European Journal of Epidemiology
https://doi.org/10.1007/s10654-025-01340-8

OPHTHALMIC EPIDEMIOLOGY

Air pollutants, genetic susceptibility, and the risk of age-related macular degeneration: a large prospective cohort study

Shengli Chen[1] · Gongyue Wang[2] · Xin Guan[1] · Chenming Wang[1] · Yang Xiao[1] · Xingdi Li[1] · Shiru Hong[1] · Yuhan Zhou[1] · Yingqian You[1] · Ye Fu[1] · Yuxi Wang[1] · Yichi Zhang[1] · Hui Zhao[1] · Yingchen Zhang[1] · Yang Cheng[2] · Huan Guo[1] · Huatao Xie[2]

Received: 30 May 2025 / Accepted: 19 November 2025

Abstract

Age-related macular degeneration (AMD) is a leading cause of irreversible vision loss worldwide. However, evidence regarding the relationship between air pollution and AMD is limited, and the modifying effect of genetic susceptibility on this association remains unknown. A total of 445,237 participants without AMD at baseline were included from the UK Biobank. The concentrations of nitrogen dioxide (NO_2), nitrogen oxides (NO_x), particulate matter ($PM_{2.5}$, PM_{10}, $PM_{2.5–10}$) were collected by using land-use regression models. Air pollution score (APS) was constructed through summing each pollutant weighted by the regression coefficients with AMD from single-pollutant model. Cox proportional hazard models were used to evaluate hazard rations (HRs) and 95% confidence intervals (95%CIs) of associations between air pollutants and polygenic risk score (PRS) with incident AMD. During a median follow-up of 13.83 years, we observed 9,635 incident AMD events. The HR (95%CI) of incident AMD for each standard deviation increase in NO_2, NO_x, $PM_{2.5}$, PM_{10}, and APS were 1.04(1.02, 1.06), 1.03(1.01, 1.05). 1.04(1.02, 1.07), 1.02(1.00, 1.04), and 1.04(1.02, 1.06), respectively. Significant additive interaction effects of NO_2, NO_x, $PM_{2.5–10}$, APS and PRS with incident risk of AMD were observed, with the relative excess risk due to the interaction (RERI), attributable proportion (AP), and their 95% CIs of 0.10(0.01, 0.18) and 0.05(0.01, 0.11) for NO_2, 0.11(0.01, 0.19) and 0.05(0.02, 0.10) for NO_x, 0.15(0.06, 0.23) and 0.08(0.03, 0.13) for $PM_{2.5–10}$, and 0.12(0.03, 0.20) and 0.06(0.01, 0.11) for APS, respectively. Compared with participants exposed to low level of above air pollutants and low PRS, those exposed to high air pollution and high PRS had almost double incident risk of AMD [HR(95%CI) ranged from 1.83(1.68, 1.99) to 2.03(1.86, 2.21)]. Long-term exposure to air pollutants NO_2, NO_x, $PM_{2.5}$, and PM_{10} showed positive associations with increased risk of AMD, which could be further enhanced by genetic susceptibility.

Keywords Air pollution · Genetic susceptibility · Age-related macular degeneration · Interaction · Cohort study

Abbreviations

NO_2	Nitrogen dioxide
NO_x	Nitrogen oxides
$PM_{2.5}$	Fine particulate matter with diameter < 2.5 μm
PM_{10}	Particulate matter with diameter < 10 μm
$PM_{2.5–10}$	Particulate matter with aerodynamic diameter between 2.5 and 10 μm

Introduction

Age-related macular degeneration (AMD) is a complex, multifactorial disease characterized by progressive degeneration of the macula, the central region of the retina, and

✉ Huan Guo
ghuan5011@hust.edu.cn

✉ Huatao Xie
huataoxie@hust.edu.cn

[1] Department of Occupational and Environmental Health, Key Laboratory of Environment and Health, Ministry of Education and State Key Laboratory of Environmental Health (Incubating), School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China

[2] Department of Ophthalmology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, Hubei, China

Published online: 12 January 2026

represents as a leading cause of permanent vision loss worldwide [1, 2]. The pooled global prevalence of AMD is estimated up 8.7% [3] and the number of affected individuals is expected to increase to 288 million by 2040 [4]. It is of great concern that AMD will pose an increasing threat to global public health due to the population aging. Therefore, identifying the potential risk factors of AMD is crucial to reduce the burden of this disease.

Ambient air pollution has emerged as a major environmental threat to the global disease burden [5]. The human ocular system may be susceptible to environmental damage due to its direct exposure to various external pollutants [6]. Although several epidemiological studies have explored the association between air pollution exposure and AMD, the findings in this field were limited and conflicting [7–12]. For instance, a national cross-sectional study showed a positive correlation between particulate matter (PM) with diameters ≤ 2.5 μm ($PM_{2.5}$) exposure and AMD prevalence across 10 provinces in rural China [12]. Another longitudinal cohort study conducted in Taiwan also showed that $PM_{2.5}$ is a risk factor for the development of AMD [10]. In contrast, a large cross-sectional study involving 115,954 European participants did not observe significant associations of exposure to nitrogen dioxide (NO_2), nitrogen oxides (NO_x), PM ≤ 10 μm (PM_{10}) and PM with diameters of 2.5–10 μm ($PM_{2.5–10}$) with AMD [11]. Actually, in the real world, people are usually exposure to various air pollutants simultaneously [13, 14]. but most previous studies have focused on individual pollutant. Hence, more prospective studies are required to elucidate the long-term effects of various air pollutants on AMD incidence.

Growing evidence has revealed that genetic factors also play a key role in the etiology of AMD [2, 15]. Comprehensive genome-wide association studies (GWAS) have identified certain genetic variants associated with AMD risk [16]. Although individual variants account for only a relatively modest proportion on the heritability, using polygenic risk score (PRS) has proven to be an effective method for quantifying the cumulative effect of multiple risk-associated variants [17]. Moreover, given that the effects of environment factors may be modified by genetic predispositions [18], exploring gene-environment interactions may provide novel insights into the precise prediction and targeted interventions for AMD [19]. However, whether and how the genetic susceptibility modifies the associations between ambient air pollutions and AMD remains largely unknown.

Taking advantage of the national information from the UK Biobank, the present study aimed to investigate the effects of individual and combined air pollutants, including NO_2, NO_x, $PM_{2.5}$, PM_{10} and $PM_{2.5–10}$, on the incident risk of AMD. We further assessed the potential gene-air pollution interactions and explored their joint effects of air pollution and genetic susceptibility on AMD incidence.

Methods

Study population

The UK Biobank is a national prospective study of over half a million participants aged 40–69 years recruited from 22 assessment centers across the UK between 2006 and 2010. It was designed to support in-depth investigations of the genetic and non-genetic determinants of disease in middle and older age. The UK Biobank seeks to advance understanding and promote innovative research by integrating detailed exposure assessments with long-term follow-up and broad phenotypic characterisation, and by providing open access to its data and samples. Extensive information was collected at baseline, including questionnaires, biological samples and clinical measurements [20]. All participants provided informed written consent, and the study protocol was approved by the North West Multi-Centre Research Ethics Committee.

In the present study, we first excluded participants with pre-existing AMD at baseline (n = 689). Subsequently, we excluded individuals with missing information on air pollution (n = 41,248), and genetic data (n = 14,977). Ultimately, a total of 445,237 participants were included for the final analysis (Figure S1).

