Association of ambient air pollution with age-related macular degeneration and retinal thickness in UK Biobank

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ABSTRACT

Aim To examine the associations of air pollution with both self-reported age-related macular degeneration (AMD), and in vivo measures of retinal sublayer thicknesses.

Methods We included 115 954 UK Biobank participants aged 40–69 years old in this cross-sectional study. Ambient air pollution measures included particulate matter, nitrogen dioxide (NO_2) and nitrogen oxides (NO_x). Participants with self-reported ocular conditions, high refractive error (< −6 or > +6 diopters) and poor spectral-domain optical coherence tomography (SD-OCT) image were excluded. Self-reported AMD was used to identify overt disease. SD-OCT imaging derived photoreceptor sublayer thickness and retinal pigment epithelium (RPE) layer thickness were used as structural biomarkers of AMD for 52 602 participants. We examined the associations of ambient air pollution with self-reported AMD and both photoreceptor sublayers and RPE layer thicknesses.

Results After adjusting for covariates, people who were exposed to higher fine ambient particulate matter with an aerodynamic diameter <2.5 µm ($PM_{2.5}$, per IQR increase) had higher odds of self-reported AMD (OR=1.08, p=0.036), thinner photoreceptor synaptic region (β=−0.16 µm, p=2.0 × 10^{-5}), thicker photoreceptor inner segment layer (β=0.04 µm, p=0.001) and thinner RPE (β=−0.13 µm, p=0.002). Higher levels of $PM_{2.5}$ absorbance and NO_2 were associated with thicker photoreceptor inner and outer segment layers, and a thinner RPE layer. Higher levels of PM_{10} (PM with an aerodynamic diameter <10 µm) was associated with thicker photoreceptor outer segment and thinner RPE, while higher exposure to NO_x was associated with thinner photoreceptor synaptic region.

Conclusion Greater exposure to $PM_{2.5}$ was associated with self-reported AMD, while $PM_{2.5}$, $PM_{2.5}$ absorbance, PM_{10}, NO_2 and NO_x were all associated with differences in retinal layer thickness.

INTRODUCTION

Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in adults 50 years and above in high-income countries.[1] Dry AMD is characterised by progressive dysfunction of the retinal pigment epithelium (RPE), photoreceptor loss and retinal degeneration.[2] By 2020, the global projected number of people with AMD is approximately 200 million, increasing to nearly 300 million by 2040.[3] Well-known risk factors include older age, smoking and genetic factors.[1] A constellation of adverse factors (both risk genotypes, smoking and body mass index (BMI) ≥25) together increases the risk 19-fold.[4] As smoking tobacco is a risk factor, it is plausible that ambient air pollution may also be a modifiable risk factor.

Air pollution is one of the world's most important environmental health risks. It is associated with increased mortality and morbidity.[5] Exposure to air pollution is associated with pulmonary and cardiovascular disease[6] and eye diseases including glaucoma[7] and AMD.[8] The mechanisms of air pollution-induced health effects may likely involve oxidative stress and inflammation.[9] The retina is one of the highest oxygen-consuming tissues in the human body and resides in an environment that is primed for the generation of reactive oxygen species and resultant oxidative damage.[10] Oxidative damage increases with age, resulting in retinal dysfunction and cell loss. Rapid, non-invasive optical coherence tomography (OCT) imaging of the retina is now commonly used by community opticians and hospital eye clinics and to assess retinal structural changes associated with AMD, and to guide its management.[11]

If air pollution has an adverse effect on AMD risk, this may offer a new range of interventions for controlling this important condition. We examined data from UK Biobank (UKBB), a large community-based cohort study. The aim of our study was to evaluate the relationship between ambient air pollution, AMD status and OCT imaging derived structural features of the disease: photoreceptor sublayer and RPE layer thickness.

METHODS

Study population

UKBB is a very large community-based cohort of 502 656 UK residents registered with the National Health Service and aged 40–69 years at enrolment. Baseline examinations were carried out between 2006 and 2010 at 22 study assessment centres. The

North West Multi-centre Research Ethics Committee approved the study in accordance with the principles of the Declaration of Helsinki. The overall study protocol (http://www.ukbiobank.ac.uk/resources/) and protocols for individual tests (http://biobank.ctsu.ox.ac.uk/crystal/docs.cgi) are available online. Participants answered a wide-ranging touch-screen questionnaire covering demographic, socioeconomic, lifestyle, systemic and ocular diseases information. Definition of hypertension was based on self-reported data. Physical measures included height and weight. BMI was defined as weight divided by height squared.

