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Associations of long-term joint exposure to multiple ambient air pollutants with the incidence of age-related eye diseases

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ABSTRACT

Objectives: The associations between long-term joint exposure to low levels of multiple air pollutants and the incidence of common age-related eye diseases (AREDs), including cataract, glaucoma, and age-related macular degeneration (AMD), remain underexplored.

Methods: We conducted a prospective cohort study using UK Biobank data from 441,567 participants without cataract, glaucoma, or AMD at baseline. An air pollution score was constructed to assess the combined effect of multiple air pollutants, including $PM_{2.5}$, $PM_{2.5-10}$, PM_{10}, NO_2 and NO. Cox proportional hazards models were used to evaluate associations.

Results: Over a median follow-up of 14.41 years, 55,104 participants developed cataract, 11,940 glaucoma, and 9060 AMD. A relatively stronger association was observed between combined exposure to multiple pollutants and AREDs incidence compared to exposure to individual pollutants. For every interquartile range increase in the air pollution score, the risk of incident AREDs increased by 4–5 % (cataract, HR [95 % CI], 1.05 [1.04–1.06]; glaucoma, 1.04 [1.02, 1.06]; AMD, 1.04 [1.01, 1.07]), suggesting the potential additive or synergistic effects of exposure to pollutant mixtures. Compared to individuals in the lowest exposure quartile, those in the highest had a 13 %, 9 %, and 14 % greater risk of developing cataract (1.13 [1.10–1.16]), glaucoma (1.09 [1.03–1.15]), and AMD (1.14 [1.07–1.22]), respectively.

Conclusions: Long-term joint exposure to multiple air pollutants, even at low concentrations, is associated with an increased risk of AREDs incidence, suggesting that reducing air pollution level could improve human ocular health. These findings provide a more comprehensive understanding of air pollution's impact on ocular health in the real world.

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1. Introduction

Common age-related eye diseases (AREDs), such as cataract, glaucoma, and age-related macular degeneration (AMD), are leading global causes of blindness and visual impairment in adults aged 50 years and older in 2020 (GBD, 2019 Blindness and Vision Impairment Collaborators, 2021; Voleti et al., 2013). According to the reports from the World Health Organization (WHO) in 2004, cataract, glaucoma, and AMD accounted for approximately 47.8 %, 12.3 %, and 8.7 % of global blindness, respectively (Resnikoff et al., 2004). The number of global blindness caused by these eye diseases is also substantially escalating in parallel with the aging global population, imposing a heavy burden on public eye healthcare systems and resulting in significant economic losses (Vision Loss Expert Group of the Global Burden of Disease Study & GBD 2019 Blindness and Vision Impairment Collaborators, 2024a, 2024b, 2024c). Given that cataract, glaucoma, and AMD can coexist with aging and share common risk factors (Voleti et al., 2013), it is imperative to conduct comprehensive evaluations of these conditions to facilitate early identification and intervention of relevant risk factors, thereby preventing these eye diseases onset and progression.

The detrimental impact of ambient air pollution on ocular health has drawn increasing attention (Lin et al., 2022). A growing body of observational studies has showed the associations between air pollution and the prevalence of cataract (Choi et al., 2018; Grant et al., 2021), glaucoma (Chua et al., 2019; Grant et al., 2021; Ma et al., 2024; Yang et al., 2021), and AMD (Chua et al., 2022; Grant et al., 2021; He et al., 2023; Ju et al., 2022). For instance, recent studies from China have revealed that short-term exposure to air pollution significantly elevates the risk of glaucoma-related outpatient visits (Li et al., 2022; Wang et al., 2022). However, only three studies from Korea (Shin et al., 2020) and China (Chang et al., 2019; Liang et al., 2022) have explored the long-term effects of air pollution on the incidence of cataract and AMD in the general population. Notably, the majority of these epidemiological studies have been conducted in Asian regions characterized by high air pollution levels (Chang et al., 2019; Chiang et al., 2021; Choi et al., 2018; He et al., 2023; Ju et al., 2022; Liang et al., 2022; Luo et al., 2022; Ma et al., 2024; Shin et al., 2020; Sun et al., 2021; Wu et al., 2024; Yang et al., 2021). Data from western countries with relatively low air pollution levels remained scarce (Chua et al., 2019, 2022; Grant et al., 2021), leaving it unclear whether these associations also exist in regions with lower levels of air pollution.

Furthermore, existing studies have predominantly focused on the individual effects of specific pollutants on age-related eye diseases, often neglecting the joint effect of multiple air pollutants. Since individuals are exposed to a combination of multiple air pollutants in the real world, and the high levels of collinearity among different pollutants can affect the accuracy of effect estimates, making it important to evaluate the combined impacts of multiple air pollutants on ocular health (Oakes et al., 2014).

Therefore, we conducted a prospective, population-based cohort study to assess the associations between long-term joint exposure to multiple air pollutants and the risks of incident cataract, glaucoma, and AMD by generating an air pollution score that encompassed the major air pollutants in the United Kingdom (UK). This investigation utilized data from the UK Biobank, which recruited nearly half a million participants with comprehensive information on individual demographic characteristics, medical conditions, lifestyle, and air pollution exposure.

2. Methods

2.1. Study design and population

The UK Biobank is a population-based prospective study, with over 500,000 participants aged 37–73 years recruited from 22 centers across England, Scotland, and Wales between 2006 and 2010. It has collected detailed information from the participants, including sociodemographic information, physical examinations, medical history, biological samples, and imaging data through various methods, such as touch-screen questionnaires, verbal interviews, and health records (Sudlow et al., 2015). This cohort study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Participants diagnosed with cataract, glaucoma, or AMD at baseline and during follow-up were confirmed through linkage to self-report (based on clinical diagnosis and subsequently checked with nurses), primary care records, inpatient hospital data, and death records in the UK Biobank, and defined by the International Classification of Diseases, Tenth Revision (ICD-10) codes.

