Ambient PM$_{2.5}$ and O$_3$ and their combined effects on prevalence of presbyopia among the elderly: A cross-sectional study in six low- and middle-income countries

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**HIGHLIGHTS**

• We examined the effects of PM$_{2.5}$ and O$_3$ on prevalence of presbyopia
• Each 10 μg/m$^3$ increase in PM$_{2.5}$ corresponded to a 15% increase in presbyopia
• Each 10 μg/m$^3$ increase in O$_3$ was associated with a 37% increase in presbyopia
• There seems a synergistic interaction between PM$_{2.5}$ and O$_3$ on presbyopia

**ABSTRACT**

Background: Ambient air pollutant directly contacts with the eyes, however, the effect of ambient fine particulate matter (PM$_{2.5}$) and ozone (O$_3$) on vision impairment, such as presbyopia, has been kept largely unknown.

Methods: We surveyed a total of 36,620 participants aged 50 years and above in six low- and middle-income countries. Ambient annual concentrations of PM$_{2.5}$ and O$_3$ for the residential community were estimated using satellite data and chemical transport model. A mixed effects model was utilized to assess the effects of ambient PM$_{2.5}$ and O$_3$ on presbyopia, as well as their combined effects.

Results: A total of 13,841 presbyopia cases were identified among the participants with a prevalence rate of 41.17%. For both PM$_{2.5}$ and O$_3$, we found a J-shaped exposure-response relationship with the threshold being identified at 15 μg/m$^3$ for PM$_{2.5}$ and 55 μg/m$^3$ for O$_3$. The odds ratio (OR) of presbyopia was 1.15 (95% CI: 1.09, 1.21) for each 10 μg/m$^3$ increase in PM$_{2.5}$ above 15 μg/m$^3$ and 1.37 (95% CI: 1.23, 1.54) for O$_3$ above 55 μg/m$^3$ after adjusting for various potential confounding factors. There appeared to be a synergistic interaction between
Presbyopia

Low- and middle-income countries

ambient PM$_{2.5}$ and O$_3$ on presbyopia in the additive model, the combined effect was significantly larger than the sum of their individual effects, with a synergistic index of 2.39.

Conclusion: This study supports that exposures to ambient PM$_{2.5}$ and O$_3$ might be important risk factors of presbyopia among old adults, and simultaneously exposure to high level of the two pollutants could intensify their individual effects.

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2.4. Covariates

A series of covariates were collected in this survey. Weight and height were measured to calculate the body mass index (BMI). Marital status was divided into married (currently married or cohabiting) and unmarried (never married, separated, divorced, or widowed). Household income was categorized into two levels (low or high) using median income as the threshold. Tobacco consumption was also grouped into “ever smoked” and “never smoked”. Alcohol consumption was categorized into two broad groups: non-drinkers and drinkers. The occupations of participants were categorized into those related to air pollution exposure (e.g., mineral, construction, cleaning, renovation, and mechanic-related work) and those not related to air pollution exposure (e.g., administrative, office work, service, academic, sales, fishery, and unemployed) (Ostro et al., 2010).

Participants were also asked about the types of fuel most frequently used for domestic cooking, as well of ventilation while cooking. Ventilation in the cooking area of the dwelling was categorized as present or not. Two fuel types were predominately used: clean fuels (including electricity and natural gas), and unclean fuels (such as coal, wood, dung and agricultural residues).

A few country-level indicators were also collected and controlled in the model, including the gross domestic product (GDP) per capita (Central Intelligence Agency, n.d.), proportion of the population residing in urban areas, health care expenditure per capita, and the Gini coefficient (one indicator of income inequality with values ranging from 0 (equality) to 1 (inequality)) (World Bank, n.d.).

2.5. Statistical analysis

For case and referent groups, the values of mean and standard deviation (SD) were calculated for continuous variables and the statistical difference was examined using student-t-tests. Frequencies were calculated for categorical variables and $\chi^2$ tests were used to examine the statistical difference.

To consider the nested data structure (individuals within communities within countries), we applied a three-level logistic regression model, with participants being the first-level units, community being the second-level units, and country being the third-level units (Lin et al., 2017).

We firstly examined the concentration-response relationship between exposure to PM$_{2.5}$ (and O$_3$) and presbyopia using a natural spline smoothing function (Tian et al., 2016). Our initial analyses suggested a J-shaped relationship and the existence of threshold in the effects of both air pollutants. The concentration-response curve showed that there was no significant effect below a certain concentration level and an approximately linear effect above the threshold. We identified the threshold using the Akaike Information Criterion (AIC). In brief, we tested multiple thresholds in the model, for example, by visual inspection of the concentration-response curve, we may observe that the potential threshold might be between 13 and 16 $\mu$g/m$^3$ for PM$_{2.5}$ and between 53 and 56 $\mu$g/m$^3$ for O$_3$, and we then fitted two models with the cut-off changing within the concentrations (by each 0.5 $\mu$g/m$^3$), the one with minimum sum of the AIC of the two models will be identified as the threshold (Zhang et al., 2016).