Ocular assessment

Ocular assessment was introduced as an enhancement in 2009 for six assessment centres which are spread across the UK.[12] Habitual visual acuity (VA) was measured using a logarithm of the minimum angle of resolution (LogMAR) chart (Precision Vision, LaSalle, Illinois, USA) on a computer screen under standard illumination.[12 13] Refractive error was measured using an autorefractor (Tomey RC 5000, Nagoya, Japan).[14] High-resolution OCT imaging was performed using the Topcon 3D OCT 1000 Mk2 (Topcon Inc, Oakland, New Jersey, USA) in a dark room, without pupillary dilation using the 3D macular volume scan (scan settings: 512 horizontal A scans per B scan; 128 B scans in a 6×6 mm raster pattern). The Topcon Advanced Boundary Segmentation (TABS) Algorithm (V.1.6.1.1)[15] was used to detect retinal layer boundaries and measure the thickness of the RPE[16] and photoreceptor sublayers (online supplemental figure 1). The TABS segmentation algorithm has been validated previously showing a high degree of precision and reproducibility compared with manual segmentation methods.[15] Strict quality control was implemented to exclude images of poor quality as described in detail previously.[17] OCT scans with image quality score (signal strength) <45 were excluded. Several segmentation indicators were calculated to identify poor scan quality or segmentation failures. Participants with the poorest 20% of images for each of these indicators were also excluded. These indicators included an inner limiting membrane (ILM) indicator, a validity count and motion indicators. The ILM indicator was a measure of the minimum localised edge strength around the ILM boundary across the entire scan. It is useful for identifying blinks, scans that contain regions of severe signal fading and segmentation errors. The validity count indicator is used to identify scans with a significant degree of clipping in the OCT scan's z-axis dimension. The motion indicators use both the nerve fibre layer and the full retinal thicknesses, from which Pearson correlations and absolute differences between the thickness data from each set of consecutive B-scans are calculated. The lowest correlation and the highest absolute difference in a scan serve as the resulting indicator scores and identify blinks, eye motion artefacts and segmentation failures. The image quality score and the aforementioned indicators usually are highly correlated.[18]

Definition of AMD status

Definition of AMD status was based on self-reported data. AMD status was determined as those who selected 'macular degeneration' from a predefined list of eye disorders to the question 'Has a doctor ever told you that you have any of the following problems with your eyes?' We also carried out a validation of self-reported AMD status by carrying out masked grading of the retinal OCT and fundus images for features of AMD based on the Beckman AMD classification on a random subset of age-matched participants.[19]

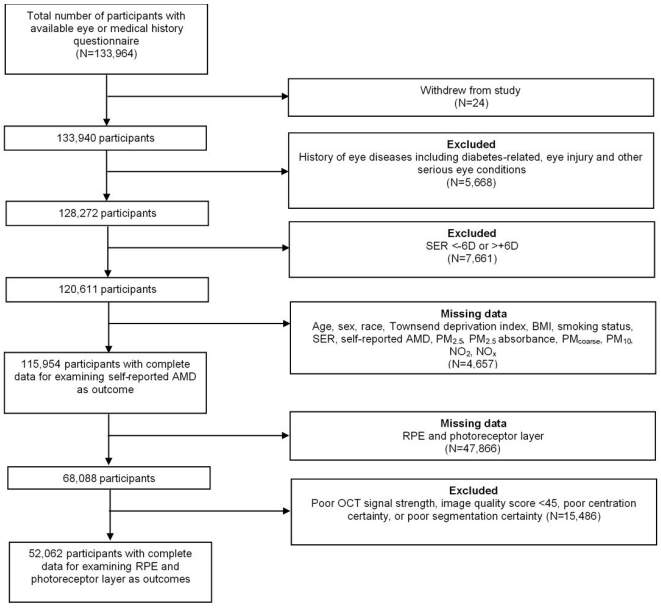

Figure 1 Flowchart of participants included in the study. AMD, age-related macular degeneration; BMI, body mass index; D, Diopters; NO_2, nitrogen dioxide, NO_x, nitrogen oxide; OCT, optical coherence tomography; $PM_{2.5}$, particulate matter (aerodynamic diameter of less than 2.5 µm); $PM_{2.5}$ absorbance, particulate matter (a measurement of the blackness of $PM_{2.5}$ filter—a proxy for elemental or black carbon); PM_{coarse}, particulate matter (aerodynamic diameter between 2.5 and 10 µm); PM_{10}, particulate matter (aerodynamic diameter of less than 10 µm); RPE, retinal pigment epithelium; SER, spherical equivalent refraction.

Estimates of air pollution

The air pollution estimates were provided by the Small Area Health Statistics Unit (http://www.sahsu.org/) as part of the BioSHaRE-EU Environmental Determinants of Health Project (http://www.bioshare.eu/), and were linked centrally to the assessment data by UKBB analysts (http://biobank.ctsu.ox.ac.uk/crystal/docs/EnviroExposEst.pdf). Detailed estimates of air pollution parameters have been published.[20] The annual average concentration of $PM_{2.5}$ (aerodynamic diameter of less than 2.5 µm), PM_{coarse} (aerodynamic diameter between 2.5 and 10 µm), PM_{10} (aerodynamic diameter of less than 10 µm), $PM_{2.5}$ absorbance (a measurement of the blackness of $PM_{2.5}$ filter—a proxy for elemental or black carbon), nitrogen dioxide (NO_2) and nitrogen oxides (NO_x) were calculated centrally by the UKBB using a land use regression model developed by the European Study of Cohorts for Air Pollution Effects (ESCAPE) project (http://www.escapeproject.eu/).[21] By using the predictor variables obtained from the Geographic Information System such as traffic, land use and topography, the land use regression models calculate the spatial variation of annual average air pollution concentration at participants' residential addresses given at baseline visit. NO_2 annual concentration data were available for 4 years (2005, 2006, 2007 and 2010), while PM_{10} data were available for 2007 and 2010. We averaged the values to obtain the mean estimate. All other particulate matter and nitrogen pollutants had the exposure data for a single year (2010).