From the participants enrolled between March 13, 2006, and October 1, 2010, we excluded participants who had a prior diagnosis of cataract, glaucoma, or AMD at baseline (n = 20,770). Participants with missing information on air pollution exposure were also excluded (n = 39,911) (Figure S1 in Supplement).

2.2. Air pollution assessment

Annual average air pollution estimates for the year 2010, including particulate matter with aerodynamic diameter of 2.5 µm or less ($PM_{2.5}$), PM with aerodynamic diameter between 2.5 µm and 10 µm ($PM_{2.5–10}$), PM with aerodynamic diameter less than 10 µm (PM_{10}), nitrogen dioxide (NO_2), and nitrogen oxides (NO_x), were collected by the UK Biobank using the land-use regression (LUR) models, which were derived from the European Study of Cohorts for Air Pollution Effects (ESCAPE, http://www.escapeproject.eu/) (Beelen et al., 2013; Eeftens et al., 2012). Based on a range of predictive variables derived from the Geographic Information System (GIS), including traffic intensity, population, topography, and land use, land use regression (LUR) models were applied to estimate air pollutant exposure levels, which were subsequently assigned to participants' home addresses for exposure assessment. Given that air pollution estimates were representative for the year 2010, these annual average concentrations were utilized as proxies of long-term air pollution exposure. The concentration of nitric oxide (NO) was determined by subtracting NO_2 from NO_x (Cyrys et al., 2012).

To assess the joint exposure to multiple air pollutants, we created separate air pollution scores for each age-related eye disease. Air pollution scores were constructed by summing concentrations of five air pollutants ($PM_{2.5}$, $PM_{2.5–10}$, PM_{10}, NO_2, and NO), weighted by the multivariable-adjusted risk estimates (β coefficients) specific to each eye disease (Batty et al., 2020; Li et al., 2024; Wang et al., 2021; Zhang et al., 2023). The β coefficients were derived from the final model, where each air pollutant was included individually as the independent variable. The air pollution score was calculated using the following formula (1):

$$Air\ pollution\ score = (\beta_{PM_{2.5}} \times PM_{2.5} + \beta_{PM_{2.5-10}} \times PM_{2.5-10} + \beta_{PM_{10}} \times PM_{10} + \beta_{NO_2} \times NO_2 + \beta_{NO} \times NO) \times \left(5 \Big/ \sum \beta\right) \quad (1)$$

2.3. Outcome identification

The identification of age-related eye diseases during the follow-up period was determined by using the International Classification of Diseases, Tenth Revision (ICD-10) codes. Specifically, cataract was coded as H25-H26, and H28 (Chen et al., 2024); glaucoma as H40 and H42 (Sun et al., 2022); and AMD as H35.3 (Lehrer et al., 2022). The details of ICD-10 codes were as follows: H25, senile cataract; H26, other cataract; H28, cataract and other disorders of lens in diseases classified elsewhere; H40, glaucoma; H42, glaucoma in diseases classified elsewhere; H35.3, degeneration of macula and posterior pole.

2.4. Covariates

Based on previous literature exploring factors related to age-related eye diseases, we selected sociodemographic information (age [years], sex [female or male], ethnicity [white or other], Townsend Deprivation Index [TDI], education [University or college degree, or other]), health-related information (body mass index [BMI; calculated as weight in kilograms divided by height in meters squared; kg/m^2], smoking status [never, previous, or current smoking], alcohol intake frequency [Never/special occasions only, one to three times a month, once or twice a week, three or four times a week, or daily/almost daily]), medical history (hypertension [yes or no], diabetes mellitus [yes or no], hyperlipidemia [yes or no]), as covariates. In the sensitivity analysis, more lifestyle factors including physical activity, healthy diet score, and sleep duration were further adjusted. The detailed information for covariates is described in **eMethods** in Supplement.

2.5. Statistical analysis

The characteristics of the study population were described as mean with standard deviation (SD) or median with interquartile range (IQR) for continuous variables and as number (percentage) for categorical variables. Covariates with missing data were handled as a separate category.

Participants were followed up from baseline until the date of diagnosis of cataract, glaucoma, or AMD, loss to follow-up, death, or September 1, 2023, whichever came first. In this study, we used Cox proportional hazards models to assess the associations of individual air pollutants and air pollution score (treated as a continuous variable or divided into quartile) with incidence of cataract, glaucoma, and AMD, respectively. The outcomes of these analyses were presented in the form of hazard ratios (HRs) and corresponding 95 % confidence intervals (CIs). The proportional hazards assumption underlying our models was tested using Schoenfeld residuals, and no violations were identified. Using the Akaike information criterion,(Rutherford et al., 2015) we applied restricted cubic spline functions with 3 knots (at 10th, 50th, and 90th percentiles) to illustrate the exposure-response relationships between air pollution and the risk of incident cataract, glaucoma, and AMD.

The association between air pollution and risk of developing cataract, glaucoma, and AMD were further stratified according to age (< 65 versus ≥ 65 years), sex (female versus male), ethnicity (white versus other), smoking status (never versus previous or current smoking), alcohol drinking status (never versus previous or current drinking), hypertension history (no versus yes), diabetes mellitus history (no versus yes), and hyperlipidemia history (no versus yes). The modification effect was assessed with likelihood-ratio tests by comparing models with and without a cross-product interaction term of air pollution and the stratified factor.

Furthermore, several sensitivity analyses were conducted to examine the validity of the results. First, we performed multiple imputation using chained equations to impute missing covariates in the dataset and conducted an analysis with the completed dataset. Second, we further adjusted for health diet score, physical activity, and sleep duration to control for potential confounders of lifestyle factors. Third, considering that the occupational exposure may be an additional potential confounders, we excluded participants with “blue collar” history to minimize the influence of occupational exposure. Fourth, a sensitivity analysis was conducted by considering how long the participants have lived at the same address. Fifth, new air pollution scores were constructed by incorporating only significant air pollutants for each of three age-related eye diseases to verify the robustness of our findings. Sixth, we developed a directed acyclic graph (DAG) to determine whether potential covariates should be adjusted in the models. Guided by the DAG (Figure S2 in Supplement), we identified and retained a minimally sufficient set of variables for adjustment, including age, sex, ethnicity, assessment center, TDI, education, and smoking status. Additionally, we performed a sensitivity analysis using these selected covariates. All statistical analyses were performed with R software, version 4.3.3 (R Project for Statistical Computing). Two-tailed $P < 0.05$ was considered significant.

