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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

GRAPHICAL ABSTRACT

Can air pollution exposure induce presbyopia?

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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

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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.

1. Introduction

Both short-term and long-term exposures to ambient levels of air pollution have been consistently linked with a number of negative health outcomes, particularly respiratory and cardiovascular diseases (Honda et al., 2017; Lin et al., 2016a; Neupane et al., 2010; Yu et al., 2012). Among various air pollutants, $PM_{2.5}$ (particles equal to or smaller than 2.5 μm in aerodynamic diameters) and ozone (O_3) have been suggested to be more harmful (Lin et al., 2016b; Schwartz, 2016).

Some $PM_{2.5}$ chemical constituents and O_3 have a direct irritant and oxidant effect on the mucous membranes of the body (Torricelli et al., 2014). Sparse evidence, however, has been available on the adverse effects on the eyes of these air pollutants, despite the fact that the eyes are directly and constantly exposed to the external air pollutants. It has been suggested that the eyes are particularly relevant to the impacts of air pollutants (Novaes et al., 2007; Vitar et al., 2015). In fact, clinical observation and temporal development trends of the ocular surface in association with exposure to ambient air pollutants have been reported previously (Gupta et al., 2002; Saxena et al., 2003). In short, people who are exposed to higher levels of air pollution have reported more frequent ocular discomfort symptoms, such as irritation, burning, redness, and itching (Novaes et al., 2007; Saxena et al., 2003). These observations indicated that ambient air pollution exposure may increase the risk of vision impairment in the form of such disorders as presbyopia.

Presbyopia is the gradual loss of the eyes' ability to focus on nearby objects (Patel and West, 2007). It poses a remarkable disease burden to both individuals and the society stemming from the need for correction of refractive errors and avoiding visual impairment. It is of great public health importance to examine the environmental determinants of presbyopia, as the associated vision impairment has been reported to be an important predictor of quality of life and mortality (McCarty et al., 2001).

Furthermore, though a few studies have examined the individual health effect of particulate pollution and O_3, literature on their interactive effects has been largely sparse (Chen et al., 2007; Qiu, 2012). In three studies from Moscow of Russia, Shanghai of China and Mexico City, a synergistic interaction between PM_{10} and O_3 on mortality was reported (Chen et al., 2007; Revich and Shaposhnikov, 2010; Téllez Rojo et al., 2000). On the other hand, a few studies found a negative interactive effect, for example, in one Hong Kong study, the investigators observed that exposure to O_3 could mitigate the adverse effects of PM pollution on cardiovascular and respiratory morbidity (Qiu, 2012); and in a Seoul study, the effects of O_3 decreased from when the concentrations of particulate pollution changed from below to above the median level, suggesting a negative interaction between them (Hong et al., 2002). However, no evidence on the interactive effects of $PM_{2.5}$ and O_3 has been available, given that both air pollutants have the irritate effects on the eyes (Vitar et al., 2015), we thus hypothesized that ambient $PM_{2.5}$ and O_3 may have both independent and interactive associations with the prevalence of presbyopia.

This study investigated whether exposure to ambient $PM_{2.5}$ and O_3 was associated with presbyopia among the 36,620 elderly participants aged 50 years and older from six low- and middle-income countries. We also examined their combined effects on presbyopia in the study population.

2. Methods

2.1. Study population

The Study on global AGEing and adult health (SAGE) surveyed with adults in six low- and middle-income countries: China, Ghana, India, Mexico, the Russian Federation and South Africa (Kowal et al., 2012). The baseline data, conducted from 2007 to 2010, were used for this analysis. A standardized questionnaire was used to interview the participants aged 50 years and older selected through a multistage random cluster sampling approach (Wu et al., 2013). The survey consisted of questions reflecting demographic, economic, social, behavioral, and health characteristics and factors. The primary sampling units were stratified by region and location (e.g., urban/rural) and, within each stratum, enumeration areas were then selected (Kowal et al., 2012).

2.2. Diagnosis of presbyopia

Participants will be recognized as presbyopia cases if they meet one of the following criteria: 1) one has been diagnosed as a presbyopia case by a health professional; 2) one has difficulty in seeing and recognizing an object at arm's length (for example, reading); 3) one has to use eyeglasses or contact lenses in order to see up close (for example at an arm's length when reading).