Air pollution assessment

The annual average concentrations of ambient air pollutants, including NO_2, NO_x, $PM_{2.5}$, PM_{10} and $PM_{2.5–10}$ were estimated using Land Use Regression (LUR) models developed by the European Study of Cohorts for Air Pollution Effects (ESCAPE) project (https://biobank.ndph.ox.ac.uk/ukb/refer.cgi?id=2010). The LUR models were based on monitoring data collected by the ESCAPE project between 26 January 2010 and 18 January 2011, with air pollution estimates representative of the year 2010. Generally, LUR is a widely adopted method for capturing spatial variation in ambient pollution, incorporating geospatial predictor variables such as traffic intensity, topography, and land use derived from the Geographic Information System (GIS). Leave-one-out cross-validation showed good model performance for air pollutants [21, 22]. Then, air pollution concentrations were assigned to each UK Biobank participant according to their baseline residential address, geocoded to 100 m × 100 m grid cells.

To capture the combined effects of various air pollutants, we constructed an air pollution score (APS) through

summing up concentrations of five ambient air pollutants (NO_2, NO_x, $PM_{2.5}$, PM_{10} and $PM_{2.5-10}$), weighted by their respective risk estimates (β coefficients) for AMD obtained from the fully-adjusted model (Table S1). This method of calculating APS has been well accepted in previous UK Biobank studies to reflect the combined effects of multiple air pollutants on health outcomes [23]. The equation was: $APS = [\beta_{(NO_2)} \times NO_2 + \beta_{(NO_x)} \times NO_x + \beta_{(PM_{2.5})} \times PM_{2.5} + \beta_{(PM_{10})} \times PM_{10} + \beta_{(PM_{2.5-10})} \times PM_{2.5-10}] \times (5/\sum \beta)$. The APS ranges from 43.76 to 154.45, with higher score indicating greater exposure to air pollution. In sensitivity analysis, we also calculated a weighted APS excluding $PM_{2.5-10}$, based on the remaining four air pollutants.

Definition of the genetic risk

Genetic risk was assessed using the standard AMD PRS set provided by the UK Biobank, which was calculated on all individuals by meta-analysis of multiple external GWAS data [24]. Detailed procedures about genotyping, imputation, and quality control have been described previously [25]. In brief, the UK Biobank employed standardized subgroups and uniform definitions for diseases and quantitative traits to ensure consistent PRS evaluation. The AMD PRS values ranged from − 4.32 to 4.94, with a higher score indicating greater genetic predisposition. Participants were then categorized into low and high genetic risk based on the median of the PRS.

Assessment of outcomes

Incident cases of AMD were identified by linking to the national hospital inpatient admissions, where AMD was recorded as either the primary or secondary diagnosis according to the 9th Revision International Classification of Diseases (ICD-9: 3625) or 10th Revision (ICD-10: H35.3). Person-years of follow-up was calculated as the interval from the enrollment date to the time of the first AMD diagnosis, death, withdrawal from the study, or the end of the follow-up (31 December 2022), whichever came first.

Assessment of covariates

Several potential covariates were included based on the prior literatures. Theses covariates included sociodemographic factors (age, sex, ethnicity, education level, household income and paid employment status), lifestyles (body mass index [BMI], smoking status, healthy diet score, physical activity and alcohol intake), and self-reported history of chronic diseases (e.g., hyperlipidemia, hypertension and diabetes). The healthy diet score was computed based on the following dietary components: fresh fruit, fish, vegetables, processed meat and unprocessed red meat [26]. The total diet score ranged from 0 to 5, with one point awarded for each favorable diet factor. More detailed information on covariate definitions is provided in supplementary methods. Additionally, missing data for categorical variables were assigned as a missing indicator category, while missing value for continuous variables were imputed with the median value.

Statistical analysis

Baseline characteristics of the participants were described using mean ± standard deviation (SD) for continuous variables and frequency (proportion) for categorical variables, while the concentrations of air pollution were presented as the median (interquartile range, IQR). Differences in basic information between groups stratified by AMD status were examined using Student's *t*-test, Mann-Whitney U-test, or Chi-square test where appropriate.

Cox proportional hazards model was applied to evaluated the hazard ratio (HR) and 95% confidence interval (CI) for AMD associated with the individual air pollutant, APS, and PRS. We incorporated several potential confounders for adjustment. In the basic model (Model 1), we only adjusted for age and sex. In the fully-adjusted model (Model 2), we further adjusted for educational level, ethnicity, BMI, household income, paid employment status, smoking status, alcohol intake, physical activity, healthy diet score, self-reported hypertension, diabetes and hyperlipidemia. Ambient air pollutants were analyzed as continuous variable (per SD increment) and categorical variable (quartiles). We conducted subgroup analyses by age at recruitment (< 60, and ≥ 60 years) and tested the interaction effects between age group and air pollution using likelihood ratio tests. In genetic analysis, we further adjusted the genetic batches and the first ten genetic principal components. Schoenfeld residuals were used to verify the proportional hazard assumption. In addition, we explored the dose–response relationships between air pollution and risk of AMD by restricted cubic spline regression with three knots placed at the 10th, 50th, and 90th percentiles, and restricted pollutant concentrations to the top 99% percentile to avoid the possible influences of extreme values. Furthermore, we imputed population attributable fractions (PAFs) to quantify the proportion of AMD cases that could be theoretically prevented if air pollutant concentrations were reduced to the target level [27]. According to the World Health Organization (WHO) interim target guidelines, the cut-offs for NO_2, $PM_{2.5}$, PM_{10} were 20, 10, and 20 μg/m^3, respectively [28]; while cutoffs for NO_x (42.15 μg/m^3) and $PM_{2.5-10}$ (6.11 μg/m^3) were their median concentrations (the two pollutants not included in

the WHO global air quality guidelines) [18]. The 95%CIs of PAFs were estimated by bootstrapping using 1000 independent replications.

To evaluate the joint effects of air pollution exposure and genetic factors on AMD risk, we divided participants into eight groups based on their PRS and air pollution quartiles. The reference group was defined as individuals with low genetic risk and exposure to the lowest quartile of air pollution. We further quantified the gene-environment interactions on additive scales using two indexes: the relative excess risk due to the interaction (RERI) and the attributable proportion due to the interaction (AP) [29]. The 95% CIs of RERI and AP did not include zero indicated the presence of additive interaction.

We conducted several sensitivity analyses to examine the robustness and reliability of the results. First, we reconstructed a new APS that only incorporated NO_2, NO_x, $PM_{2.5}$, PM_{10}. Second, we excluded incident AMD cases within the first two year of follow-up to minimize the potential reverse causality. Third, to minimize potential misclassification of long-term air pollution exposure, we restricted our analysis to participants who had resided at their current address for at least five years. Fourth, we re-examined the additive interactions between air pollutants and PRS on the risk of AMD in the sample weighted by inverse probability weighting (IPW) to minimize potential selection bias due to the missing data. Fifth, we further performed quantile-based g computation (Q-g comp) to estimate the effect of air pollutants mixture on incident AMD.

All analyses were performed using R software (version of 4.2.2). A two-tailed *P*-value < 0.05 was indicated statistical significance.

Results

Demographic characteristics of study population

Table 1 showed baseline characteristics of participants. Among the included 445,237 participants, the mean age was 56.56 ± 8.09 and 45.9% were men. During a median follow-up of 13.83 years, we observed 9,635 (2.16%) incident AMD events. Compared to participants without AMD, people who had incident AMD were more likely to be older, women, less educated, lower household income, unemployment, higher BMI, former smokers, physically inactive, more frequent alcohol intake and healthier diet, and have a history of hypertension, diabetes and hyperlipidemia. The media (IQR) concentrations of NO_2, NO_x, $PM_{2.5}$, PM_{10}, $PM_{2.5-10}$ and APS was 26.06 (9.84), 42.15 (16.56), 9.93 (1.28), 16.02 (1.76), 6.11 (0.79), and 60.55 (9.85) $\mu g/m^3$, respectively.