3. Results

3.1. Descriptives

The demographic information of the 441,567 participants (mean [SD] age, 56.32 [8.09] years; 54.38 % female; 93.97 % White European) are presented in Table 1. Over a median (IQR) follow-up period of 14.41 (13.64–15.07) years, 55,104, 11,940, and 9060 incident cataract, glaucoma, and AMD events were identified, respectively (Figure S1 in Supplement). The mean (SD) annual concentrations of air pollutants were as follows: $PM_{2.5}$, 9.99 (1.06) μg/m^3, $PM_{2.5–10}$, 6.43 (0.90) μg/m^3, PM_{10}, 16.23 (1.90) μg/m^3, NO_2, 26.64 (7.63) μg/m^3, NO, 17.35 (9.09) μg/m^3 (Detailed data in Table S2 in Supplement), which were below the annual limits for $PM_{2.5}$, PM_{10} and NO_2 in the UK air quality standards as well as WHO Air Quality Guidelines in 2005 (Table S1 in Supplement). The Spearman correlation coefficients among the five air pollutants ranged from 0.28 to 0.85 (Table S3 in Supplement), indicating varying degrees of association, with some pollutants exhibiting high collinearity. The distribution of air pollution scores among participants with the three age-related eye diseases, measured within a range of 47.18–361.18, is displayed in Table S4, where higher scores denote greater combined exposure to air pollutants. Additionally, the weights of each air pollutant used to calculate air pollution scores for three eye diseases are provided in Table S5.

3.2. Associations of individual air pollutants with age-related eye diseases

The hazard ratios (HRs) for both continuous and quartile values of air pollution exposure in relation to cataract, glaucoma and AMD are displayed individually (Table S6 in Supplement). Long-term exposure to individual pollutants, including $PM_{2.5}$, PM_{10}, NO_2, and NO, was significantly associated with an increased risk of developing cataract. Specifically, the HRs per IQR increment were 1.06 (95 % CI, 1.05–1.07) for $PM_{2.5}$, 1.01 (95 % CI, 1.00–1.02) for PM_{10}, 1.05 (95 % CI, 1.04–1.07) for NO_2, and 1.03 (95 % CI, 1.02–1.04) for NO (all $P < 0.05$). However, there was no statistically significant association between $PM_{2.5–10}$ and cataract incidence. For glaucoma and AMD, significantly elevated risks were associated with individual exposure to $PM_{2.5}$, NO_2, and NO, whereas no significant associations were observed for $PM_{2.5–10}$ or PM_{10} (Detailed data in Table S6 in Supplement).

When comparing participants residing in areas with the highest quartile of air pollutants (Q4) to those in the lowest quartile (Q1), significant associations were observed between $PM_{2.5}$, NO_2, NO, and the incidence of cataract, glaucoma, and AMD (all P for trend < 0.05). In contrast, the highest quartiles of $PM_{2.5–10}$ and PM_{10} were not significantly associated with an increased risk of these three age-related eye diseases (Detailed data in Table S6 in Supplement).

3.3. Associations of joint exposure to multiple air pollutants with age-related eye diseases

We further combined five air pollutants to generate a weighted air pollution score across three age-related eye diseases. The HRs (95 % CIs) for air pollution score were 1.05 (1.04–1.06) for cataract ($P < 0.001$), 1.04 (1.02–1.06) for glaucoma ($P < 0.001$), and 1.04 (1.01–1.07) for AMD ($P = 0.002$). Compared to the lowest quartile of air pollution score, the HRs (95 % CIs) for cataract, glaucoma, and AMD in the highest quartile were 1.13 (1.10–1.16), 1.09 (1.03–1.15), and 1.14 (1.07–1.22), respectively (all P for trend < 0.05) (Table 2).

Figs. 1–3 delineate the exposure-response associations between

Table 1
Characteristics of the study population and air pollution exposures stratified by cataract, glaucoma, and AMD.