Inclusion and exclusion criteria

A uniform set of exclusion criteria was applied in the analysis of AMD status, photoreceptor layer and RPE thickness (figure 1). We excluded data from: (1) participants who withdrew consent;

or (2) had self-reported diabetes-related eye disease, eye injury resulting in vision loss or other serious eye conditions; high refractive error (< −6 diopters [D] or > +6D) or (3) participants who had poor OCT image scans using TABS software.[16 22] These participants were excluded because of the well-recognised impact these factors have on retinal layer thickness.[23]

Statistical analysis

The present analysis was based on cross-sectional data collected at one point in time. For this analysis, if both eyes of a patient were eligible for inclusion in the analysis, one eye was randomly selected using STATA software (V.13, StataCorp LP, College Station, Texas, USA). We examined the baseline characteristics of participants included for each specific outcome (self-reported AMD and retinal layers). Descriptive statistics for continuous variables are presented as mean (SD), whereas categorical variables are presented as number (percentage). We examined the associations of each air pollutant (independent variables) with self-reported AMD (dependent variable) using logistic multivariable regression models, adjusted for age, sex, race, Townsend deprivation index, BMI, smoking status and refractive error. The associations of air pollutants with photoreceptor sublayers and RPE thicknesses (dependent variables) were adjusted for the same variables, using linear multivariable regression models. The effect estimates represent the change in self-reported AMD and retinal layers variables per IQR increment in air pollution. Statistical significance was set at $p<0.05$ for the outcomes self-reported AMD and RPE thickness. When photoreceptor sublayer thickness was analysed as an outcome, statistical significance was set at $p<0.002$ after Bonferroni correction as we examined six different types of air pollutants with four distinct photoreceptor-related layers. In sensitivity analysis, we examined the associations of air pollutants with visually significant self-reported AMD. Visually significant self-reported AMD was defined as self-reported AMD participants with VA worse than LogMAR 0.3 (equivalent to Snellen 20/40), while non-visually significant self-reported AMD was defined as those with VA of LogMAR 0.3 or better.

RESULTS

Of the 133 964 participants who completed ocular assessment, 24 participants withdrew their consent. Of the 133 940, we excluded 13 329 participants according to the exclusion criteria (figure 1), leaving data on 120 611 participants. There were complete data (age, sex, race, Townsend deprivation index, BMI, smoking status, refractive error, self-reported AMD and air pollution measures) for 115 954 participants. Of the 115 954, there was complete OCT imaging data on retinal layers for 68 088 participants. We excluded 15 486 participants according to the exclusion criteria for OCT. Hence, 52 062 participants were included in the analysis for examining RPE and photoreceptor layer thickness. This large number of exclusions for retinal layers was because of a later start for OCT imaging in UKBB, meaning a smaller number of people were scanned.

The characteristics of participants with data on self-reported AMD and a subgroup with data on retinal layer are shown in table 1. Both groups had similar sociodemographic and clinical characteristics. Compared with participants with self-reported AMD, those without self-reported AMD were more likely non-white (9.1% vs 7.0%; p=0.01), younger (56.8 years vs 61.6 years), more likely male (46.0% vs 40.9%), more likely to come from a more deprived area (less negative Townsend deprivation index, −1.1 vs −1.4) and more likely to be smokers (9.7% vs 7.6%, all $p<0.001$, online supplemental table 1). The distribution of ambient air pollution exposure of participants with data on self-reported AMD and a subgroup with retinal layer data are shown in online supplemental table 2). The mean (SD) of the various retinal layers are as follows: total length of photoreceptor (142.1 µm (8.2 µm)), photoreceptor synaptic region (80.4 µm (6.6 µm)), photoreceptor inner segment (23.8 µm (2.0 µm)), photoreceptor outer segment (37.9 µm (4.3 µm)) and RPE (25.6 µm (7.2 µm)). Of the 115 954 participants, 1286 (1.1%) were diagnosed with AMD. Masked grading of OCT and retinal fundus images from 119 participants (60 with self-reported AMD and 59 without self-reported AMD) showed that 75% of those with self-reported AMD had OCT features of AMD while only 12% of those without self-reported AMD had OCT features of AMD.

Table 1 Demographic, systemic and ocular characteristics of participants with availability of data on self-reported AMD and retinal layers

	Participants with data on self-reported AMD (n=115 954)	Participants with data on retinal layers (n=52 602)
Sociodemographic factors		
Age	56.8 (8.0)	56.4 (8.1)
Sex		
Men	53 218 (46%)	24 753 (47%)
Women	62 736 (54%)	27 849 (53%)
Race		
White	105 465 (91%)	48 475 (92%)
Non-white	10 489 (9%)	4127 (8%)
Townsend deprivation index	−1.1 (3.0)	−1.2 (2.9)
Clinical factors		
BMI (kg/m^2)	27.3 (4.5)	27.2 (4.4)
Smoking status		
Never	64 554 (56%)	29 238 (56%)
Previous	40 224 (35%)	18 421 (35%)
Current	11 176 (10%)	4943 (9%)
Spherical equivalent (diopters)	−0.1 (2.1)	0.0 (2.0)

Numbers are mean (SD) or n (%), unless otherwise stated.
AMD, age-related macular degeneration; BMI, body mass index; NO_2, nitrogen dioxide; NO_x, nitrogen oxide; PM_{10}, particulate matter (aerodynamic diameter of less than 10 µm); $PM_{2.5}$, particulate matter (aerodynamic diameter of less than 2.5 µm); $PM_{2.5}$ absorbance, particulate matter (a measurement of the blackness of $PM_{2.5}$ filter—a proxy for elemental or black carbon); PM_{coarse}, particulate matter (aerodynamic diameter between 2.5 and 10 µm).