Association of air pollution with incident AMD

The associations of air pollutants with AMD were presented in Table 2. Schoenfeld residual test indicated that suggesting that the conditional proportional hazards assumption was satisfied (Fig. S2). Specifically, after multivariable adjustment, per SD increase in NO_2, NO_x, $PM_{2.5}$, and PM_{10}, the HR (95%CI) for incident risk of AMD was 1.04 (1.02, 1.06), 1.03 (1.01, 1.05), 1.04 (1.02, 1.07), and 1.02 (1.00, 1.04), respectively. However, we did not observe a significant linear association between per SD increase in $PM_{2.5-10}$ and AMD (HR, 1.02; 95%CI, 0.99–1.04; $P = 0.117$). When compared to participants in the lowest quartile (Q1) subgroup of NO_2, NO_x, $PM_{2.5}$, PM_{10}, and $PM_{2.5-10}$, those in the highest quartile had a separate HR (95%CI) of 1.12 (1.06, 1.19), 1.14 (1.08, 1.21), 1.15 (1.09, 1.22), 1.07 (1.01, 1.13), and 1.08 (1.02, 1.14).

APS was significantly associated with incident AMD in both continuous and quartile forms (Table 2). For each SD increase in the APS, the HR (95%CI) for AMD risk was 1.04 (1.02, 1.06). Participants in the highest quartile (Q4) of APS had a 16% higher risk of AMD than those in the lowest quartile [HR (95%CI) = 1.16 (1.09–1.23)]. Subgroup analysis indicated that all five pollutants and APS demonstrated significant associations with AMD among elderly participants (all *P* for interaction < 0.001) (Table S2). The sensitive analysis demonstrated that the results were generally robust when excluding $PM_{2.5-10}$ in the APS (Table S3), excluding participants with less than 2 years of follow-up (Table S4), limiting participants who had resided at their current address for at least five years (Table S5), using the Q-g comp to estimating the effect of air pollutants mixture (Figure S3).

The dose-response curves depicting the relationships between NO_2, NO_x, $PM_{2.5}$, and APS with incident AMD were almost non-linear (Fig. 1). Notably, the curves exhibited a significantly steeper slope at relatively lower concentrations of air pollutants, whereas the association plateaued or showed a modest decline at higher exposure levels. Moreover, reducing NO_2, NO_x, and $PM_{2.5}$ to the interim target levels could lead to a significant reduction in AMD incidence, ranging from 3.40% to 8.20% (all $P < 0.05$) (Table S6).

Association of PRS with incident AMD

After adjusting for various covariates, the incident risk of AMD associated with each per-SD increase in PRS of AMD was 1.46 (95% CI, 1.43–1.49). Similarly, when stratified by PRS, participants in the high genetic risk category had a 1.75-fold (HR, 1.75; 95% CI, 1.68–1.82) risk of AMD than those with the low genetic risk (Table S7).

Table 1 Baseline characteristics of participants

Characteristics	Total	Age-related macular degeneration	
		No	Yes
Number of participants	445,237	435,602	9635
Age (mean ± SD), years	56.56 ± 8.09	56.42 ± 8.08	62.89 ± 5.34
Sex			
Women	241,045 (54.1)	235,173 (54.0)	5872 (60.9)
Men	204,192 (45.9)	200,429 (46.0)	3763 (39.1)
Ethnicity			
White	418,514 (94.0)	409,379 (94.0)	9135 (94.8)
Asian	10,397 (2.3)	10,171 (2.3)	226 (2.3)
Black	7401 (1.7)	7285 (1.7)	116 (1.2)
Others	6762 (1.5)	6660 (1.5)	102 (1.1)
Missing	2163 (0.5)	2107 (0.5)	56 (0.6)
Education			
Low	75,248 (16.9)	72,722 (16.7)	2526 (26.2)
Intermediate	222,945 (50.1)	218,368 (50.1)	4577 (47.5)
High	141,247 (31.7)	138,853 (31.9)	2394 (24.8)
Missing	5797 (1.3)	5659 (1.3)	138 (1.4)
Household income			
< £18,000	86,487 (19.4)	83,694 (19.2)	2793 (29.0)
£18,000–30,999	96,985 (21.8)	94,627 (21.7)	2358 (24.5)
£31,000–51,999	98,778 (22.2)	97,149 (22.3)	1629 (16.9)
£52,000–100,000	76,705 (17.2)	75,834 (17.4)	871 (9.0)
> £100,000	20,318 (4.6)	20,161 (4.6)	157 (1.6)
Missing	65,964 (14.8)	64,137 (14.7)	1827 (19.0)
Paid employment			
No	187,441 (42.1)	180,869 (41.5)	6572 (68.2)
Yes	255,463 (57.4)	252,442 (58.0)	3021 (31.4)
Missing	2333 (0.5)	2291 (0.5)	42 (0.4)
BMI, n (%)			
<25 kg/m^2	146,405 (32.9)	143,583 (33.0)	2822 (29.3)
25–30 kg/m^2	190,625 (42.8)	186,458 (42.8)	4167 (43.2)
≥ 30 kg/m^2	108,207 (24.3)	105,561 (24.2)	2646 (27.5)
Smoking status			
Never	242,468 (54.5)	237,752 (54.6)	4716 (48.9)
Former	154,558 (34.7)	150,540 (34.6)	4018 (41.7)
Current	45,903 (10.3)	45,076 (10.3)	827 (8.6)
Missing	2308 (0.5)	2234 (0.5)	74 (0.8)
Physical activity			
Low	68,186 (15.3)	66,723 (15.3)	1463 (15.2)
Intermediate	145,600 (32.7)	142,525 (32.7)	3075 (31.9)
High	145,405 (32.7)	142,456 (32.7)	2949 (30.6)
Missing	86,046 (19.3)	83,898 (19.3)	2148 (22.3)
Alcohol intake			
Daily or almost daily	91,270 (20.5)	89,129 (20.5)	2141 (22.2)
Three or four times a week	102,602 (23.0)	100,601 (23.1)	2001 (20.8)
Once or twice a week	114,166 (25.6)	111,946 (25.7)	2220 (23.0)
One to three times a month	49,343 (11.1)	48,373 (11.1)	970 (10.1)
Special occasions only	51,235 (11.5)	49,926 (11.5)	1309 (13.6)
Never	35,614 (8.0)	34,646 (8.0)	968 (10.0)
Missing	1007 (0.2)	981 (0.2)	26 (0.3)
Healthy diet score			
0–1	95,682 (21.5)	93,897 (21.6)	1785 (18.5)
2–3	278,328 (62.5)	272,336 (62.5)	5992 (65.2)
4–5	57,803 (13.0)	56,266 (12.9)	1537 (16.0)
Missing	13,424 (3.0)	13,103 (3.0)	321 (3.3)

Table 1 (continued)

