The Relationship Between Ambient Atmospheric Fine Particulate Matter ($PM_{2.5}$) and Glaucoma in a Large Community Cohort

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See the Appendix for the members of the UK Biobank Eye and Vision Consortium.

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Purpose. Glaucoma is more common in urban populations than in others. Ninety percent of the world's population are exposed to air pollution above World Health Organization (WHO) recommended limits. Few studies have examined the association between air pollution and glaucoma.

Methods. Questionnaire data, ophthalmic measures, and ambient residential area air quality data for 111,370 UK Biobank participants were analyzed. Particulate matter with an aerodynamic diameter < 2.5 µm ($PM_{2.5}$) was selected as the air quality exposure of interest. Eye measures included self-reported glaucoma, intraocular pressure (IOP), and average thickness of macular ganglion cell–inner plexiform layer (GCIPL) across nine Early Treatment Diabetic Retinopathy Study (ETDRS) retinal subfields as obtained from spectral-domain optical coherence tomography. We examined the associations of $PM_{2.5}$ concentration with self-reported glaucoma, IOP, and GCIPL.

Results. Participants resident in areas with higher $PM_{2.5}$ concentration were more likely to report a diagnosis of glaucoma (odds ratio = 1.06, 95% confidence interval [CI] = 1.01–1.12, per interquartile range [IQR] increase $P = 0.02$). Higher $PM_{2.5}$ concentration was also associated with thinner GCIPL ($\beta = -0.56$ µm, 95% CI = −0.63 to −0.49, per IQR increase, $P = 1.2 \times 10^{-53}$). A dose–response relationship was observed between higher levels of $PM_{2.5}$ and thinner GCIPL ($P < 0.001$). There was no clinically relevant relationship between $PM_{2.5}$ concentration and IOP.

Conclusions. Greater exposure to $PM_{2.5}$ is associated with both self-reported glaucoma and adverse structural characteristics of the disease. The absence of an association between $PM_{2.5}$ and IOP suggests the relationship may occur through a non–pressure-dependent mechanism, possibly neurotoxic and/or vascular effects.

Keywords: glaucoma, GCIPL, optical coherence tomography, intraocular pressure, fine particulate matter

The World Health Organization (WHO) ranks exposure to ambient air pollution as one of the main contributors to burden of global disease.[1,2] Air pollution is associated with pulmonary and cardiovascular disease, as well as central nervous system conditions such as Alzheimer's disease (AD), Parkinson's disease, and stroke.[2,3] Among all air pollutants, long-term exposure to particulate matter ≤2.5 µm in aerodynamic diameter ($PM_{2.5}$) is one of the strongest and most consistent predictors of mortality.[2]

Glaucoma is a common, age-related degenerative neuropathy and a leading cause of global blindness. Raised intraocular pressure (IOP) is the major modifiable risk factor for glaucoma and is sufficient but not necessary to cause the disease.[4] Glaucoma is a complex disease with polygenic heritability, with over 100 single nucleotide polymorphisms (SNPs) accounting for approximately 26% of the risk of disease among UK residents.[5] However, the precise etiological mechanisms involved in the development of glaucoma remain obscure. People living in urban areas are reported to be 50% more likely to have glaucoma than those rural areas, making air pollution a plausible risk factor for glaucoma.[6] Very recently, an association between glaucoma disability and national levels of $PM_{2.5}$ has been proposed.[7] Diseases of the cardiovascular and central nervous systems and glaucoma share some pathophysiological mechanisms including inflammation and increased oxidative stress.[8,9] The advent of spectral-domain optical coherence tomography (SD OCT) now allows precise, reproducible in vivo quantification of the thickness of individual retinal layers. Of

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relevance to this analysis, the measurement of macular ganglion cell–inner plexiform layer (GCIPL)[10] thickness is useful in the detection of glaucoma.[11]

If air pollution shows an adverse association with glaucoma, this may offer a novel, potentially modifiable risk factor, and would add weight to campaigns to reduce particulate air pollutants. We used data from the UK Biobank, a large, community-based cohort study, to evaluate the relationship between $PM_{2.5}$ microparticulate air pollutants, self-reported glaucoma, IOP, and macular inner retinal anatomical features associated with glaucoma.