Following the univariate regression models, multivariate regression models were then fit to control for some important covariates. The covariates in the multivariate model were selected based on three criteria: (1) variables are known or hypothesized risk factors of ambient air pollution and presbyopia; (2) the association between air pollution and presbyopia changed by $>10\%$ when adding a new variable in the model; and (3) some important factors, such as sex, age, smoking, were still included in the final model, even if they did not meet the first two criteria. Our final multivariate model thus included sex, age, BMI, marital status, education attainment, smoking status, alcohol consumption, household income, occupation pollution exposure, domestic fuel type and ventilation.

2.6. Interaction

We further examined the possible interaction between PM$_{2.5}$ and O$_3$ in relation to the prevalence of presbyopia in both multiplicative and additive interaction models. Multiplicative interaction was assessed by including a product term between PM$_{2.5}$ and O$_3$ into the regression model. Additive interactions were examined using the synergy index (SI) (Andersson et al., 2005). We classified PM$_{2.5}$ and O$_3$ into two levels (low and high) using the median value as the cut-point, based on which, we created a new variable to represent the combination of these two variables. As a categorical variable, it had four categories: 1) low PM$_{2.5}$ exposure and low O$_3$ exposure; 2) low PM$_{2.5}$ and high O$_3$ exposure; 3) high PM$_{2.5}$ and low O$_3$ exposure; and 4) high PM$_{2.5}$ and high O$_3$ exposure. The formula to calculate the synergy index can be specified as:

$$SI = \frac{OR_{11} - 1}{(OR_{01} - 1) + (OR_{10} - 1)}$$

where OR$_{11}$ represents the risk in high-high category, OR$_{01}$ is the risk in low-high category, and OR$_{10}$ is the risk in the high-low category. An SI greater than one denoted a synergetic interaction, meaning that the joint effects of PM$_{2.5}$ and O$_3$ were larger than the sum of their individual effects. An SI smaller than one indicated an antagonistic interaction, meaning that simultaneously exposure to the two pollutants, one pollutant could reduce the effect of the other (Andersson et al., 2005).

We also checked the robustness of the estimated by running a few sensitivity analyses. Specifically, we used the average concentrations of air pollution of one, two, four and five years before the survey period. Additional country-level covariates were further adjusted to control for potential confounding.

All the analyses were performed using the package “MASS” in R version 3.2.2. In all analyses, an a priori p-value $<0.05$ was considered statistically significant.

3. Results

A total of 36,742 participants aged 50 years and older were included in this survey. Among them, 3122 participants had missing values for age, sex or other important covariates, the remaining 33,620 participants were included in this analysis (Table 1). The general characteristics were comparable between the included and excluded participants, such as O$_3$ concentration (60.63 $\mu$g/m$^3$ and 60.76 $\mu$g/m$^3$), and similar BMI (24.55 kg/m$^2$ and 25.95 kg/m$^2$), indicating a representative sample of the participants included in this analysis. The mean concentration of PM$_{2.5}$ and O$_3$ in the six countries was 23.04 $\mu$g/m$^3$ and 60.63 $\mu$g/m$^3$. South Africa had the lowest level of PM$_{2.5}$ with an annual concentration of 5.97 $\mu$g/m$^3$; while China and India had the highest PM$_{2.5}$

![Table 1](image-url)
concentration (33.00 μg/m³ and 31.06 μg/m³, respectively); Russia and South Africa had the lowest O\(_3\) concentration (49.70 μg/m³ and 49.77 μg/m³), and India had the highest O\(_3\) concentration (68.51 μg/m³).

Out of the 33,620 participants, 13,841 (41.17%) were identified as presbyopia cases. Table 2 presents the demographic characteristics of presbyopia cases and non-presbyopia participants. Participants with presbyopia were statistically older than the non-presbyopia respondents (64.3 years versus 62.9 years), had higher BMI values (25.31 versus 24.02 kg/m²), and higher exposure levels of ambient PM\(_{2.5}\) (23.65 versus 22.63 μg/m³), but lower O\(_3\) exposure level (59.96 versus 61.10 μg/m³). Cases were more likely to be males, married, non-smokers, drinkers, live in urban areas, have higher education levels, expose to occupational pollution, higher household income, use clean fuels, and report a lower rate of domestic ventilation.