Characteristic		No. (G)			
		Participants (N = 441,567)	Cataract cases (N = 55,104)	Glaucoma cases (N = 11,940)	AMD cases (N = 9060)
Person-years		5886,422[a]/ 6114,259[b]/ 6149,776[c]	479,578	91,168	85,989
Age, mean (SD), y		56.32 (8.09)	61.96 (5.82)	60.56 (6.65)	62.77 (5.41)
Sex					
	Female	240,139 (54.38)	32,761 (59.45)	6367 (53.32)	5592 (61.72)
	Male	201,428 (45.62)	22,343 (40.55)	5573 (46.68)	3468 (38.28)
Ethnicity					
	White	414,954 (93.97)	51,371 (93.23)	11,156 (93.43)	8612 (95.06)
	Other	24,258 (5.49)	3428 (6.22)	722 (6.05)	396 (4.37)
	Missing	2355 (0.53)	305 (0.55)	62 (0.52)	52 (0.57)
Townsend deprivation index					
	< median[d] (less deprived)	220,118 (49.85)	27,597 (50.08)	6052 (50.69)	4583 (50.58)
	≥ median (more deprived)	220,938 (50.03)	27,471 (49.85)	5880 (49.25)	4473 (49.37)
	Missing	511 (0.12)	36 (0.07)	8 (0.07)	4 (0.04)
Education					
	University or college degree	144130 (32.64)	14,930 (27.09)	3443 (28.84)	2303 (25.42)
	Other	292,128 (66.16)	39,355 (71.42)	8331 (69.77)	6641 (73.30)
	Missing	5309 (1.20)	819 (1.49)	166 (1.39)	116 (1.28)
BMI level[e]					
	Underweight	2072 (0.47)	229 (0.42)	56 (0.47)	29 (0.32)
	Normal	138,876 (31.45)	15,344 (27.85)	3552 (29.75)	2583 (28.51)
	Overweight	185,308 (41.97)	23,412 (42.49)	5077 (42.52)	3802 (41.96)
	Obese	106,569 (24.13)	14,782 (26.83)	2997 (25.10)	2423 (26.74)
	Missing	8742 (1.98)	1337 (2.43)	258 (2.16)	223 (2.46)
Smoking status					
	Never	240,882 (54.55)	27,640 (50.16)	6250 (52.35)	4435 (48.95)
	Previous	152,059 (34.44)	22,043 (40.00)	4548 (38.09)	3754 (41.43)
	Current	46,042 (10.43)	5009 (9.09)	1064 (8.91)	799 (8.82)
	Missing	2584 (0.59)	412 (0.75)	78 (0.65)	72 (0.79)
Alcohol intake frequency					
	Never/Special occasions only	85,713 (19.41)	12,856 (23.33)	2607 (21.83)	2130 (23.51)
	One to three times a month	49,064 (11.11)	5760 (10.45)	1233 (10.33)	912 (10.07)
	Once or twice a week	113,768 (25.76)	13,131 (23.83)	2838 (23.77)	2113 (23.32)
	Three or four times a week	101,862 (23.07)	11,455 (20.79)	2648 (22.18)	1910 (21.08)
	Daily or almost daily	89,876 (20.35)	11,725 (21.28)	2580 (21.61)	1969 (21.73)
	Missing	1284 (0.29)	177 (0.32)	34 (0.28)	26 (0.29)
Hypertension					
No		NA	28,954 (52.54)	6768 (56.68)	4529 (49.99)
Yes		NA	26,150 (47.46)	5172 (43.32)	4531 (50.01)
Diabetes mellitus					
No		NA	47,478 (86.16)	10,539 (88.27)	7795 (86.04)
Yes		NA	7626 (13.84)	1401 (11.73)	1265 (13.96)
Hyperlipidemia					
No		NA	37,497 (68.05)	8685 (72.74)	6049 (66.77)
Yes		NA	17,607 (31.95)	3255 (27.26)	3011 (33.23)
$PM_{2.5}$, mean (SD), μg/m^3		9.99 (1.06)	10.01 (1.05)	10.00 (1.07)	10.01 (1.03)
$PM_{2.5-10}$, mean (SD), μg/m^3		6.43 (0.90)	6.42 (0.89)	6.43 (0.90)	6.43 (0.91)
PM_{10}, mean (SD), μg/m^3		16.23 (1.90)	16.24 (1.88)	16.24 (1.89)	16.25 (1.89)
NO_2, mean (SD), μg/m^3		26.64 (7.63)	26.65 (7.53)	26.64 (7.71)	26.55 (7.36)
NO, mean (SD), μg/m^3		17.35 (9.09)	17.45 (9.09)	17.43 (9.29)	17.35 (8.85)

Abbreviation: AMD, age-related macular degeneration; SD, standard deviation; BMI, body mass index; $PM_{2.5}$, fine particulate matter with diameter ≤ 2.5 μm; $PM_{2.5-10}$, fine particulate matter with diameter between 2.5 μm and 10 μm; PM_{10}, particulate matter with diameter ≤ 10 μm; NO_2, nitrogen dioxide; NO, nitric oxide.
[a] Cataract.
[b] Glaucoma.
[c] AMD.
[d] The median value of Townsend deprivation index was −2.17.
[e] BMI level was categorized as follows: (1) Underweight: < 18.5 kg/m^2; (2) normal: 18.5–24.9 kg/m^2; (3) overweight: 25–29.9 kg/m^2; and (4) obese: ≥ 30 kg/m^2.

individual air pollutants, air pollution score, and the incidence of cataract, glaucoma, and AMD, respectively. There was a non-linear relationship between cataract incidence and air pollution score, $PM_{2.5}$, PM_{10}, NO_2 and NO (all *P* for non-linearity < 0.05) (Fig. 1). For glaucoma, a linear increase was observed for air pollution score, $PM_{2.5}$, and NO_2 (*P* for non-linearity > 0.05), while a non-linear association was found between NO (*P* for non-linearity $= 0.007$) and glaucoma risk (Fig. 2). The curves for air pollution score, $PM_{2.5}$, NO_2, and NO displayed non-linear relationships with AMD incidence (all *P* for non-linearity $<$ 0.05) (Fig. 3). Of note, the exposure–response curves for air pollution score displayed a monotonically increasing trend with the risks of incident cataract and AMD in the low concentration range. As air pollution score increased further, the risk of cataract continued to rise but at a slower pace (Fig. 1A), while AMD risk initially increased before gradually decreasing (Fig. 3A).

3.4. Subgroup and sensitivity analyses

Subgroup analyses revealed that age, sex, ethnicity and hypertension significantly modified the risks of both cataract and glaucoma incidence.

Table 2
Associations of incidence of cataract, glaucoma, and AMD with exposure to air pollution score.

Air pollution score	HRs (95 % CIs)	*P* values	*P* for trend
Cataract, 9.36 (95 % CI, 9.28–9.44) cases per 1000 person-years			
Q1	1 [Reference]	NA	< 0.001
Q2	1.07 (1.04, 1.09)	< 0.001	
Q3	1.08 (1.05, 1.11)	< 0.001	
Q4	1.13 (1.10, 1.16)	< 0.001	
Continuous, per IQR increase	1.05 (1.04, 1.06)	< 0.001	NA
Glaucoma, 1.95 (95 % CI, 1.92–1.99) cases per 1000 person-years			
Q1	1 [Reference]	NA	< 0.001
Q2	1.00 (0.95, 1.05)	0.998	
Q3	1.07 (1.01, 1.13)	0.012	
Q4	1.09 (1.03, 1.15)	0.002	
Continuous, per IQR increase	1.04 (1.02, 1.06)	< 0.001	NA
AMD, 1.47 (95 % CI, 1.44–1.50) cases per 1000 person-years			
Q1	1 [Reference]	NA	< 0.001
Q2	1.10 (1.04, 1.17)	0.001	
Q3	1.11 (1.04, 1.17)	0.001	
Q4	1.14 (1.07, 1.22)	< 0.001	
Continuous, per IQR increase	1.04 (1.01, 1.07)	0.002	NA

Cox regression models adjusted for age, sex, ethnicity, assessment center, TDI, education, BMI, smoking status, alcohol intake frequency, hypertension, diabetes mellitus, and hyperlipidemia.
Abbreviations: HRs, hazard ratios; CIs, confidence intervals; Q, quartile; IQR, interquartile range; NA, not applicable; AMD, age-related macular degeneration; TDI, Townsend deprivation index; BMI, body mass index.