Characteristics	Total	Age-related macular degeneration	
		No	Yes
Self-reported hypertension			
No	333,877 (75.0)	327,518 (75.2)	6359 (66.0)
Yes	111,360 (25.0)	108,084 (24.8)	3276 (34.0)
Self-reported diabetes			
No	421,651 (94.7)	412,965 (94.8)	8686 (90.2)
Yes	23,586 (5.3)	22,637 (5.2)	949 (9.8)
Self-reported hyperlipidemia			
No	365,801 (82.2)	358,927 (82.4)	6874 (71.3)
Yes	79,436 (17.8)	76,675 (17.6)	2761 (28.7)
NO_2 level [μg/m^3, median (IQR)]	26.06 (9.84)	26.06 (9.85)	26.08 (9.54)
NO_x level [μg/m^3, median (IQR)]	42.15 (16.56)	42.15 (16.57)	42.15 (16.08)
$PM_{2.5}$ level [μg/m^3, median (IQR)]	9.93 (1.28)	9.93 (1.28)	9.94 (1.24)
PM_{10} level [μg/m^3, median (IQR)]	16.02 (1.76)	16.02 (1.76)	16.03 (1.72)
$PM_{2.5-10}$ level [μg/m^3, median (IQR)]	6.11 (0.79)	6.11 (0.79)	6.10 (0.81)
Air pollution score [μg/m^3, median (IQR)]	60.55 (9.85)	60.55 (9.85)	60.60 (9.45)

Educational levels were classified into three categories: low (no relevant qualifications); intermediate (A levels, O levels/GCSEs, CSEs, NVQ/HND/HNC, other professional qualifications); high (college or university degree). Physical activity status was classified into three categories: low [< 600 metabolic equivalent (MET) minutes/week], moderate (600 to < 3000 MET) or high (3000 + MET)

Interaction and joint association of air pollution and PRS with incident AMD

We then explored the relationship between air pollution and AMD among participants with different levels of PRS (Table 3). Specifically, the adverse effects of all five air pollutants and APS on AMD were generally higher among participants in the high PRS group than those with low PRS. Remarkably, significant associations between $PM_{2.5}$ and APS with AMD risk was observed even in the low PRS group (Table 3). There were significant additive interactions between PRS and exposure to NO_2, NO_x, $PM_{2.5-10}$, and APS on incident risk of AMD (Table 3). For instance, among participants with the highest quartile (Q4) of APS and with high PRS, the RERI was 0.12 (95% CI: 0.03, 0.20) and the AP was 0.06 (95% CI: 0.01, 0.11), indicating that the additive interaction contributed a relative excess risk of 0.12 and accounted for 6% of the risk of AMD in this subgroup. Similar significant additive interactions were also noted for NO_2, NO_x, and $PM_{2.5-10}$, with RERI (95% CI) and AP (95% CI) of 0.10 (0.01, 0.18) and 0.05 (0.01, 0.11) for NO_2, 0.11 (0.01, 0.19) and 0.05 (0.02, 0.10) for NO_x, and 0.15 (0.06, 0.23) and 0.08 (0.03, 0.13) for $PM_{2.5-10}$, respectively. The sensitive analysis showed that these results remained consistent when the inverse probability weighting model was used (Table S8).

The joint effects of air pollution and genetic susceptibility on AMD risk were further tested and shown in Fig. 2. Specifically, compared with those with low PRS and exposed to lowest (Q1) quartile of air pollutants NO_2, NO_x, $PM_{2.5}$, PM_{10}, $PM_{2.5-10}$, and APS, those with high PRS and highest (Q4) quartile of these pollutants had the highest risk of incident AMD, with the HR (95%CI) = 1.90 (1.75, 2.07), 1.95 (1.79, 2.12), 2.03 (1.86, 2.21), 1.88 (1.73, 2.04), 1.83 (1.68, 1.99), 1.98 (1.82, 2.16), respectively.

Discussion

In this large-scale prospective study, we observed the significant positive associations of long-term exposure to NO_2, NO_x, $PM_{2.5}$, PM_{10} and APS with increase incident risk of AMD. Non-linear exposure–response curves indicated that the risk of incident AMD increased more steeply at lower pollution levels and plateaued at higher exposures. Our results also demonstrated the additive interactions of exposure to NO_2, NO_x, $PM_{2.5-10}$ and APS with genetic risk score on incident AMD, with enhanced adverse effects of air pollution among those with higher genetic susceptibility. In particularly, compared with participants with low PRS and lowest air pollution exposure, those with highest quartile air pollution exposure and high PRS had almost double the risk of AMD.

Ambient air pollution has emerged as a major environmental issue with substantial health implications, and some studies have linked the air pollution to age-related eye disease [30]. To date, few epidemiological studies have examined the associations between air pollution and AMD incidence, with inconsistent results. In line with our findings, a prospective cohort study included 39,819 participants in Taiwan reported that exposure to NO_2 was associate with an increased risk of AMD [9]. Similarly, a meta-analysis included eight studies indicated that exposure to NO_2 and $PM_{2.5}$ was associated with an increased risk of AMD

Table 2 Association between air pollution and risk of age-related macular degeneration

Air pollution	Events/person year	Model 1		Model 2	
		HR (95%CI)	*P*	HR (95%CI)	*P*
NO_2level					
Q1	2358/1,536,239	Ref			
Q2	2445/1,535,989	1.06 (1.00, 1.12)	0.059	1.03 (0.98, 1.09)	0.263
Q3	2511/1,530,005	1.13 (1.07, 1.20)	**<0.001**	1.10 (1.04, 1.16)	**0.001**
Q4	2321/1,523,509	1.17 (1.11, 1.24)	**<0.001**	1.12 (1.06, 1.19)	**<0.001**
Per SD		1.06 (1.04, 1.08)	**<0.001**	1.04 (1.02, 1.06)	**<0.001**
NO_xlevel					
Q1	2313/1,535,876	Ref			
Q2	2504/1,530,509	1.11 (1.05, 1.18)	**<0.001**	1.09 (1.03, 1.15)	**0.003**
Q3	2437/1,525,519	1.14 (1.07, 1.20)	**<0.001**	1.10 (1.04, 1.16)	**0.001**
Q4	2381/1,533,837	1.20 (1.13, 1.27)	**<0.001**	1.14 (1.08, 1.21)	**<0.001**
Per SD		1.05 (1.03, 1.07)	**<0.001**	1.03 (1.01, 1.05)	**0.002**
$PM_{2.5}$level					
Q1	2265/1,515,558	Ref		Ref	
Q2	2462/1,531,845	1.10 (1.04, 1.17)	**<0.001**	1.08 (1.02, 1.15)	**0.007**
Q3	2443/1,528,060	1.14 (1.08, 1.21)	**<0.001**	1.10 (1.04, 1.17)	**<0.001**
Q4	2465/1,550,279	1.21 (1.14, 1.28)	**<0.001**	1.15 (1.09, 1.22)	**<0.001**
Per SD		1.06 (1.04, 1.08)	**<0.001**	1.04 (1.02, 1.07)	**<0.001**
PM_{10}level					
Q1	2348/1,527,696	Ref		Ref	
Q2	2402/1,531,463	1.04 (0.99, 1.10)	0.225	1.02 (0.96, 1.08)	0.478
Q3	2481/1,531,703	1.11 (1.05, 1.18)	**<0.001**	1.09 (1.03, 1.15)	**0.005**
Q4	2404/1,534,879	1.09 (1.03, 1.16)	**0.002**	1.07 (1.01, 1.13)	**0.029**
Per SD		1.03 (1.01,1.06)	**<0.001**	1.02 (1.00, 1.04)	**0.020**
$PM_{2.5-10}$level					
Q1	2291/1,487,454	Ref		Ref	
Q2	2554/1,576,453	1.07 (1.01, 1.13)	**0.016**	1.06 (1.00, 1.12)	**0.043**
Q3	2310/1,515,073	1.04 (0.98, 1.10)	0.220	1.02 (0.96, 1.08)	0.508
Q4	2480/1,546,761	1.10 (1.04, 1.17)	**<0.001**	1.08 (1.02, 1.14)	**0.007**
Per SD		1.02 (1.00, 1.04)	**0.043**	1.02 (0.99, 1.04)	0.117
Air pollution score[a]					
Q1	2271/1,535,623	Ref		Ref	
Q2	2510/1,529,620	1.13 (1.07, 1.20)	**<0.001**	1.11 (1.05, 1.17)	**<0.001**
Q3	2472/1,526,312	1.18 (1.11, 1.25)	**<0.001**	1.14 (1.08, 1.21)	**<0.001**
Q4	2382/1,534,186	1.21 (1.14, 1.28)	**<0.001**	1.16 (1.09, 1.23)	**<0.001**
Per SD		1.06 (1.04, 1.08)	**<0.001**	1.04 (1.02, 1.06)	**<0.001**