Participants exposed to higher levels of $PM_{2.5}$ concentration were 8% more likely to have self-reported AMD (OR 1.08, 95% CI 1.01 to 1.16; p=0.036, per IQR increase, table 2). Following Bonferroni correction, higher levels of $PM_{2.5}$ and NO_x were associated with thinner photoreceptor synaptic region (table 3). In contrast, per IQR increase in $PM_{2.5}$, $PM_{2.5}$ absorbance and NO_2 were associated with a thicker photoreceptor inner segment layer. Exposure to higher levels of $PM_{2.5}$ absorbance, PM_{10} and NO_2 were associated with a thicker photoreceptor outer segment layer (table 3). Higher concentration of $PM_{2.5}$, $PM_{2.5}$ absorbance, PM_{10} and NO_2 were associated with a thinner RPE layer (table 4). In addition, we examined the association of smoking status with self-reported AMD. Among participants with self-reported AMD, 510 (39.7%)/1286 and 101 (7.9%)/1286 were previous and current smokers, respectively. After adjusting for age, sex, race, Townsend deprivation

Table 2 Association of ambient air pollution with self-reported AMD

	Multivariate regression	
	OR (95% CI)	P value
Air pollution factors		
$PM_{2.5}$ (μg/m^3)	1.08 (1.01 to 1.16)	**0.036**
$PM_{2.5}$ absorbance (μg/m^3)	1.00 (0.93 to 1.07)	0.95
$PM_{2.5-10}$ (μg/m^3)	1.01 (0.96 to 1.07)	0.58
PM_{10} (μg/m^3)	0.94 (0.86 to 1.02)	0.11
NO_2 (μg/m^3)	0.99 (0.91 to 1.08)	0.80
NO_x (μg/m^3)	1.03 (0.97 to 1.09)	0.34

The OR represents per IQR increase in exposure variable.
Values are adjusted for age, sex, race, Townsend deprivation index, BMI, smoking status and spherical equivalent refraction.
Bold values denote statistical significance at P<0.05 level.
AMD, age-related macular degeneration; BMI, body mass index; NO_2, nitrogen dioxide; NO_x, nitrogen oxide; PM_{10}, particulate matter (aerodynamic diameter of less than 10 μm); $PM_{2.5}$, particulate matter (aerodynamic diameter of less than 2.5 μm); $PM_{2.5}$ absorbance, particulate matter (a measurement of the blackness of $PM_{2.5}$ filter—a proxy for elemental or black carbon); PM_{coarse}, particulate matter (aerodynamic diameter between 2.5 and 10 μm).

index, BMI, SER and $PM_{2.5}$, compared with never smoking, previous and current smokers were not associated with self-reported AMD (p>0.05). We have additionally adjusted for hypertension in the multivariable models in view of its relationship with AMD[24] and air pollution.[25] The associations of air pollutants with self-reported AMD, photoreceptor sublayers and RPE thickness did not differ after additional adjustment for hypertension. Sensitivity analysis showed that participants with higher exposure to $PM_{2.5}$ was marginally associated with visually significant self-reported AMD (n=167, OR 1.18, 95% CI 0.98 to 1.41; p=0.08, per IQR increase) compared with participants with either no self-reported AMD or those with non-visually significant self-reported AMD, although it was not statistically significant. None of the other air pollutants were statistically significant with visually significant self-reported AMD. In the sensitivity analysis, we have also additionally adjusted for smoking pack years and there was a borderline significant association between $PM_{2.5}$ and self-reported AMD (OR 1.07, 95% CI 0.99 to 1.16; p=0.07, per IQR increase).

DISCUSSION

In this large study of UKBB participants, we have identified novel associations between ambient outdoor air pollutant levels at participants' residential addresses with self-reported AMD, and also with retinal structure (including thickness of photoreceptor and RPE layers on OCT imaging).

Our results showed that greater ambient $PM_{2.5}$ exposure was associated with increased odds of AMD and corresponding retinal thicknesses (specifically photoreceptor sublayer and RPE). No such significant associations were observed for PM_{coarse}. This may be explained by differences in the sites of deposition in the respiratory tract and the sources and chemical composition for these different-sized PM.[26] PM_{coarse} are primarily produced from mechanical grinding, windblown dust and agricultural activities, and mainly deposit in the upper and larger airways. In contrast, $PM_{2.5}$ particles are mainly from combustion process and are able to reach the smaller airways and alveoli and are transmitted to the blood,[27] causing a cascade of physiological events associated with morbidity and mortality.[5 28] The deeper penetration of $PM_{2.5}$ may account for the stronger associations of $PM_{2.5}$ with self-reported AMD and structural biomarkers observed in our study.

Table 3 Association of ambient air pollution with thickness of the photoreceptor sublayers

	Multivariate regression											
	Total photoreceptor			Photoreceptor synaptic region			Photoreceptor inner segment			Photoreceptor outer segment		
	β	(95% CI)	P value	β	(95% CI)	P value	β	(95% CI)	P value	β	(95% CI)	P value
Air pollution factors												
$PM_{2.5}$ (μg/m^3)	−0.07	(−0.16 to 0.02)	0.15	−0.16	(−0.23 to 0.09)	**2.0×10^{-5}**	0.04	(0.02 to 0.06)	**0.001**	0.05	(0.003 to 0.10)	0.04
$PM_{2.5}$ absorbance (μg/m^3)	0.06	(−0.03 to 0.14)	0.22	−0.10	(−0.17 to 0.03)	0.004	0.04	(0.02 to 0.06)	**2.0×10^{-4}**	0.12	(0.07 to 0.17)	**8.7×10^{-7}**
PM_{coarse} (μg/m^3)	−0.04	(−0.11 to 0.02)	0.18	−0.03	(−0.08 to 0.02)	0.21	−0.008	(−0.02 to 0.007)	0.32	−0.003	(−0.04 to 0.03)	0.85
PM_{10} (μg/m^3)	0.04	(−0.06 to 0.14)	0.47	−0.05	(−0.13 to 0.03)	0.24	−0.002	(−0.01 to 0.007)	0.63	0.09	(0.04 to 0.15)	**0.001**
NO_2 (μg/m^3)	0.15	(0.04 to 0.26)	0.004	−0.06	(−0.14 to 0.03)	0.19	0.04	(0.02 to 0.07)	**0.001**	0.17	(0.11 to 0.22)	**1.1×10^{-8}**
NO_x (μg/m^3)	−0.02	(−0.09 to 0.06)	0.63	−0.10	(−0.16 to 0.04)	**0.001**	0.03	(0.008 to 0.04)	0.004	0.05	(0.01 to 0.09)	0.009