However, no significant modifying effects were observed on the associations between air pollutants and the risk of incident AMD (Figures S3-S5 in Supplement).

The associations between both individual air pollutants and air pollution score with the risks of incident cataract, glaucoma, and AMD remained robust in sensitivity analyses (Tables S7-S12 and Figure S2 in Supplement).

4. Discussion

This prospective, population-based study involved 441,567 participants with a median follow-up of 14.41 years. To our knowledge, it is one of the longest cohort studies providing novel epidemiologic evidence that long-term exposure to both individual and combined air pollutants could increase the risks of incident cataract, glaucoma, and AMD. Notably, the joint effect of multiple air pollutants on age-related eye diseases were assessed by an air pollution score, which affirmed the integrated impact of air pollutants on ocular health. Furthermore, our study was conducted on populations residing in the UK, where air pollution levels are relatively low, suggesting that even low levels of air pollution can still exert adverse impacts on the development of cataract, glaucoma, and AMD. Therefore, our study may provide further evidence highlighting the importance of air pollution control for ocular health, even in regions with relatively low pollution levels.

4.1. The individual effect of each air pollutant on age-related eye diseases: a comparison with previous studies

In our study, we identified significant associations between individual air pollutants, including $PM_{2.5}$, NO_2, and NO, and the incidence of three common age-related eye diseases. Additionally, PM_{10} was positively associated with an increased risk of cataract. Previous studies have also provided evidence supporting the detrimental effects of exposure to individual pollutants, such as $PM_{2.5}$, PM_{10} and NO_2, on the risks of cataract (Choi et al., 2018; Grant et al., 2021; Shin et al., 2020), glaucoma (Chua et al., 2019; Grant et al., 2021; Ma et al., 2024; Wang et al., 2022; Wu et al., 2024; Yang et al., 2021), and AMD (Chua et al., 2022; Grant et al., 2021; Ju et al., 2022). For example, a longitudinal study from Korea reported significant associations between incident cataract and PM_{10} and NO_2, similar to our results. However, this study did not find a significant association with $PM_{2.5}$ (Shin et al., 2020), which was not consistent with the significant adverse effect of $PM_{2.5}$

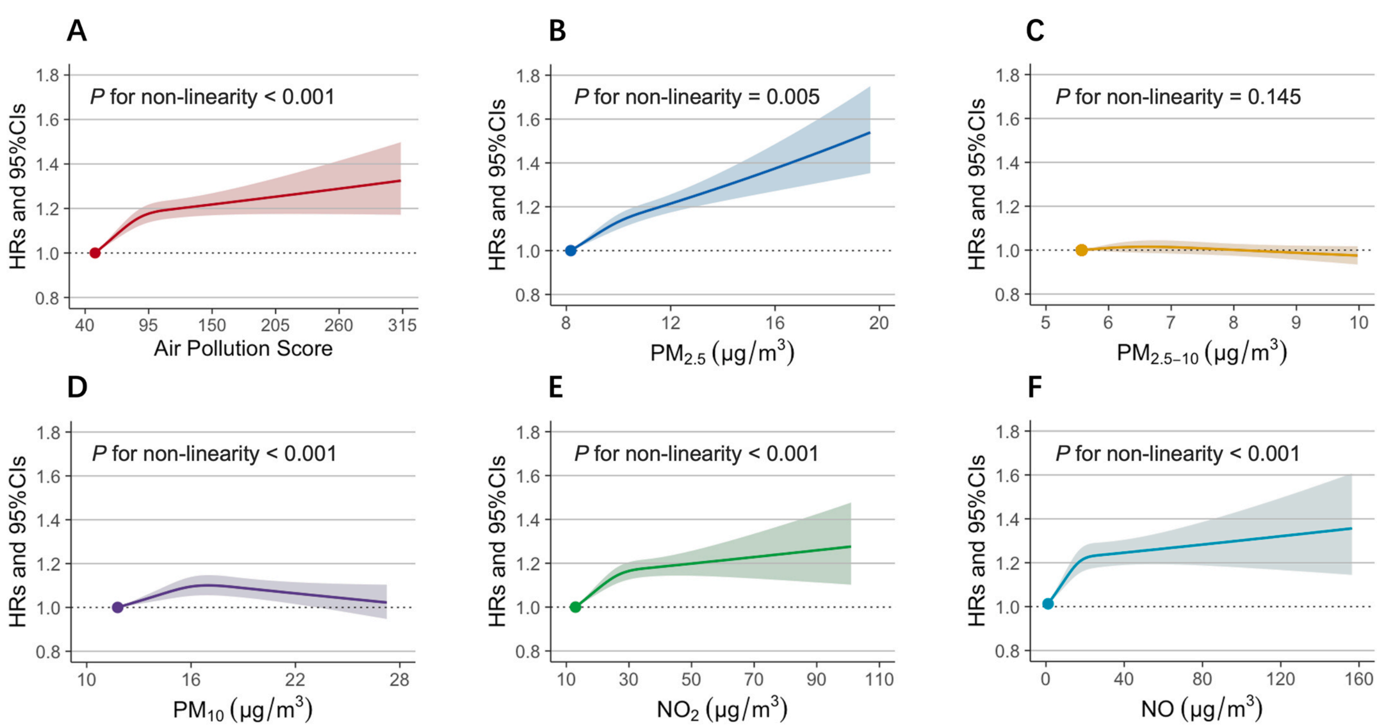

Fig. 1. Exposure-response associations between air pollution and the risk of incident cataract. A restricted cubic spline regression model with 3 knots (at the 10th, 50th, and 90th percentiles) was used to estimate the exposure-response associations between air pollution and the risk of incident cataract among participants. Hazard ratios (HRs, solid lines) and 95 % confidence intervals (95 % CIs, shaded areas) were adjusted for age, sex, ethnicity, assessment center, Townsend Deprivation Index, education, body mass index, smoking status, alcohol intake frequency, hypertension, diabetes mellitus, and hyperlipidemia.