Table 1 shows J-shaped concentration-response relationships of ambient PM\(_{2.5}\) and O\(_3\) with presbyopia in the multivariate regression models. It seemed that there was a concentration threshold for both air pollutants; our analysis identified the threshold concentrations being at 15 μg/m³ for PM\(_{2.5}\) and 55 μg/m³ for O\(_3\), respectively, higher than which there was an increasing prevalence of presbyopia, so in the subsequent analyses, we examined the effects of ambient PM\(_{2.5}\) and O\(_3\) higher than threshold concentration.

Table 3 shows the associations of exposure to PM\(_{2.5}\) and O\(_3\) with the prevalence of presbyopia. The odds ratio (OR) of presbyopia was 1.15 (95% CI: 1.09, 1.21) for each 10 μg/m³ increase in ambient PM\(_{2.5}\) above 15 μg/m³ and 1.37 (95% CI: 1.23, 1.54) for each 10 μg/m³ increase in ambient O\(_3\) above 55 μg/m³, respectively. The subgroup analyses for the effects of PM\(_{2.5}\), by sex and age group found comparable effects between males and females, however, we found a larger effect of PM\(_{2.5}\) in young participants than old participants. For the effects of O\(_3\), we found no statistical significant differences between males and females and between the two age groups.

Table 4 depicts the interaction between PM\(_{2.5}\) and O\(_3\) on the prevalence of presbyopia. Using the low PM\(_{2.5}\)-low O\(_3\) group as the reference, we found the OR in the other three groups (low-high, high-low and high-high) were higher than one; the interaction was statistically significant in multiplicative model (p = 0.14); and in the additive interaction model, we found a larger joint effect than the sum of their individual effects, indicating a synergistic interaction. For instance, the individual effect of PM\(_{2.5}\) and O\(_3\) was 1.22 (95% CI: 0.92, 1.61) and 1.22 (95% CI: 1.02, 1.46), while their joint effect was 2.04 (95% CI: 1.64, 2.54) with a synergistic index (SI) of 2.39.

The sensitivity analyses suggested that the results in the main models were robust (Supplementary Table S1). For example, when using the mean concentrations PM\(_{2.5}\) and O\(_3\) from one, two, four and five years before the survey, the analyses produced similar results with those in the main model. When including both pollutants in the same model simultaneously, the effects of PM\(_{2.5}\) and O\(_3\) remained statistically significant, but the magnitudes became smaller. And after further adjusting for country-level covariates, we observed similar effects of PM\(_{2.5}\) (OR = 1.16, 95% CI: 1.09, 1.24) and O\(_3\) (OR = 1.39, 95% CI: 1.25, 1.55).

![Fig. 1. The concentration-response curves for the effects of ambient PM\(_{2.5}\) and O\(_3\) on presbyopia among the adults in the six low- and middle-income countries.](image-url)
4. Discussion

To the best of our knowledge, this was the first epidemiologic study to link ambient PM$_{2.5}$ and O$_3$ with presbyopia. Using a large sample of adult participants from six low- and middle-income countries, we found a significant association of exposure to PM$_{2.5}$ and O$_3$ with the prevalence of presbyopia. Of particular, we observed threshold in the effects of both pollutants, and a synergistic interaction of PM$_{2.5}$ and O$_3$ on the effect of presbyopia in the study population.

Though majority of previous studies did not detect a threshold concentration for the health effects of various air pollutants (Samoli et al., 2005), this study found a J-shaped concentration-response relationship with a threshold for both air pollutants, suggesting that there was no obvious effect of PM$_{2.5}$ below 15 mg/m$^3$ and O$_3$ lower than 55 mg/ m$^3$. The discrepancy might be that previous studies have mainly focused on cardiovascular and respiratory diseases (Neuberger et al., 2007), while this study examined the effects on eye health.

One interesting finding of this study was that young participants (50–65 years) were more sensitive to the effects of ambient PM$_{2.5}$ than old participants (>65 years), which was biologically plausible, as presbyopia usually began to occur around 50 years of age, and sensitive to the effects of external environment at that age period; while at the older age (>65 years), the status usually remained relatively stable (Fisher, 1973).

The effects of ambient PM$_{2.5}$ and O$_3$ on presbyopia observed in this study were convergent with previous studies. For example, exposure to ambient air pollution has been associated with subclinical impairment in the ocular surface and the tear film (Gupta et al., 2002; Saxena et al., 2003). Studies from Sao Paulo, Brazil found exposure to traffic-derived air pollution was associated with ocular discomfort symptoms (Novaes et al., 2010) and goblet-cell hyperplasia (Novaes et al., 2007). And one study reported that ambient PM$_{2.5}$ was associated with tarsal goblet cell density, and suggested that mucin 5 AC mRNA might be one adaptive ocular surface response to long-term exposure to air pollution (Toricelli et al., 2014).