The β coefficients represent per IQR increase in exposure variable.
Values are adjusted for age, sex, race, Townsend deprivation index, BMI, smoking status and refractive error.
Bold values denote statistical significance at P<0.002 level after Bonferroni correction.
BMI, body mass index; NO_2, nitrogen dioxide; NO_x, nitrogen oxide; PM, particulate matter; PM_{10}, PM <10 μg/m^3; $PM_{2.5}$, PM <2.5 μg/m^3; $PM_{2.5}$ absorbance, a measurement of the blackness of $PM_{2.5}$ filter—a proxy for elemental or black carbon; PM_{coarse}, PM between 2.5 and 10 μg/m^3.

Table 4 Association of ambient air pollution with thickness of the RPE layer

	Multivariate regression	
	RPE	
	β (95% CI)	P value
Air pollution factors		
$PM_{2.5}$ (μg/m^3)	−0.13 (−0.21 to −0.05)	**0.002**
$PM_{2.5}$ absorbance (μg/m^3)	−0.09 (−0.17 to −0.008)	**0.03**
PM_{coarse} (μg/m^3)	−0.02 (−0.08 to 0.04)	0.50
PM_{10} (μg/m^3)	−0.12 (−0.21 to −0.02)	**0.01**
NO_2 (μg/m^3)	−0.12 (−0.21 to −0.02)	**0.01**
NO_x (μg/m^3)	−0.05 (−0.12 to 0.02)	0.17

The β coefficients represent per IQR increase in exposure variable.
Values are adjusted for age, sex, race, Townsend deprivation index, BMI, smoking status and refractive error.
Bold values denote statistical significance at P<0.05 level.
BMI, body mass index; NO_2, nitrogen dioxide; NO_x, nitrogen oxide; PM_{10}, particulate matter less than 10 μm in aerodynamic diameter; $PM_{2.5}$, particulate matter less than 2.5 μm in aerodynamic diameter; $PM_{2.5}$ ab, ($PM_{2.5}$ absorbance) a measurement of the blackness of $PM_{2.5}$ filter—a proxy for elemental or black carbon; PM_{coarse}, particulate matter between 2.5 μm to 10 μm in aerodynamic diameter; RPE, retinal pigment epithelium.;

NO_2 is a product of combustion, primarily from traffic and industrial sources, and one of the most notable ambient air pollutants associated with health effects.[29 30] Similarly, NO_x is produced from the reaction of nitrogen and oxygen gases in the air during combustion.[31] NO_x contributes to the formation of fine particles and ground level ozone. $PM_{2.5}$ absorbance, a measurement of the blackness of $PM_{2.5}$ filter—a proxy for elemental or black carbon, is also an indicator of combustion particles. Since the major source of NO_2, NO_x and $PM_{2.5}$ absorbance is from combustion particles, it may explain the similar associations observed between these air pollutants with the retinal structures. A recent longitudinal population-based study using data from the Taiwan National Health Insurance Programme between years 2000 and 2010 included 39 819 AMD-free participants, with 1442 participants developing AMD during the 11 year follow-up. AMD status was defined via International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). Compared with participants in the lowest exposure quartile, those in the highest quartile of NO_2 and carbon monoxide (CO) had increased risk of self-reported AMD (NO_2: HR=1.91, 95% CI 1.64 to 2.23, p<0.001 and CO: HR=1.84, 95% CI 1.50 to 2.15, p<0.001, respectively).[8] The difference in findings between ours and the Taiwanese study may be related to the study population, definition and proportion of AMD cases, type and method of estimating the exposure of air pollutants and type of covariates adjusted in the multivariable models. Compared with our study, the Taiwan study included slightly older participants (mean=62 years vs 56 years), had a slightly higher proportion of AMD (3.6% vs 1.1%) and estimated a smaller number of air pollutants (two air pollutants including NO_2 and CO vs six air pollutants). In addition, the participant's living area was defined based on the treatment venue for acute upper respiratory tract infection in the Taiwan study. The effect of pollution on retinal structure associated with AMD were not examined in the Taiwan study.

Ambient air pollution could plausibly be associated with AMD through oxidative stress or inflammation. Oxidative damage induces many adverse biological effects including lipid, protein, DNA oxidation, initiation of proinflammatory processes[28] and RPE apoptosis.[32] Atrophic or 'dry' AMD, also known as geographic atrophy is by degeneration of RPE cells, followed by loss of photoreceptor cells and choriocapillaris.[33] Since the RPE is involved in the turnover of photoreceptor outer segments, RPE dysfunction may lead to thickening of photoreceptor outer segments.

