associations between increased risk of COPD and traffic-related pollution among females (Schikowski et al., 2014). In a cohort study in Oslo, Norway, significant associations were reported between ambient PM$_{2.5}$ and COPD mortality (Naess et al., 2007). And a 40% increase in the risk of COPD was observed for each 10 μg/m$^3$ increase in PM$_{2.5}$ in a Canadian study (Pinault et al., 2016). A positive association between PM$_{2.5}$ and prevalence of COPD was also reported from a study among the Chinese population (Liu et al., 2016). Similarly, traffic-related air pollution exposure was also related to an increased risk of COPD (Schikowski et al., 2005). On the other hand, one cohort study from Vancouver, Canada did not detect any significant association between PM$_{2.5}$ and morbidity and mortality of COPD (Gan et al., 2013). Non-significant association was also observed in two cohort studies (Atkinson et al., 2014) (Dimakopoulou et al., 2014) and one spatial analysis (Hao et al., 2015).

Our analysis further demonstrated that males, the lower educated, and older adults might be the more sensitive to PM$_{2.5}$ exposure; this observation was consistent with previous studies (Pinault et al., 2016). However, the stronger effect among never-smokers compared with smokers were beyond our expectation. One possible reason might be the failure to control for second-hand smoking in this study. A high second-hand smoking exposure has been observed in the study population. For example, as high as 70% of nonsmokers in China and 52% in India were exposed to second-hand smoking (World Health Organization). Second-hand smoking exposure could result in respiratory inhalation of higher doses of air pollutants, which may lead to significant effects on COPD among the never-smokers (Vineis et al., 2005). Furthermore, studies have reported that there are some genetic differences between smokers and never-smokers (Rhee et al., 2003), and these differences may make never-smokers more susceptible to the effects of PM$_{2.5}$ exposure.

One major finding of this study was the attributable risk of COPD due to ambient PM$_{2.5}$. We estimated that about 14% of the COPD cases could be prevented in the study population by attaining the WHO air quality guideline of annual PM$_{2.5}$. This estimation, compared with those only reporting the association between PM$_{2.5}$ and COPD, provided more useful information for policymakers to consider more stringent air pollution control measures. This effort has also been made in several similar studies. One study from Guangzhou, China estimated that about 10.9% of COPD mortality could be attributable to ambient PM$_{10}$ (Li et al., 2016). Our recent studies estimated that about 12% of hypertension cases in Chinese adults and 7% of stroke cases in low- and middle-income countries could be attributable to PM$_{2.5}$ (Lin et al., 2017).

### Table 2

<table>
<thead>
<tr>
<th>Overall</th>
<th>No. of COPD</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>988</td>
<td>1.19 (1.11, 1.27)</td>
<td>1.21 (1.13, 1.30)</td>
<td></td>
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<tr>
<td>Sex</td>
<td></td>
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<tr>
<td>Female</td>
<td>504</td>
<td>1.07 (0.98, 1.16)</td>
<td>1.09 (1.00, 1.19)</td>
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<tr>
<td>Male</td>
<td>484</td>
<td>1.20 (1.11, 1.28)</td>
<td>1.23 (1.14, 1.33)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>&lt; 65 yrs</td>
<td>456</td>
<td>1.12 (1.03, 1.21)</td>
<td>1.09 (1.01, 1.18)</td>
<td></td>
</tr>
<tr>
<td>≥ 65 yrs</td>
<td>532</td>
<td>1.13 (1.04, 1.23)</td>
<td>1.17 (1.08, 1.27)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>678</td>
<td>1.14 (1.06, 1.22)</td>
<td>1.13 (1.05, 1.21)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>310</td>
<td>1.02 (0.90, 1.15)</td>
<td>0.94 (0.83, 1.06)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>652</td>
<td>1.13 (1.04, 1.22)</td>
<td>1.16 (1.07, 1.27)</td>
<td></td>
</tr>
<tr>
<td>Ever</td>
<td>336</td>
<td>1.11 (1.03, 1.20)</td>
<td>1.14 (1.05, 1.23)</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Season of survey</td>
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<tr>
<td>Warm</td>
<td>552</td>
<td>1.13 (1.05, 1.21)</td>
<td>1.15 (1.06, 1.24)</td>
<td></td>
</tr>
<tr>
<td>Cold</td>
<td>436</td>
<td>1.42 (1.20, 1.68)</td>
<td>1.18 (1.00, 1.38)</td>
<td>&gt; 0.05</td>
</tr>
</tbody>
</table>

* The number of COPD cases above the threshold concentration (30 μg/m$^3$);  
* Adjusted for sex, age, BMI, education, smoking, alcohol drinking and occupational exposure.

### Table 3

<table>
<thead>
<tr>
<th>Overall</th>
<th>Attributable cases</th>
<th>Population attributable fraction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>259 (147, 405)</td>
<td>13.79 (7.82, 21.62)</td>
<td></td>
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</table>

* The smoothing curve of the exposure-response relationship between ambient PM$_{2.5}$ and prevalence of COPD.
The exact biological mechanisms for the observed association remain unknown. The previous findings on impaired lung function associated with air pollution exposure might be helpful to understand our result. One study reported that high PM$_{2.5}$ exposure was associated with lower lung function among the Framingham offspring (Rice et al., 2015). In another study, exposure to ambient PM$_{10}$ was found to be associated with decreases in FVC and FEV$_1$ (Ackermann-Liebrich et al., 2015). Experimental studies have reported that diesel exhaust exposure could induce inflammatory response in airways and lungs (Ghio et al., 2012). Additionally, air pollution is linked to up-regulation of gene expression to increase the production of proinflammatory mediators in the lower respiratory tract, such as interleukin-8 (Salvi et al., 2000). It was also possible that the oxidative stress caused by excessive reactive oxygen species might have played an important role (Kelly, 2003).

Our study had several limitations inherent to large-population-based epidemiologic studies. The COPD cases were determined based on self-reported diagnosis history and medication use. The prevalence (6.4%) observed in this study was relatively lower than that from one recent systematic review (Adeloye et al., 2015), which showed an estimated rate of 10.6% in low- and middle-income countries. This suggests that our approach might have under-estimated the prevalence of the exposure in this study, this issue warrants further examination in future studies. We were unable to establish a causal relationship between ambient PM$_{2.5}$ and COPD based on the cross-sectional nature of this study. We used a three-year average concentration of satellite-derived PM$_{2.5}$ as an exposure surrogate. These measurements may not reflect direct levels of individual exposures, and thus exposure misclassification was possible. Missing information was one concern. However, this issue is unlikely affected by PM$_{2.5}$ exposure, and should have little impact on the associations. Furthermore, though we have tried to control for some important potential confounding factors, some residual confounding was still possible due to the lack of some other important covariates, such as dietary factors, noise exposure and second-hand smoking. We were unable to adjust for other air pollutants and meteorological factors due to data unavailability.

In summary, the results confirm that PM$_{2.5}$ exposure would be an important risk factor for COPD, and is associated with remarkable disease burden in the countries studied.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2018.01.029.

References