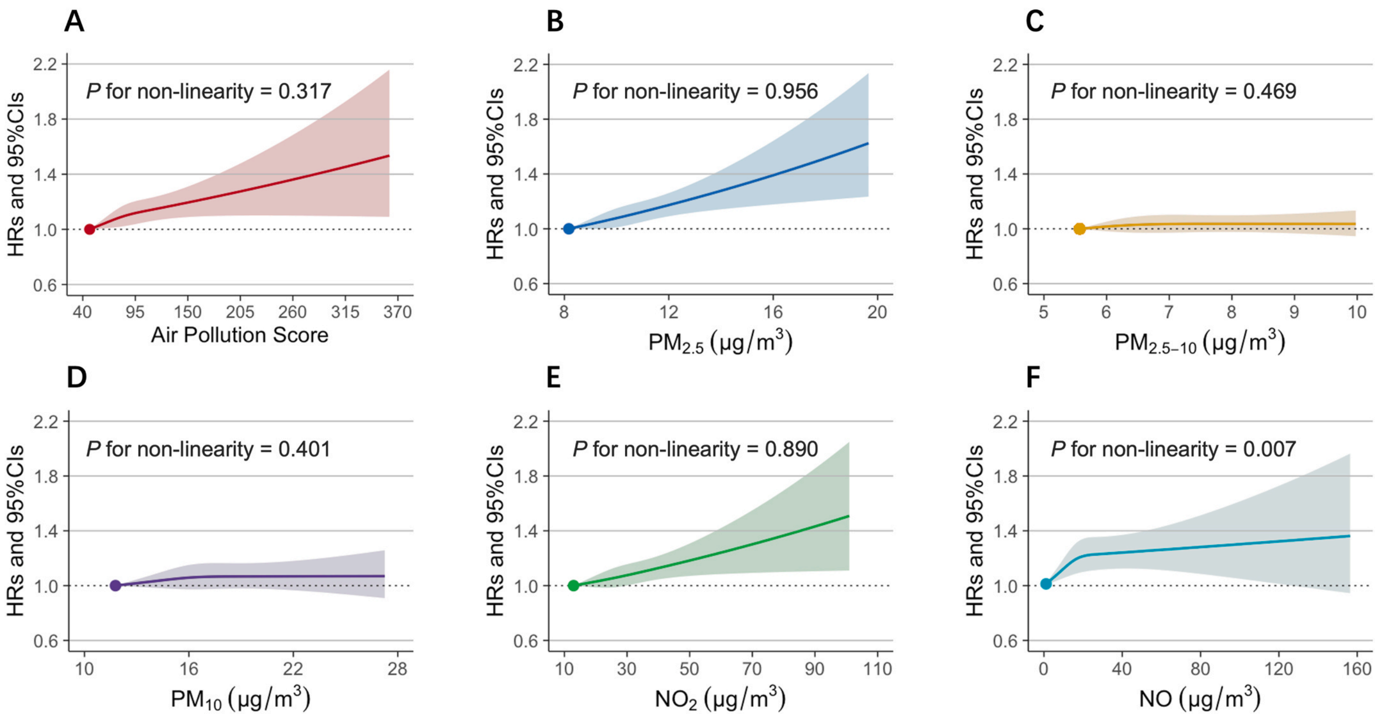

Fig. 2. Exposure-response associations between air pollution and the risk of incident glaucoma. A restricted cubic spline regression model with 3 knots (at the 10th, 50th, and 90th percentiles) was used to estimate the exposure-response associations between air pollution and the risk of incident glaucoma among participants. Hazard ratios (HRs, solid lines) and 95 % confidence intervals (95 % CIs, shaded areas) were adjusted for age, sex, ethnicity, assessment center, Townsend Deprivation Index, education, body mass index, smoking status, alcohol intake frequency, hypertension, diabetes mellitus, and hyperlipidemia.