A substantial number of studies have examined the etiology of presbyopia, suggesting that both environmental and genetic factors contribute to its occurrence (Mantelli et al., 2011). While the mechanisms for the observed effects of ambient PM$_{2.5}$ and O$_3$ on presbyopia remained largely unclear, we offer the following speculation that both PM$_{2.5}$ and O$_3$ directly contact the eyes, long-term exposures may lead to chronic inflammation response and oxidative stress, which are involved in the pathology of vision impairment (Novaes et al., 2010; Vitar et al., 2015). Previous studies have suggested that exposure to higher levels of air pollution could lead to declines in cell viability, proliferation, as well as inflammatory response mediated by interleukin (IL)-6 (Vitar et al., 2015). Furthermore, it has also been reported that O$_3$ and the chemical constituents of the fine particles may interact with different epithelial cells through oxidative processes (Kelly et al., 2003). The oxidative process is characterized by an increase in the reactive oxygen species (ROS), which could lead to oxidant injury (Chuang et al., 2013). Human lenses usually have a distinct viscoelastic behavior and indeed studies have suggested that loss of elasticity of the crystalline lens is associated with the occurrence and severity of presbyopia (Khalaj et al., 2014). Thus, it is possible that the chronic inflammation and oxidative stress resulting from exposure to ambient PM$_{2.5}$ and O$_3$ could function to reduce the elasticity of the lens.

Our study observed that ambient PM$_{2.5}$ and O$_3$ had a synergistic interaction on presbyopia. The underlying mechanism remained largely unknown. However, a few biological pathways have been proposed for the interaction between PM pollution and O$_3$ on cardiovascular and respiratory health outcomes, which may help to explain the current findings. For example, the synergistic interaction of PM pollution and O$_3$ was also reported in a few experimental studies on rats, which might be that the particles served as carriers for the gaseous pollutants, delivering this irritant gas to the body (Last et al., 1986; Warren and Last, 1987), and co-existence of particles and O$_3$ could increase the responsiveness of airway in mice (Goldsmith et al., 2002). It was also possible that the chemical reaction on the particle surface in the atmosphere or the pulmonary environment could play a role in the interaction between particle and O$_3$ (Schlesinger, 1995). A study examined the interaction between ozone and airborne particulate matter and observed that the combined exposure caused significantly more effects than individual exposure to ozone or particle exposures, and the effects could be reflected in the release of cytokines and changes of the respiratory function (Malhove et al., 2005). Another explanation might be due to the similar pathological pathways of the effects of both pollutants, such as inflammatory response and oxidation, interacting with cytokine receptors in the endothelial cells (Pope III et al., 2004), causing inflammation and oxidative stress of the eyes. It was also that exposure to higher level of O$_3$ may decrease the clearance and increase the deposition and retention of the fine particles, and thus enhance their effects on the occurrence of presbyopia.

One implication of this study was the recommendation to avoid exposure to higher levels of ambient PM$_{2.5}$ and O$_3$ to protect eye health. Individuals should consider this when participating in outdoor activities, as there is a potential for cumulative damage over the life-course.

Several limitations should be acknowledged. Our cross-sectional research design cannot establish a causal relationship between ambient air pollution (PM$_{2.5}$ and O$_3$) and presbyopia. The questionnaire-based diagnosis used for the definition of presbyopia might have led to some degree of misclassification. We compared the prevalence obtained in this study with similar studies using the standard diagnosis method and found that ours was relatively lower (Lu et al., 2011; Naidoo et al., 2013). This suggests that under-reporting was possible in our study. However, under-reporting should be non-differential across different geographic areas in this study as we used the same survey method. Additionally, we used satellite-based estimates of ambient PM$_{2.5}$ concentrations as one proxy of the exposure, which may have produced errors and uncertainty in our measurement of exposure. Finally, due to a lack of information regarding the potential confounding factors of family history of presbyopia, other pollution exposure, and weather variables, we failed to adjust for them in the statistical model.

<table>
<thead>
<tr>
<th>Category</th>
<th>Adjusted OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PM$_{2.5}$+O$_3$</td>
<td>1.00</td>
</tr>
<tr>
<td>Low-low</td>
<td>1.22 (1.02, 1.46)</td>
</tr>
<tr>
<td>Low-high</td>
<td>2.12 (0.92, 1.61)</td>
</tr>
<tr>
<td>High-low</td>
<td>2.04 (1.64, 2.54)</td>
</tr>
<tr>
<td>High-high</td>
<td>2.39</td>
</tr>
<tr>
<td>Synergy index</td>
<td>0.04</td>
</tr>
</tbody>
</table>

* We controlled for age, sex, BMI, marital status, residence, education level, household income, smoking, occupation pollution exposure, domestic fuel type and ventilation.
5. Conclusions

In summary, our study suggests that exposure to ambient PM$_{2.5}$ and $O_3$ might be important risk factors in the development of presbyopia. Moreover, it seems that simultaneously exposure to high level of the two pollutants would enhance their individual effects.