Our results showed that $PM_{2.5}$ and NO_x were associated with a thinner photoreceptor synaptic region. This is in agreement with a reduction in the number of photoreceptor synaptic terminals overlying drusen in AMD.[34] In contrast, $PM_{2.5}$, $PM_{2.5}$ absorbance and NO_2 were associated with thicker photoreceptor inner segment, while $PM_{2.5}$ absorbance, NO_2 and PM_{10} were associated with thicker photoreceptor outer segment. As mitochondria are prominent in photoreceptor inner segments, oxidative stress may induce mitochondrial swelling,[35] leading to a slight thickening in the photoreceptor inner segment. Abnormalities in the photoreceptor inner and outer segments have also been reported in retinal toxicity associated with hydroxychloroquine.[36] Our study did not show an association between air pollution and average total photoreceptor layer thickness, which may be explained by thinning of the synaptic region cancelling out the thickening of the inner/outer segments. In a study by Schuman *et al*, although the authors reported decreased photoreceptor thickness over drusen, there was a lack of widespread photoreceptor loss.[37] Hence, it is possible that there was focal loss of the photoreceptor thickness in our study but an overall loss of photoreceptor layer was not observed.

Cigarette smoking may also contribute to particulate matter air pollution.[38] Because of the previously recorded, very strong link between AMD and smoking,[39] and the plausible link between smoking and particulate air pollution, we examined the association between smoking status of participants with self-reported AMD and did not observe a significant association. This suggests that the relationship between $PM_{2.5}$ and self-reported AMD is not mediated by cigarette smoke. The prevalence of late AMD standardised to the UK population aged 50 years or more and 65 years or more was 2.4% and 4.8%, respectively. Prevalence of geographic atrophy was 1.3% and 2.5% for the respective age groups.[40] The European Eye Epidemiology (E3) Consortium performed a meta-analysis and showed that overall prevalence was 13.2% for early AMD and 3.0% for late AMD for people aged 70 years or older.[41] Compared with the E3 Consortium, participants in UKBB are slightly younger and include a healthier population than the rest of UK population.[42] The self-reported AMD cases in our study may represent AMD in the early stages. We compared the VA between participants with and without self-reported AMD. Among those with self-reported AMD, there was a higher proportion of participants with visual impairment (VA worse than LogMAR 0.3) compared with those without visual impairment (1.8% vs 1.0%; p<0.001). The proportion of self-reported AMD (1.1%) in our study may have been underestimated and it is likely that the risk estimates may have been underestimated.

In addition to the increased risk of AMD associated with higher exposure to air pollution in the Taiwanese study, other studies in the UKBB[43] and China[7] have reported increased odds of glaucoma with higher exposure to $PM_{2.5}$. In the UKBB study of 111 370 participants, greater exposure to $PM_{2.5}$ was associated with both self-reported glaucoma and retinal structures associated with the disease.[43] Wang *et al* reported that higher average levels of $PM_{2.5}$ was associated with higher burden of glaucoma disability, using national level data.[7] The New England-based Normative Aging Study showed an association between black carbon exposure with IOP that was greater in individuals with a high oxidative stress allelic score.[44] Taken together, our results support published findings of increased risk of eye diseases or association with retinal structures in participants with higher

exposure to ambient air pollution. As certain groups of individuals including people with diabetes mellitus[45] or hypertension[24] may have increased risk of AMD, it will be useful to explore if these groups of individuals are at greater risk of eye disease when exposed to air pollution in future analysis.

Strength of this study include its large sample size and the highly accurate and reproducible measurements of the OCT retinal thickness. Limitations of the study include the UKBB is a volunteer cohort, and participants are likely healthier than the general population. Outdoor air pollution was estimated using the participants' home address and do not explain all variation in indoor concentrations. As most individuals spend a large amount of time indoors, individual exposure to all forms of air pollution may differ from that indicated by the ambient outdoor figures. This is most likely to be non-differential between cases and controls and will therefore skew the associations towards the null. Another limitation of this analysis was the use of self-report as the sole determinant of AMD status rather than incorporating a qualitative analysis of the colour fundus photographs and spectral-domain optical coherence tomography (SD-OCT) imaging, though we did carry out masked grading of retinal imaging in a proportion of participants. This may result in non-differential misclassification bias and most likely bias the estimates towards the null. Although we applied strict automated quality control criteria including a manual check of SD-OCT scans with high and low outlying layer thickness,[17] it was not practical to manually check all OCT scans for segmentation accuracy. Selection bias may exist: out of the 115 954 participants with data on self-reported AMD, 52 602 participants had measurements on outer retinal layers. However, the baseline characteristics (table 1) across the two AMD-associated outcome groups appear to be similar. The cross-sectional design of our study limits the ability to determine the causality between ambient air pollution and AMD-associated outcomes. Further research is needed to probe the relationship between prior air pollution exposure and risk of incident disease.

In this large study of an older middle-aged UK population, higher $PM_{2.5}$ exposure was associated with a higher risk of self-reported AMD, while all pollutants except PM_{coarse} were associated with changes in retinal structure (in either photoreceptor sublayer and/or RPE layer thickness). Overall, our findings suggest that ambient air pollution, especially fine PM or those of combustion-related particles, may affect AMD risk. It is possible that the structural features observed may be unrelated to AMD, but associated with pollution-induced retinal toxicity. However, the direction of the relationships between air pollution and both AMD and associated retinal layer thicknesses indicate higher exposure to air pollution may make the cells more vulnerable and increase the risk of AMD. Our findings add to the growing evidence of the damaging effects of ambient air pollution, even in the setting of relative low exposure of ambient air pollution. As UKBB is a very large prospective cohort, we anticipate being able to explore the effect of particulate matter on future risk of AMD. Further studies examining both outdoor and indoor ambient air pollution estimates on AMD and outer retinal structures may help to substantiate our findings and understand the implications for retinal disease associated with ageing. If our findings are replicated, this would support the view that air pollution is an important modifiable risk factor for AMD.