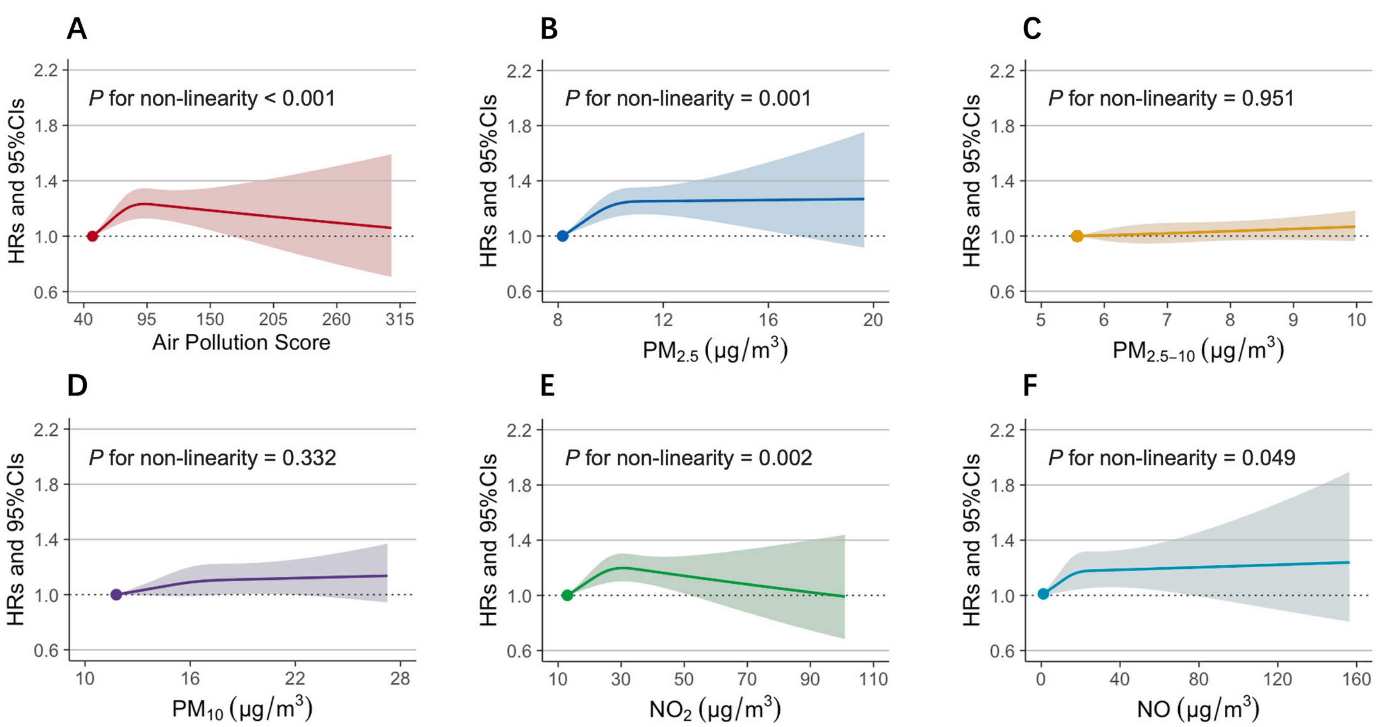

Fig. 3. Exposure-response associations between air pollution and the risk of incident age-related macular degeneration. A restricted cubic spline regression model with 3 knots (at the 10th, 50th, and 90th percentiles) was used to estimate the exposure-response associations between air pollution and the risk of incident cataract among participants. Hazard ratios (HRs, solid lines) and 95 % confidence intervals (95 % CIs, shaded areas) were adjusted for age, sex, ethnicity, assessment center, Townsend Deprivation Index, education, body mass index, smoking status, alcohol intake frequency, hypertension, diabetes mellitus, and hyperlipidemia.

observed in our study. This discrepancy may stem from differences in exposure assessment. The prior study relied on the nearest fixed monitoring stations, which may not accurately capture individual-level exposure. In contrast, LUR models applied in our study incorporate geographic variables to estimate air pollution levels at each participant's residence, providing a more precise assessment of individual exposure.

Our findings of positive associations between individual pollutants and both glaucoma (Chiang et al., 2021; Chua et al., 2019; Li et al., 2022; Luo et al., 2022; Ma et al., 2024; Sun et al., 2021; Wu et al., 2024; Yang et al., 2021) and AMD (Chang et al., 2019; He et al., 2023; Liang et al., 2022) aligned with those of previous studies conducted in the UK and China, which have demonstrated that higher levels of $PM_{2.5}$ and NO_2 were associated with an increased risk of developing glaucoma and AMD under both short-term and long-term exposure.

4.2. The joint effect of multiple air pollutants on age-related eye diseases

Given that individuals are exposed to a complex mixture of air pollutants and that high collinearity exists among different pollutants, estimating the combined effect of multiple air pollutants on human health is essential. However, research on the joint impact of various pollutants on ocular health is lacking. In our study, we employed a weighted regression model to assess combined exposure to multiple air pollutants, a method widely utilized to evaluate their joint effect (Batty et al., 2020; Li et al., 2024; Wang et al., 2021; Zhang et al., 2023). Of note, compared to the effects of individual pollutants, a relatively stronger association was observed between air pollution score and three age-related eye diseases. This finding suggests that air pollution score may serve as a more comprehensive measure of air pollution, as it captures the influence of pollutant mixtures while accounting for their intercorrelations. Therefore, reassessing the relationship between combined air pollution exposure and health outcomes is crucial, particularly in previous studies where only the effects of individual pollutants were estimated, and no significant associations were identified. A more comprehensive evaluation of joint exposure not only addresses this gap but also provides a clearer understanding of the real-world impact of air pollution on human health.

Additionally, non-linear associations between air pollution score and both cataract and AMD were observed in the exposure-response relationships. The risks of cataract and AMD increased sharply at low exposure concentrations, but as pollution levels rose and reached a certain threshold, the rate of increase slowed, or even began to decline gradually. This phenomenon may be explained by more vulnerable individuals seeking medical attention earlier, or adopting behavioral modifications, such as limiting outdoor exposure, in response to worsening air quality (Ma et al., 2024). In contrast, glaucoma exhibited a linear, cumulative association with air pollution score, highlighting the sustained detrimental effects of long-term pollutant exposure. These varying exposure-response patterns may reflect the complex biological impacts of air pollution on age-related eye diseases.

4.3. Potential biological mechanisms

Several studies, involving both animal and in vitro experiments, have explored the biological mechanisms linking air pollutants to age-related eye diseases, providing evidence of oxidative stress and inflammatory responses induced by air pollution in ocular structures (Grant et al., 2022). Particulate matter, nitrogen dioxides (NO_x), ozone (O_3), and sulfur dioxide (SO_2) in the atmosphere can generate cellular reactive oxygen and nitrogen species (ROS/RNS), leading to oxidative damage of various biomolecules, including the membrane luminal and secretory proteins, and acting as cataract-genic stressors (Beebe et al., 2010; Periyasamy et al., 2017; Poljšak et al., 2014). Studies on mouse models and human trabecular meshwork cells suggested that $PM_{2.5}$ exposure may contribute to glaucoma by elevating intraocular pressure and activating the pyrin domain-containing-3 (NLRP3) inflammasome pathway, which can impair aqueous outflow and increase IOP, ultimately leading to glaucoma development (Li et al., 2021). For AMD, chronic oxidative stress and inflammation attribute to its progression (Liu et al., 2022). Ambient $PM_{2.5}$ has been positively associated with pro-angiogenesis molecules that promote vascular endothelial dysfunction, contributing to the neovascularization process in AMD and potential visual impairment (Grant et al., 2021; Riggs et al., 2020). Additionally, oxidative damage may be exacerbated with age, as $PM_{2.5}$ has been shown to induce retinal cell dysfunction by triggering epithelial-mesenchymal transition (EMT) and activating downstream cellular ROS. Therefore, the aging retina may be particularly vulnerable to air pollution-induced damage (Lee et al., 2020; Lin et al., 2022; Ruan et al., 2020).