HR, hazard ratio; CI, confidence interval; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; $PM_{2.5}$, fine particulate matter with diameter < 2.5 μm; PM_{10}, particulate matter with diameter < 10 μm; $PM_{2.5-10}$, particulate matter with aerodynamic diameter between 2.5 and 10 μm

[a]Air pollution score ranges: quartile 1: (43.96–55.67); quartile 2: (55.68–60.54); quartile 3: (60.55–65.52); and quartile 4: (65.53–156.80). Media (IQR) of the air pollution score is 60.55(9.85). Mode l was adjusted for age and sex. Model 2 was further adjusted education level, ethnicity, BMI, household income, paid employment status, smoking status, alcohol intake, physical activity, healthy diet score, self-reported hypertension, diabetes and hyperlipidemia. Bold values indicate statistical significance at $P<0.05$.

[31]. A recent review further highlighted that exposure to air pollutants can accelerate or exacerbate the prevalence and morbidity of AMD [32]. In our study, we did not find a significant linear association of $PM_{2.5-10}$ and incident AMD, which is similar to prior findings [33]. This null result is biologically reasonable because $PM_{2.5-10}$ originates mainly from mechanical resuspension of crustal and road dust, resulting in significant compositional and source heterogeneity that reduces its toxicological potency and increases exposure-measurement error [34]. These factors may collectively reduce the observable epidemiological relationship relative to $PM_{2.5}$. Chua et al. only found a significant association between $PM_{2.5}$ exposure and self-reported AMD in a cross-sectional study based on European participants, but not for NO_2, NO_x, PM_{10}, and $PM_{2.5-10}$ [11], which may be due to the cross-sectional design that overlooks long-term air pollution effects and the reliance on self-reported AMD data. In addition, a national cohort study in Korea observed the positive association between NO_2 exposure and AMD risk but did not found a significant association between PM_{10} exposure and AMD [35]. Overall, the heterogeneity among studies may be attributable to the differences of study designs, population characteristics, geographical conditions, and exposure assessment methods.

Our research comprehensively demonstrated the significantly increased risk of incident AMD associated with the air pollution score, which reflects the combined effects of various air pollutants co-exposure. Similar integrated scores have been applied in the field of environment health [23, 36] and epidemiological studies [37, 38], and previous studies

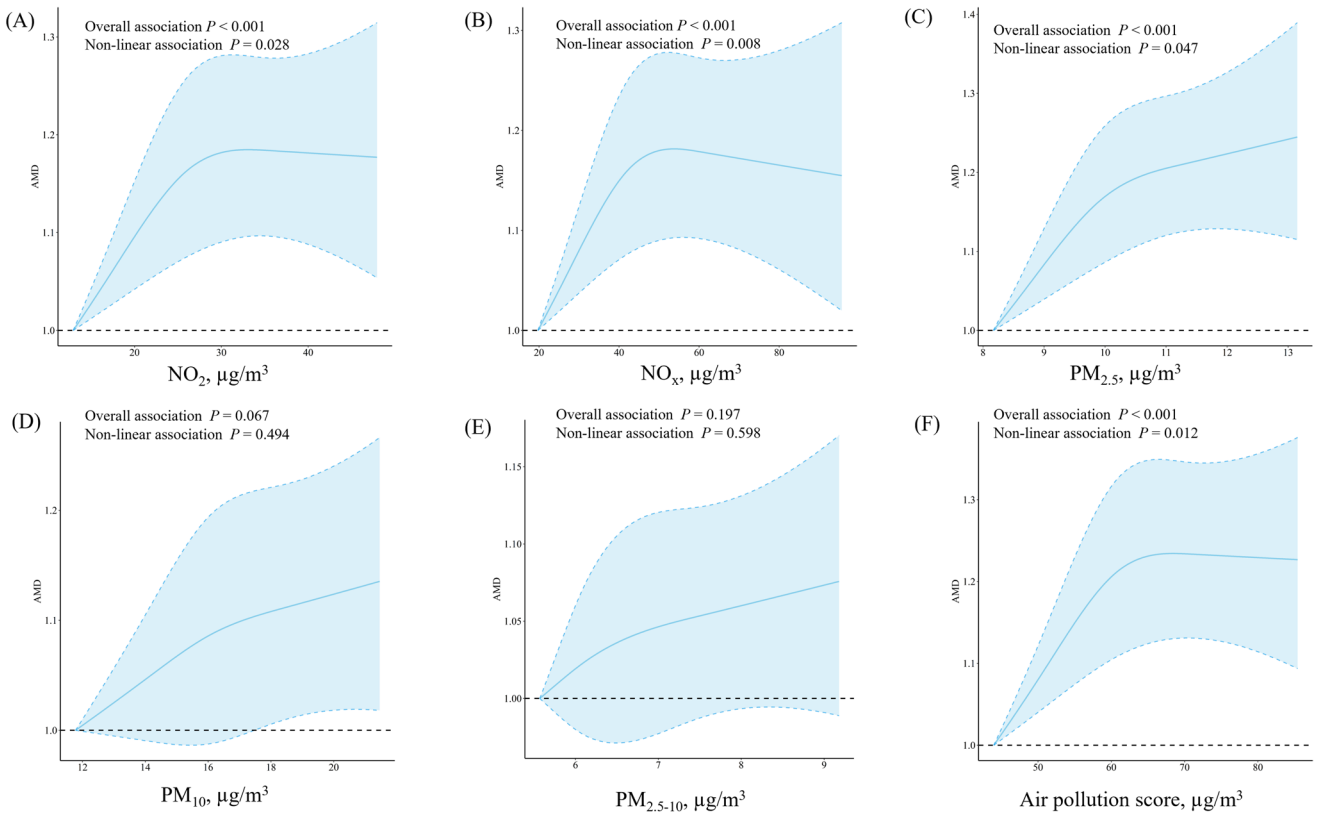

Fig. 1 Dose-response associations between air pollution and age-related macular degeneration. A restricted cubic spline regression model with three knots (at the 10th, 50th and 90th percentiles) was used to estimate the dose–response relations between air pollutants and the risk of age-related macular degeneration. We restricted pollutant concentrations to the top 99% percentile to mitigate the influence of extreme values. Hazard ratios ((HRs) solid lines) and 95% CIs (shaded areas) were adjusted for adjusted for age, sex, ethnicity, education level, household income, paid employment status, BMI, smoking status, alcohol intake, physical activity, healthy diet score, self-reported hypertension, diabetes and hyperlipidemias

have validated that this method is relatively reliable and accurate compared to other common methods for estimating exposure to mixture pollutants within the UK Biobank [39]. Nonlinear exposure-response curves were observed between NO_2, NO_x, $PM_{2.5}$, and APS and incident AMD, characterized by a steeper slope at lower exposure levels and a plateau or slight decline at higher concentrations of air pollution. These findings suggest that even exposure to air pollution levels below the UK air quality standards may still increase AMD risk. More importantly, in alignment with WHO recommendations [28], reducing air pollutants to the interim target levels could potentially decrease the incidence of AMD by 3.40%−8.20%. Our results highlight the imperative to formulate stricter air pollution control policies, and reducing exposure to multiple air pollutants may lead to a reduction of incident AMD.