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Contributors SYLC had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. PJF and PJP led conception and design of the study. SYLC, PJF and PJP contributed to the data analyses, data interpretation and wrote the draft of the manuscript. All authors reviewed the results, read and critically revised the manuscript. All authors approved the final manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Competing interests CR reports employment by Topcon Healthcare Solutions, Inc, outside the submitted work. PJF reports personal fees from Allergan, Carl Zeiss, Google/DeepMind and Santen, a grant from Alcon, outside the submitted work. PJP reports grants from Topcon Inc, outside the submitted work.

Patient and public involvement statement Not commissioned; externally peer reviewed.

Patient consent for publication Not required.

Ethics approval The North West Multi-centre Research Ethics Committee approved the study (reference no., 06/MRE08/65), in accordance with the tenets of the Declaration of Helsinki. Detailed information about the study is available at the UK Biobank web site (www.ukbiobank.ac.uk).

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Data availability statement Researchers wishing to access UK Biobank data can register and apply at https://www.ukbiobank.ac.uk/.

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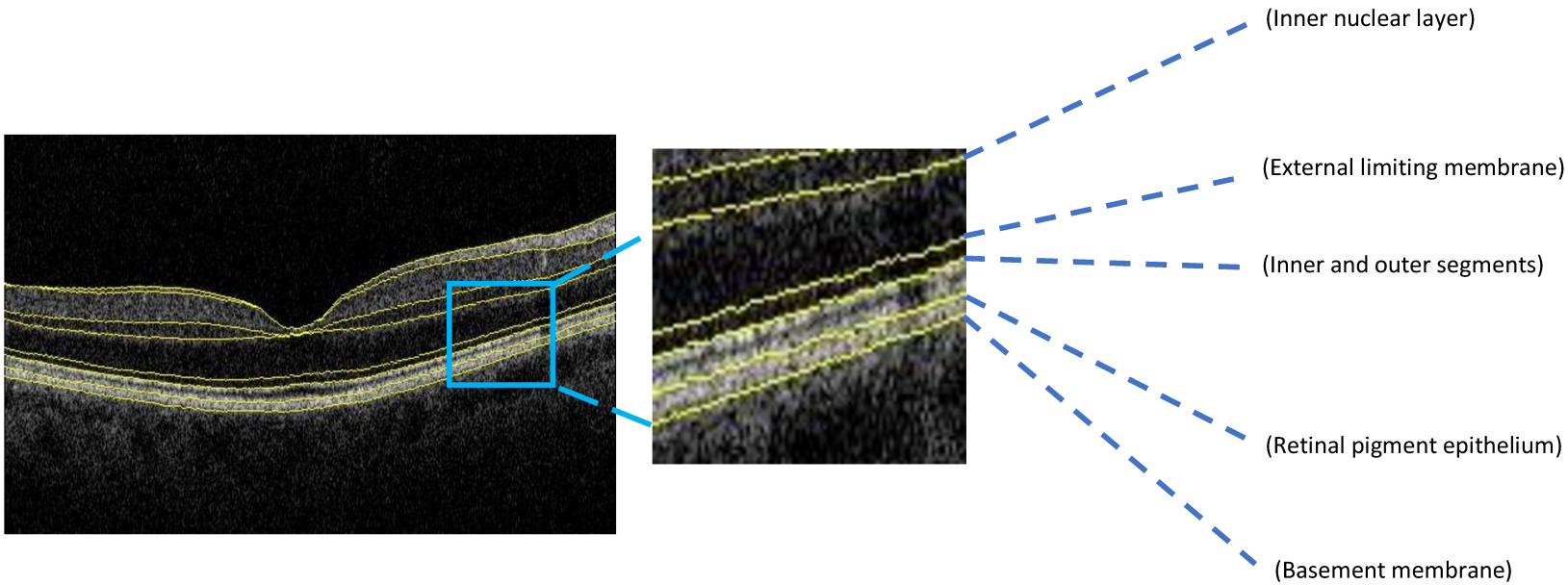


Supplementary Figure 1. Spectral-domain optical coherence tomography images with schematic showing representative of total photoreceptor (Inner nuclear layer–Retinal pigment epithelium); photoreceptor synaptic region (Inner nuclear layer- External limiting membrane); photoreceptor inner segment (External limiting membrane-Inner and outer segments); photoreceptor outer segment (Inner and outer segments-Retinal pigment epithelium) and retinal pigment epithelium (Retinal pigment epithelium-Basement membrane).