2.3. Air pollution concentration assessment

Due to lacking of the field air pollution measurement, we estimated the ambient $PM_{2.5}$ concentrations at $0.1^\circ * 0.1^\circ$ spatial resolution using remote sensing information (Van Donkelaar et al., 2010), this method has been employed in the global distribution of $PM_{2.5}$, and a validation study showed an acceptable accuracy of the estimate $PM_{2.5}$ concentrations (Van Donkelaar et al., 2010). In addition, a comparison of the health effects of $PM_{2.5}$ from the monitored and remote sensing exposure estimates showed consistent effect estimates (Jerrett et al., 2016).

The estimate of O_3 exposure was determined by using annual mean concentrations estimates derived from the Global Burden of Disease 2013 (GBD 2013) project (Brauer et al., 2015). The O_3 exposure assessments were based on chemical transport model simulations and ground measurements at $0.1^\circ * 0.1^\circ$ spatial resolution. Results of cross-validation showed that this model could well capture the annual concentration of O_3 and the estimated information has been widely applied in a few air pollution epidemiological studies (Liu et al., 2017).

The community addresses of the study participants were used to match the corresponding air pollution concentrations and used in the regression models. The areal unit has varying size because of the difference in administrative structure across the six countries. Specifically, it refers to the township or community in China, the enumeration area in Ghana and South Africa, the village or census enumeration block in India, the Basic Geo-Statistical Area in Mexico, and the ateneum in Russia. Three-year average concentrations were used as the exposure variable in the main model. We reported the effect estimates per 10 $\mu g/m^3$ increases in ambient $PM_{2.5}$ and O_3 in this study.

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 χ^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 μg/m^3 for $PM_{2.5}$ and between 53 and 56 μg/m^3 for O_3, and we then fitted two models with the cutoff changing within the concentrations (by each 0.5 μg/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. Addictive 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 participates 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 μg/m^3 and 60.76 μg/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 μg/m^3 and 60.63 μg/m^3. South Africa had the lowest level of $PM_{2.5}$ with an annual concentration of 5.97 μg/m^3; while China and India had the highest $PM_{2.5}$

Table 1
Distributions of three-year mean concentrations (μg/m^3) of $PM_{2.5}$ and O_3 among the elderly in the six countries.

	China	Ghana	India	Mexico	Russia	South Africa	Overall
Participants	12,955	4286	6533	2178	3912	3756	33,620
$PM_{2.5}$ (μg/m^3)							
Minimum	10.66	12.21	7.86	3.75	2.32	1.50	1.51
Mean	33.00	17.49	31.06	10.75	6.10	5.96	23.05
Medium	32.59	17.45	27.42	11.14	6.17	5.92	18.15
Maximum	55.53	22.79	64.08	17.03	16.90	20.55	64.08
O_3 (μg/m^3)							
Minimum	52.03	58.47	54.26	46.11	35.79	36.10	35.79
Mean	61.59	65.88	68.51	59.38	49.70	49.77	60.63
Medium	61.25	65.93	68.67	59.58	48.03	50.26	61.25
Maximum	76.65	79.63	86.08	70.71	63.01	69.96	86.08

Table 2
Characteristics of the participants with and without presbyopia among the six countries.

Variables	No presbyopia [n (%)]	Presbyopia cases [n (%)]	p Value[a]
Age (years, mean (SD))	62.9 (9.8)	64.3 (9.5)	<0.01
BMI (kg/m^2, mean (SD))	24.02 (7.21)	25.31 (6.94)	<0.01
$PM_{2.5}$ (μg/m^3, mean (SD))	22.63 (14.91)	23.65 (16.75)	<0.01
O_3 (μg/m^3, mean (SD))	61.10 (8.46)	59.96 (9.52)	<0.01
Sex	61.10 (8.46)	59.96 (9.52)	<0.01
Male	9193 (46.48)	6266 (45.27)	
Female	10,586 (53.52)	7575 (54.73)	0.03
Marital status			
Married	13,260 (67.04)	9831 (71.03)	
Unmarried	6519 (32.96)	4009 (28.97)	<0.01
Residence			
Urban	7913 (40.01)	8903 (64.32)	
Rural	11,865 (59.99)	4938 (35.68)	<0.01
Education[a]			
Primary or lower	15,369 (77.70)	7673 (55.44)	
Middle or higher	4410 (22.30)	6168 (44.56)	<0.01
Household income[a]			
Low	10,290 (52.02)	6404 (46.27)	
High	9489 (47.98)	7437 (53.73)	<0.01
Smoking status			
Never	12,346 (62.74)	8948 (64.87)	
Ever	7333 (37.26)	4846 (35.13)	<0.01
Drinking status			
Nondrinker	12,790 (64.66)	8386 (60.59)	
Drinker	6989 (35.34)	5455 (39.41)	<0.01
Occupation pollution			
Yes	1655 (8.37)	1438 (10.39)	
No	18,124 (91.63)	12,403 (89.61)	<0.01
Indoor fuel type			
Clean	8206(41.49)	9568 (69.13)	
Unclean	11,573 (58.51)	4273 (30.87)	<0.01
Ventilation			
No	15,281 (77.26)	11,347 (81.98)	
Yes	4498 (22.74)	2494 (18.02)	<0.01