The precise mechanisms linking AMD to ambient air pollution remain incompletely understood. However, emerging evidence suggests that chronic inflammation and oxidative stress may represent critical mechanistic pathways in AMD pathogenesis [15, 40]. The retina's high oxygen demand and abundance of polyunsaturated fatty acids render it highly susceptible to oxidative damage [41]. Mechanistic studies have shown that $PM_{2.5}$ exposure triggers reactive oxygen species (ROS)-driven epithelial-mesenchymal transition (EMT) in human retinal pigment epithelium (RPE) cells, resulting in a fibroblast-like phenotypic shift and enhanced cell migration [42]. EMT is implicated in RPE disorders and the development of intraocular fibrotic conditions, including AMD [43]. Additionally, animal studies have revealed that $PM_{2.5}$ impairs retinal microvascular function [44], which is a major contributor to AMD pathogenesis [45]. Prior epidemiological studies have demonstrated that both long-term and short-term exposure to $PM_{2.5}$ and NO_x increases levels of inflammatory markers [46, 47]. Other population-based studies have also reported that $PM_{2.5}$, PM_{10}, NO_2 and NO_x were all associated with adverse retinal structure [11, 48].

Our study is the first to explore the interactive and joint effects between genetic risk and air pollution on AMD risk. We observed the significant additive interactions, indicating that the additive effects of high air pollution exposure and high genetic risk exceeded the sum of their individual

Table 3 Additive interactions between air pollutants and PRS on the risk of agerelated macular degeneration

Air pollution	Low genetic risk (n=222618)		High genetic risk (n=222619)		RERI (95%CI)	AP (95%CI)
	HR (95%CI)	P	HR (95%CI)	P		
NO_2level						
Q1	Ref					
Q2	1.00 (0.91, 1.10)	0.945	1.04 (0.97, 1.12)	0.294	0.06 (−0.03, 0.15)	0.04 (−0.02, 0.09)
Q3	1.07 (0.97, 1.17)	0.183	**1.10 (1.02, 1.18)**	**0.01**	0.09 (0.00, 0.17)	0.05 (−0.01, 0.10)
Q4	1.06 (0.96, 1.17)	0.259	**1.12 (1.04, 1.21)**	**0.002**	**0.10 (0.01, 0.18)**	**0.05 (0.01, 0.11)**
NO_xlevel						
Q1	Ref		Ref			
Q2	1.06 (0.97, 1.17)	0.201	**1.10 (1.02, 1.17)**	**0.012**	**0.10 (0.01, 0.18)**	**0.05 (0.00, 0.10)**
Q3	1.07 (0.97, 1.18)	0.157	**1.10 (1.02, 1.18)**	**0.013**	0.08 (−0.01, 0.17)	0.04 (−0.01, 0.10)
Q4	1.10 (1.00 1.21)	0.057	**1.14 (1.06, 1.22)**	**<0.001**	**0.11 (0.01, 0.19)**	**0.05 (0.02, 0.10)**
$PM_{2.5}$level						
Q1	Ref		Ref			
Q2	**1.13 (1.03, 1.24)**	**0.013**	1.05 (0.98, 1.13)	0.158	−0.04 (−0.14, 0.06)	−0.02 (−0.07, 0.03)
Q3	1.09 (0.99, 1.20)	0.072	**1.10 (1.02, 1.18)**	**0.014**	0.07 (−0.03, 0.15)	0.03 (−0.02, 0.09)
Q4	**1.15 (1.04, 1.27)**	**0.005**	**1.13 (1.05, 1.22)**	**<0.001**	0.07 (−0.03, 0.16)	0.03 (−0.01, 0.08)
PM_{10}level						
Q1	Ref		Ref			
Q2	1.05 (0.96, 1.15)	0.298	1.01 (0.94, 1.08)	0.875	−0.05 (−0.10, 0.05)	−0.03 (−0.08, 0.03)
Q3	1.07 (0.97, 1.17)	0.173	**1.08 (1.01, 1.16)**	**0.028**	0.06 (−0.04, 0.14)	0.03 (−0.02 0.08)
Q4	1.03 (0.94, 1.14)	0.497	**1.08 (1.00, 1.16)**	**0.050**	0.07 (−0.03, 0.15)	0.04 (−0.01, 0.09)
$PM_{2.5-10}$level						
Q1	Ref		Ref			
Q2	0.99 (0.90, 1.09)	0.861	**1.09 (1.02, 1.17)**	**0.015**	**0.16 (0.08, 0.24)**	**0.09 (0.04, 0.15)**
Q3	0.99 (0.90, 1.08)	0.785	1.03 (0.96, 1.11)	0.422	0.05 (−0.04, 0.14)	0.03 (−0.02, 0.09)
Q4	1.01 (0.92, 1.11)	0.821	**1.11 (1.03, 1.19)**	**0.005**	**0.15 (0.06, 0.23)**	**0.08 (0.03, 0.13)**
Air pollution score						
Q1	Ref		Ref			
Q2	1.09 (0.99, 1.20)	0.067	**1.11 (1.03, 1.19)**	**0.005**	0.09 (−0.01, 0.18)	0.05 (−0.01, 0.10)
Q3	**1.11 (1.01, 1.22)**	**0.032**	**1.14 (1.06, 1.23)**	**<0.001**	**0.12 (0.02, 0.20)**	**0.06 (0.01, 0.11)**
Q4	**1.11 (1.01, 1.22)**	**0.037**	**1.15 (1.07, 1.24)**	**<0.001**	**0.12 (0.03, 0.20)**	**0.06 (0.01, 0.11)**

Model was adjusted for age, sex, education level, ethnicity, BMI, household income, paid employment status, smoking status, alcohol intake, physical activity, healthy diet score, self-reported hypertension, diabetes and hyperlipidemia, genetic batch and 10 genetic principal components. Bold values indicate statistical significance at P<0.05.

HR, hazard ratio; CI, confidence interval; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; $PM_{2.5}$, fine particulate matter with diameter < 2.5 μm; PM_{10}, particulate matter with diameter < 10 μm; $PM_{2.5-10}$, particulate matter with aerodynamic diameter between 2.5 and 10 μm

effects. Furthermore, 5–9% of AMD risk could be attributed to the additive interactions. Our results also revealed that higher levels of air pollution and greater genetic susceptibility were associated with a higher risk of AMD. Consistent with our results, a twin study revealed the significant role of genetic factors and unique environmental influences, highlighting the gene-environment interplay in AMD etiology [19]. Our findings provide novel insights into the precise prevention and control of AMD, as they can be used to identify individuals who may benefit most from targeted interventions to reduce air pollution exposure, particularly among those with high genetic risk. Future research should take a more novel approach to exploring the impact of air pollution and genetic interactions on AMD development [49].

Strengths of the present study included that we comprehensively assessed the associations of individual and combined exposure to various air pollutants with AMD risk based on the prospective design and large sample size. In addition, we firstly explored the interactive and joint effects of air pollution and genetic susceptibility on AMD incidence, enabling a more accurate evaluation of air pollution effects across different susceptibility levels. However, the current study has several limitations. First, this observational study was unable to determine a causal relationship between air pollution and AMD, despite adjusting for a range of confounding factors, including demographics, socioeconomic status, lifestyle factors, and disease conditions. Second, air pollution exposure was measured at baseline, which may have overlooked changes in air pollution levels during the follow-up period, leading to misclassification of exposure.