Supplementary Table 1. Comparison of characteristics between participants with self-reported AMD and without self-reported AMD

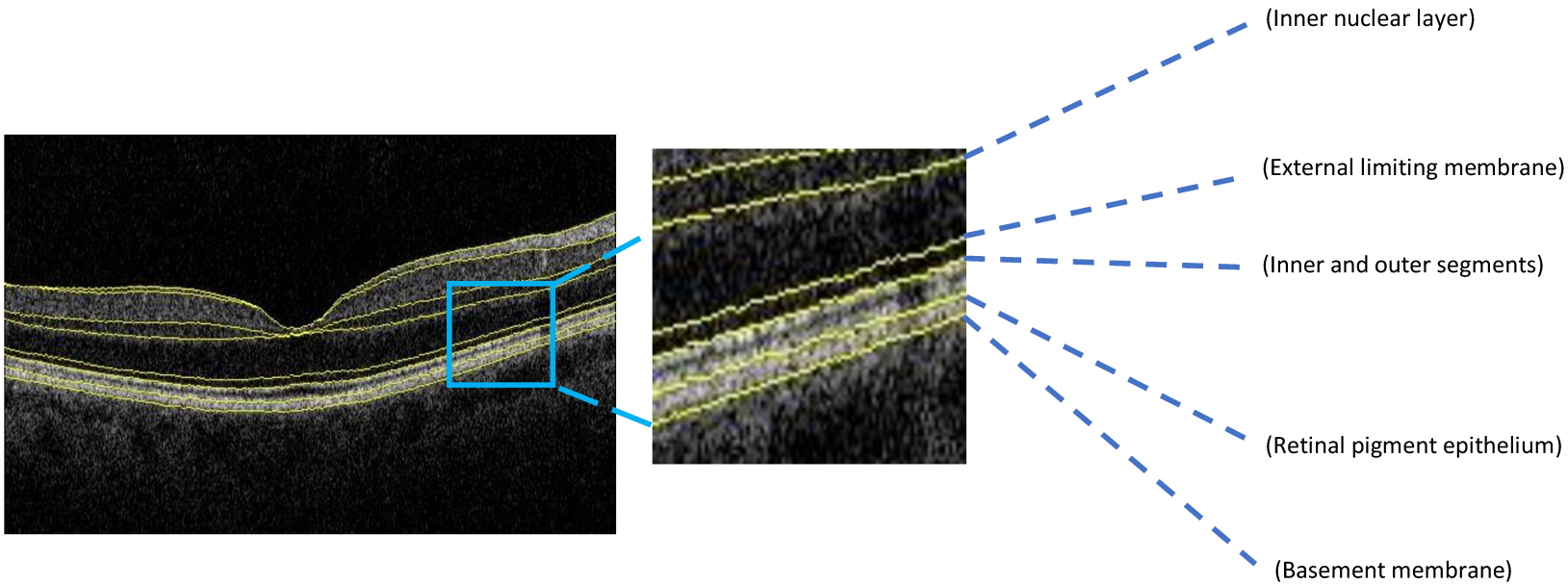
	No self-reported AMD (N=114,668)	Self-reported AMD (N=1,286)	P-value
Sociodemographic factors			
Age	56.8 (8.1)	61.6 (5.9)	<0.001
Sex			
Men	52,692 (46.0%)	526 (40.9%)	
Women	61,976 (54.0%)	760 (59.1%)	<0.001
Race			
White	104,269 (90.9%)	1,196 (93.0%)	
Non-white	10,399 (9.1%)	90 (7.0%)	0.01
Townsend deprivation index	-1.1 (3.0)	-1.5 (2.9)	<0.001
Clinical factors			
Body mass index (kg/m^2)	27.2 (4.5)	27.4 (4.3)	0.18
Smoking status			
Never	63,879 (55.7%)	675 (52.5%)	
Previous	39,714 (34.6%)	510 (39.7%)	
Current	11,075 (9.7%)	101 (7.8%)	<0.001
Spherical equivalent (diopters)	-0.08 (2.1)	-0.03 (2.3)	0.40

AMD status was classified based on self-reporting and hospital episode statistics data (ICD10).
Numbers are mean (SD) for continuous variables and no. (%) for categorical variables.
AMD= Age-related macular degeneration

Supplementary Table 2. Distribution of $PM_{2.5}$, PM_{coarse}, PM_{10}, NO_2 and NO_X of participants with availability of data on self-reported AMD and retinal layers

	Self-reported AMD (N=115,954)		Retinal layers (N=52,602)	
	Median (IQR)	Range	Median (IQR)	Range
$PM_{2.5}$ (μg/m^3)	9.91 (1.07)	(8.17, 19.69)	9.88 (1.12)	(8.17, 19.69)
$PM_{2.5}$ absorbance (μg/m^3)	1.22 (0.33)	(0.83, 4.05)	1.22 (0.33)	(0.83, 3.71)
PM_{coarse} (μg/m^3)	6.19 (0.75)	(5.57, 12.82)	6.21 (0.77)	(5.57, 11.30)
PM_{10} (μg/m^3)	19.37 (2.67)	(13.04, 29.67)	19.33 (2.77)	(13.38, 29.30)
Nitrogen dioxide (NO_2) (μg/m^3)	31.75 (12.08)	(9.44, 102.75)	31.25 (12.63)	(9.44, 86.65)
Nitrogen oxide (NO_X) (μg/m^3)	43.66 (14.38)	(19.74, 263.96)	43.17 (14.97)	(19.74, 263.96)

AMD = Age-related macular degeneration, IQR = Interquartile range, $PM_{2.5}$= Particular matter (aerodynamic diameter of less than 2.5μm), $PM_{2.5}$ absorbance= Particulate matter (a measurement of the blackness of $PM_{2.5}$ filter – a proxy for elemental or black carbon), PM_{coarse} = Particulate matter (aerodynamic diameter between 2.5 and 10μm, PM_{10}= Particulate matter (aerodynamic diameter of less than 10μm), NO2= Nitrogen dioxide, NO_x= Nitrogen oxide



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