4.4. Public health implications

This study carries significant implications for public health. First, we observed a relatively stronger association between combined exposure to multiple air pollutants and the risk of incident age-related eye diseases compared to single-pollutant exposure, indicating potential additive or synergistic effects in these eye diseases development. These findings underscored the importance of incorporating the cumulative effect of air pollutant mixtures into future air quality standards and regulations.

Second, since most previous studies were conducted in highly polluted areas where air pollution levels exceeded the annual limits set by WHO in 2005 (Chang et al., 2019; Chiang et al., 2021; Choi et al., 2018; He et al., 2023; Ju et al., 2022; Liang et al., 2022; Luo et al., 2022; Ma et al., 2024; Shin et al., 2020; Sun et al., 2021; Wu et al., 2024; Yang et al., 2021). Our findings may provide evidence that combined effect of multiple air pollutants at low concentrations on the incidence of age-related eye diseases. Considering that many countries' air quality standards are still well above the WHO Global Air Quality Guidelines in 2005, the findings suggest that stricter standards or regulations for air pollution control should be implemented in the future policy, making to alleviate the disease burden of cataract, glaucoma and AMD.

4.5. Strengths and limitations

There are several strengths in this study. First, the major strength is that we assessed the associations between long-term joint impact of multiple air pollutants and the incidence of age-related eye diseases by generating an air pollution score. This approach might address the potential bias caused by the high correlations among various air pollutants as well as reflect real-world exposure more accurately, thereby enhancing public understanding of the integrated health impact of multiple air pollutants. Second, annual air pollutants concentrations in our study were below the annual limits set by the WHO guidelines in 2005, providing new evidence that the adverse effect of air pollution on age-related eye diseases persisted even at low air pollution levels. Third, the large sample size of approximately 0.44 million adults, combined with a long follow-up period of 14.41 years and a substantial number of outcome events, offers sufficient statistical power to identify associations between air pollution and the risk of developing cataract, glaucoma, and AMD.

However, this study also has certain limitations. First, although we considered particulate matter and gaseous pollutants including $PM_{2.5}$, $PM_{2.5-10}$, PM_{10}, NO_2, and NO, information on other air pollutants (e.g., O_3, SO_2, and carbon monoxide [CO]) and atmospheric trace elements (Dong et al., 2015; Popoola et al., 2018; Wei et al., 2019) was not available. However, $PM_{2.5}$ and NO_2 are primary air pollutants in the UK (The Lancet, 2017), and we have incorporated them to assess the joint exposure to a combination of air pollutants. Second, the baseline measurement of air pollution exposure may not accurately represent its variations over the follow-up period. However, air pollution emissions remained relatively consistent between 2010 and 2019 (Department for Environment Food and Rural Affairs, 2022). Third, occupational and indoor exposure are additional potential confounders, but the concentrations of air pollutants in occupational and indoor places were not available in the UK Biobank, which would lead to potential residual confounding effect. Fourth, smoking frequency is an important confounder in our analysis and should ideally have been included as covariate. However, the data on smoking frequency contained substantial missing values, which could introduce potential bias. Consequently, we used "smoking status" as a covariate, a common approach in epidemiological studies to account for smoking-related factors (Li et al., 2024; Ma et al., 2024; Wang et al., 2021; Zhang et al., 2023). Fifth, since the participants in the UK Biobank were most healthy volunteers, selection bias may not be completely avoided. Even though the UK Biobank is a selective group in the UK population, the effect sizes appear to be comparable with those from population-representative samples (Batty et al., 2020). Sixth, although this study could not fully establish causality due to unknown confounders, its prospective and longitudinal design not only reduced recall and selection biases, but also enabled a more robust assessment of exposure-outcome relationships, thereby enhancing the epidemiological validity of the findings. Finally, the participants in the UK Biobank are of predominantly European descent, for which generalization to other populations should be undertaken with prudence.

5. Conclusions

In this large-scale, population-based, prospective cohort study, we found that long-term joint exposure to multiple air pollutants at low concentrations was associated with increased risk of incident cataract, glaucoma, and AMD. Considering that many countries' air quality standards are still well above the World Health Organization Global Air Quality Guidelines in 2005, more stringent standards or effective regulations for air pollution control should be implemented in the future policy making, aiming at mitigating air pollution and safeguarding individuals from the effects associated with age-related eye diseases.

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CRediT authorship contribution statement

Ho Mary: Writing – review & editing. **Zhang Xiu Juan:** Writing – review & editing, Conceptualization. **Zaabaar Ebenezer:** Writing – review & editing, Investigation. **Yam Jason C.:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Conceptualization. **Liu Dong:** Writing – review & editing. **Chen Li Jia:** Writing – review & editing, Project administration, Funding acquisition, Conceptualization. **Chan Poemen:** Writing – review & editing, Supervision. **Kwan Mei Po:** Writing – review & editing. **Kam Ka Wai:** Writing – review & editing, Conceptualization. **Zhang Yuzhou:** Writing – review & editing, Validation, Methodology, Investigation, Data curation, Conceptualization. **Tham Clement C.:** Writing – review & editing. **Li Yingan:** Writing – original draft, Visualization, Software, Methodology, Investigation, Formal analysis, Conceptualization. **Pang Chi Pui:** Writing – review & editing. **Young Alvin:** Writing – review & editing. **Ip Patrick:** Writing – review & editing. **Ng Mandy PH:** Writing – review & editing, Project administration.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ecoenv.2025.118052.

Data availability

The authors do not have permission to share data.

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