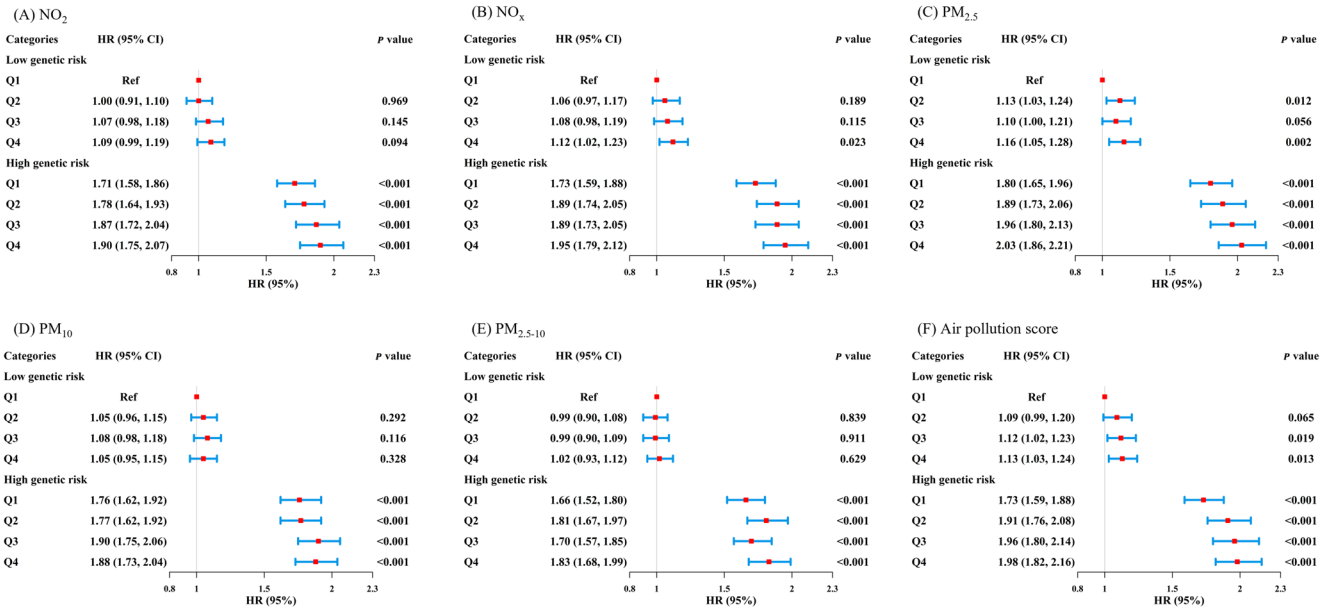

Fig. 2 Joint effect of air pollution score and genetic risk on incident age-related macular degeneration. Note: Model was adjusted for age, sex, education level, ethnicity, BMI, household income, paid employment status, smoking status, alcohol intake, physical activity, healthy diet score, self-reported hypertension, diabetes and hyperlipidemia, genetic batch and 10 genetic principal components

However, air pollution emissions in the UK remained relatively stable from 2010 to 2019 [14]. Also, the use of a single-year LUR estimate as a surrogate for long-term residential exposure is a well-established methodology in large-scale epidemiological studies of chronic diseases [14, 18, 23]. More cohort studies with repeated measurements of air pollution at different time are required to validate our findings. Third, the air pollution score was estimated by computing the individual pollutants weights by treating each as a continuous variable, whereas the air pollutants may be non-linearly associated with AMD. However, this method has been widely used in previous UK Biobank studies and has been shown to be reliable compared to other methods [23, 36, 39]. Fourth, the air pollution score did not include all air pollutants, such as O_3, which may also be related to the risk of AMD [7]. Fifth, we ascertained incident AMD cases solely using hospital inpatient records, which may have underestimated the prevalence of AMD. Finally, most of participants in our study were of European descent, generalization of the results to other ethnic populations should be undertaken with caution.

Conclusion

In summary, this large-scale prospective study is the first to demonstrated that long-term exposure to NO_2, NO_x, $PM_{2.5}$, PM_{10} was significantly associated with an increased risk of AMD, and these effects were more pronounced among subjects with high genetic susceptibility. In addition, our findings further reveal additive interactions of air pollution and PRS, highlighting the importance of improving air quality for preventing the onset of AMD, particularly among those with high genetic risk. Further studies are needed to validate our findings in different race populations and elucidate the underlying biological mechanisms.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10654-025-01340-8.

Acknowledgements We appreciate all investigators and participants in the UK Biobank.

Author contributions Shengli Chen: Conceptualization, Methodology, Formal analysis, Writing - original draft, Writing - review & editing; Gongyue Wang: Methodology, Writing - review & editing; Xin Guan, Formal analysis, Writing - review & editing; Chenming Wang, Methodology, Writing - review & editing; Yang Xiao: Writing - review & editing; Xingdi Li: Writing - review & editing; Shiru Hong: Data curation; Yuhan Zhou: Methodology, Visualization; Yingqian You, Visualization; Ye Fu: Visualization; Yuxi Wang: Writing - review & editing; Yichi Zhang: Visualization; Hui Zhao: Writing - review & editing; Yingchen Zhang: Data curation; Yang Cheng: Conceptualization; Huan Guo: Project administration, Conceptualization, Writing - original draft, Writing - review & editing, Funding acquisition; Huatao Xie: Methodology, Conceptualization, Writing - review & editing, Funding acquisition.

Funding This work was supported by the National Natural Science Foundation of China (grant no: 82373667 and 82171025); and the National Key Research and Development Program of China (grant no: 2018YFC2000203).

Data availability This research was conducted using the UK Biobank

resource under the UKB application No. 8815. The data used in this study are available to all researchers upon application.

Declarations

Conflict of interest We declare no competing interests.