[a] χ^2 tests for categorical variables and *t*-tests for continuous variables.

concentration (33.00 μg/m^3 and 31.06 μg/m^3, respectively); Russia and South Africa had the lowest O_3 concentration (49.70 μg/m^3 and 49.77 μg/m^3), and India had the highest O_3 concentration (68.51 μg/m^3).

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 versus 62.9 years), had higher BMI values (25.31 versus 24.02 kg/m^2), and higher exposure levels of ambient $PM_{2.5}$ (23.65 versus 22.63 μg/m^3), but lower O_3 exposure level (59.96 versus 61.10 μg/m^3). Cases were more likely to be males, married, nonsmokers, 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.

Fig. 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/m^3 for $PM_{2.5}$ and 55 μg/m^3 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/m^3 increase in ambient $PM_{2.5}$ above 15 μg/m^3 and 1.37 (95% CI: 1.23, 1.54) for each 10 μg/m^3 increase in ambient O_3 above 55 μg/m^3, 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 effect, 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).

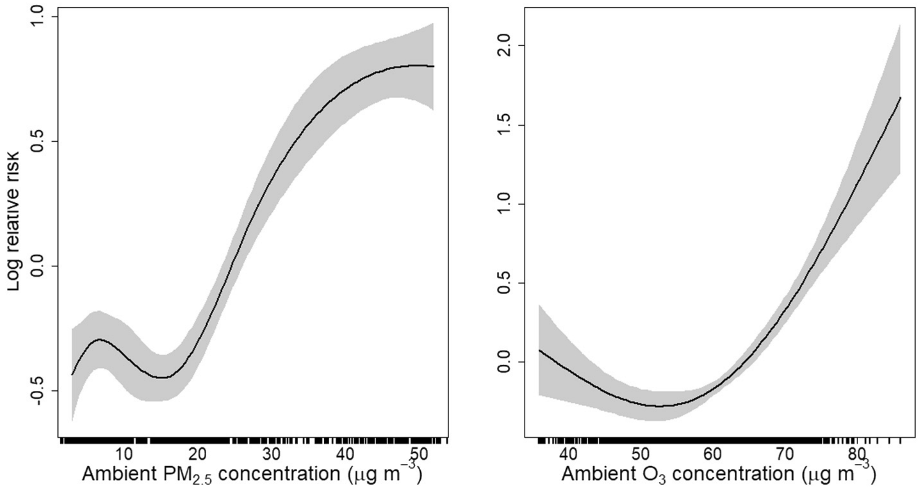

Fig. 1. The concentration-response curves for the effects of ambient $PM_{2.5}$ and O_3 on presbyopia among the adults in the six low- and middle-income countries.

Table 3
Adjusted odds ratio (OR, and 95% CI) for presbyopia associated with ambient $PM_{2.5}$ and O_3 above the corresponding threshold[a].

OR for per 10 μg/m^3 increase	$PM_{2.5}$	O_3
Overall	1.15 (1.09, 1.21)	1.37 (1.23, 1.54)
Sex		
Males	1.14 (1.07, 1.21)	1.31 (1.16, 1.49)
Females	1.16 (1.09, 1.24)	1.44 (1.25, 1.65)
Age group		
≤65 yrs	1.17 (1.11, 1.24)	1.40 (1.24, 1.59)
>65 yrs	1.10 (1.02, 1.17)	1.34 (1.15, 1.55)

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

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 than 15 μg/m^3 and O_3 lower than 55 μg/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 cells density, and suggested that mucin 5 AC mRNA might be one adaptive ocular surface response to long-term exposure to air pollution (Torricelli 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 (Mølhave 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 4
The interactive effects between ambient $PM_{2.5}$ and O_3 on the prevalence of presbyopia in the study population.

Category	Adjusted OR[a] (95% CI)
$PM_{2.5}$-O_3	
Low-low	1.00
Low-high	1.22 (1.02, 1.46)
High-low	1.22 (0.92, 1.61)
High-high	2.04 (1.64, 2.54)
Synergy index	2.39
p for multiplicative interaction	0.04

[a] 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.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2018.11.239.

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Conflict of interest

None declared.

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