References

1. Lim LS, Mitchell P, Seddon JM, Holz FG, Wong TY. Age-related macular degeneration. Lancet. 2012;379(9827):1728–38.
2. Mitchell P, Liew G, Gopinath B, Wong TY. Age-related macular degeneration. Lancet. 2018;392(10153):1147–59.
3. Wong WL, Su X, Li X, et al. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. Lancet Glob Health. 2014;2(2):e106–16.
4. Fleckenstein M, Schmitz-Valckenberg S, Chakravarthy U. Age-Related Macular Degeneration. JAMA. 2024;331(2):147–57.
5. Cohen AJ, Brauer M, Burnett R, et al. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. Lancet. 2017;389(10082):1907–18.
6. Brodzka S, Baszyński J, Rektor K, et al. Immunogenetic and environmental factors in age-related macular disease. Int J Mol Sci. 2024;25(12):6567.
7. Jia H, Guo Y, Luo H, et al. Association of long-term ozone air pollution and age-related macular degeneration in older Chinese population. Sci Total Environ. 2024;912:169145.
8. Qu Y, Jiang Y, Zhang G, et al. Association of exposure to ultraviolet radiation and warm-season ozone air pollution with incident age-related macular degeneration: A nationwide cohort study in China. Sci Total Environ. 2024;938:173580.
9. Chang K-H, Hsu P-Y, Lin C-J, Lin C-L, Juo S-HH, Liang C-L. Traffic-related air pollutants increase the risk for age-related macular degeneration. J Investig Med. 2019;67(7):1076–81.
10. Liang C-L, Wang C-M, Jung C-R, et al. Fine particulate matter measured by satellites predicts the risk of age-related macular degeneration in a longitudinal cohort study. Environ Sci Pollut Res. 2022;29(34):51942–50.
11. Chua SYL, Warwick A, Peto T, et al. Association of ambient air pollution with age-related macular degeneration and retinal thickness in UK biobank. Br J Ophthalmol. 2022;106(5):705–11.
12. He J, Liu Y, Zhang A, et al. Joint effects of meteorological factors and PM2.5 on age-related macular degeneration: a national cross-sectional study in China. Environ Health Prev Med. 2023;28(0):3–3.
13. Mauderly JLand Samet JM. Is there evidence for synergy among air pollutants in causing health effects? Environ Health Perspect. 2009;117(1):1–6.
14. Yang T, Wang J, Huang J, Kelly FJ, Li G. Long-term exposure to multiple ambient air pollutants and association with incident depression and anxiety. JAMA Psychiatr. 2023;80(4):305–13.
15. Deng Y, Qiao L, Du M, et al. Age-related macular degeneration: epidemiology, genetics, pathophysiology, diagnosis, and targeted therapy. Genes & Diseases. 2022;9(1):62–79.
16. Gorman BR, Voloudakis G, Igo RP, et al. Genome-wide association analyses identify distinct genetic architectures for age-related macular degeneration across ancestries. Nat Genet. 2024;56(12):2659–71.
17. Khera AV, Chaffin M, Aragam KG, et al. Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. Nat Genet. 2018;50(9):1219–24.
18. Huang Y, Zhu M, Ji M, et al. Air Pollution, genetic Factors, and the risk of lung cancer: A prospective study in the UK biobank. Am J Respir Crit Care Med. 2022;205(10):1254–1254.
19. Seddon JM, Cote J, Page WF, Aggen SH, Neale MC. The US twin study of Age-Related macular degeneration. Arch Ophthalmol. 2005;123(3):321–7.
20. Sudlow C, Gallacher J, Allen N, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med. 2015;12(3):e1001779.
21. Beelen R, Hoek G, Vienneau D, et al. Development of NO2 and NOx land use regression models for estimating air pollution exposure in 36 study areas in Europe – the ESCAPE project. Atmos Environ. 2013;72:10–23.
22. Eeftens M, Beelen R, de Hoogh K, et al. Development of land use regression models for PM2.5, PM2.5 absorbance, PM10 and PMcoarse in 20 European study areas; results of the ESCAPE project. Environ Sci Technol. 2012;46(20):11195–205.
23. Wang M, Zhou T, Song Y, et al. Joint exposure to various ambient air pollutants and incident heart failure: a prospective analysis in UK Biobank. Eur Heart J. 2021;42(16):1582–91.
24. Thompson DJ, Wells D, Selzam S et al. UK biobank release and systematic evaluation of optimised polygenic risk scores for 53 diseases and quantitative traits. MedRxiv [Preprint]. 2022.
25. Bycroft C, Freeman C, Petkova D, et al. The UK biobank resource with deep phenotyping and genomic data. Nature. 2018;562(7726):203–9.
26. Lloyd-Jones DM, Hong Y, Labarthe D, et al. Defining and setting National goals for cardiovascular health promotion and disease reduction. Circulation. 2010;121(4):586–613.
27. Lin C-K, Chen S-T. Estimation and application of population attributable fraction in ecological studies. Environ Health. 2019;18(1):52.
28. Department for Environment, Food and Rural Affairs, Government TUK. 2021. WHO global air quality guidelines: particulate matter (PM2.5 and PM10), ozone, nitrogen dioxide, sulfur dioxide and carbon monoxide. https://www.who.int/publications/i/item/9789240034228// (accessed 18 August 2025).
29. Li R, Chambless L. Test for additive interaction in proportional hazards models. Ann Epidemiol. 2007;17(3):227–36.
30. Grant A, Leung G, Aubin M-J, Kergoat M-J, Li G, Freeman EE. Fine particulate matter and age-related eye disease: the Canadian longitudinal study on aging. Invest Ophthalmol Vis Sci. 2021;62(10):7.
31. Wu J, Zhang Y, Xu X. Association between ambient air pollution and age-related macular degeneration: a meta-analysis. BMC Ophthalmol. 2024;24(1):202.
32. Liu L, Li C, Yu H, Yang X. A critical review on air pollutant exposure and age-related macular degeneration. Sci Total Environ. 2022;840:156717.
33. Li Y, Zhang Y, Kam KW, et al. Associations of long-term joint exposure to multiple ambient air pollutants with the incidence of age-related eye diseases. Ecotoxicol Environ Saf. 2025. https://doi.org/10.1016/j.ecoenv.2025.118052.
34. <2001——Sources. and chemical composition of atmospheric fine and coarse particles in the Helsinki area.pdf&gt.
35. Ju MJ, Kim J, Park SK, Kim DH, Choi Y-H. Long-term exposure to ambient air pollutants and age-related macular degeneration in middle-aged and older adults. Environ Res. 2022;204(Pt A):111953.
36. Guo Y, Li X, Wang M, et al. Obesity and the relation between joint exposure to ambient air pollutants and incident type 2 diabetes: a cohort study in UK biobank. PLoS Med. 2021;18(8):e1003767.
37. Ahola-Olli AV, Mustelin L, Kalimeri M, et al. Circulating metabolites and the risk of type 2 diabetes: a prospective study of 11,896 young adults from four Finnish cohorts. Diabetologia. 2019;62(12):2298–309.

38. Lourida I, Hannon E, Littlejohns TJ, et al. Association of lifestyle and genetic risk with incidence of dementia. JAMA. 2019;322(5):430–7.
39. Zhang J, Fang X-Y, Wu J, et al. Association of combined exposure to ambient air pollutants, genetic risk, and incident rheumatoid arthritis: a prospective cohort study in the UK biobank. Environ Health Perspect. 2023;131(3):37008.
40. Fleckenstein M, Keenan TDL, Guymer RH, et al. Age-related macular degeneration. Nat Rev Dis Primers. 2021;7(1):31.
41. Jarrett SG, Boulton ME. Consequences of oxidative stress in age-related macular degeneration. Mol Aspects Med. 2012;33(4):399–417.
42. Lee H, Hwang-Bo H, Ji SY, et al. Diesel particulate matter2.5 promotes epithelial-mesenchymal transition of human retinal pigment epithelial cells via generation of reactive oxygen species. Environ Pollut. 2020;262:114301.
43. Chiba C. The retinal pigment epithelium: an important player of retinal disorders and regeneration. Exp Eye Res. 2014;123:107–14.
44. Nurkiewicz TR, Porter DW, Barger M, Castranova V, Boegehold MA. Particulate matter exposure impairs systemic microvascular endothelium-dependent dilation. Environ Health Perspect. 2004;112(13):1299–306.
45. Lipecz A, Miller L, Kovacs I, et al. Microvascular contributions to age-related macular degeneration (AMD): from mechanisms of choriocapillaris aging to novel interventions. Geroscience. 2019;41(6):813–45.
46. Hajat A, Allison M, Diez-Roux AV, et al. Long-term exposure to air pollution and markers of Inflammation, Coagulation, and endothelial activation. Epidemiology. 2015;26(3):310–20.
47. Li W, Dorans KS, Wilker EH, et al. Short-term exposure to ambient air pollution and biomarkers of systemic inflammation. Arteriosclerosis, Thrombosis, Vasc Biol. 2017;37(9):1793–800.
48. Chua SYL, Khawaja AP, Dick AD, et al. Ambient air pollution associations with retinal morphology in the UK Biobank. Invest Ophthalmol Vis Sci. 2020;61(5):32.
49. Miao J, Wu Y, Lu Q. Statistical methods for gene–environment interaction analysis. WIREs Comput Stat. 2023. https://doi.org/10.1002/wics.1635.