Methods

Study Population

UK Biobank is a very large community-based cohort of 502,656 UK residents registered with the National Health Service (NHS) and aged 40 to 69 years at enrollment. Baseline examinations were carried out between 2006 and 2010 at 22 study assessment centers. This research used data from the UK Biobank Resource, under data access request number 2112 and 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 website (www.ukbiobank.ac.uk). 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 provided online in the public domain. In brief, participants answered a wide-ranging touch-screen questionnaire covering demographic, socioeconomic, lifestyle, and ocular disease information. Glaucoma status was determined according to those who answered yes to "Has a doctor ever told you that you have glaucoma?" Physical measures included blood pressure, height, and weight.[12]

Air Pollution Measurement

The air pollution measures were provided by the Small Area Health Statistics Unit (http://www.sahsu.org/; in the public domain) as part of the BioSHaRE-EU Environmental Determinants of Health Project (http://www.bioshare.eu/; in the public domain). The annual average concentration of $PM_{2.5}$ was calculated in 2010 using a land use regression (LUR) model developed by the European Study of Cohorts for Air Pollution Effects (ESCAPE) project (http://www.escapeproject.eu/; in the public domain).[13] Based on a range of Geographic Information System (GIS)–derived predictor variables such as traffic intensity, population, and land use, LUR models calculate the spatial variation of annual average air pollution concentration at participants' residential addresses given at baseline visit. The LUR model is a validated tool for modeling airborne pollutants. Results from the ESCAPE project that modeled the spatial variation of $PM_{2.5}$ in 20 European study areas reported a median explained variance of 71% (R-squared, range = 35%–94%).[13] Previous epidemiologic studies have used LUR models for estimating outdoor air pollution concentrations at the home addresses of cohort subjects.[14,15]

Ocular Measurements

Ocular measures were conducted in six assessment centers by trained staff following standard operating procedures; detailed methods have been published.[16] Refractive error was measured with an autorefractor (RC5000; Tomey, Nagoya, Japan) and spherical equivalent refraction (SER) was calculated as sphere power plus half cylinder power. IOP was measured with the Ocular Response Analyzer (ORA; Reichert, Philadelphia, PA, USA) and included both corneal-compensated IOP (IOP_{cc}) and Goldmann-correlated intraocular pressure (IOP_g) in order to examine the influence that corneal biomechanical characteristics might have on IOP measures (Luce D. *IOVS* 2006;47:ARVO E-Abstract 2266).[17] For participants using IOP-lowering medication ($n = 990$, 0.9%), we imputed pretreatment IOP by dividing by 0.7, based on the mean IOP reduction achieved by medication.[18] This approach has been used successfully in genome-wide association studies of IOP.[5,19]

Spectral-Domain Optical Coherence Tomography Imaging Protocol

SD-OCT imaging was performed using the Topcon 3D OCT-1000 Mk2 (Topcon, Inc., Oakland, NJ, USA) in 2009 and 2010. Image acquisition was performed in a dark room, without pupillary dilation using the 3D macular volume scan (512 horizontal A-scans per B-scan; 128 B-scans in a 6×6-mm raster pattern). All SD-OCT images were stored as .fds image files with no prior analysis of macular thickness. The Topcon Advanced Boundary Segmentation algorithm (Version 1.6.1.1)[20] was used to segment the thickness of the GCIPL (ganglion cell layer [GCL] + inner plexiform layer [IPL]) in the macula across nine retinal subfields in a 6-mm-diameter circle centered at the true fovea location, as defined by the Early Treatment Diabetic Retinopathy Study (ETDRS).[21] GCL is composed of ganglion cell bodies, while IPL is composed of retinal ganglion cell dendrites. Average thickness of GCIPL across all nine ETDRS zones was used in this analysis.

Inclusion and Exclusion Criteria

As we wanted to examine three distinct markers of glaucoma status, we chose a uniform set of exclusion criteria that were applied in the analysis of self-reported glaucoma, IOP, and GCIPL thickness. These comprised participants who withdrew consent; those who had a history of corneal graft surgery or refractive surgery; those who self-reported ocular conditions including diabetes-related eye disease, age-related macular degeneration, eye injury resulting in vision loss or other serious eye conditions; and high SER (< -6 diopters [D] or $> +6$ D). These participants were excluded because of the well-recognized impact these conditions have on retinal layer thickness[22] or IOP measurements.[23] Additionally, in sensitivity analyses, we applied strict quality control criteria to exclude images of poor scan quality or segmentation failure.[24] These included poor SD OCT signal strength,[24] image quality score < 45, poor centration certainty, or poor segmentation certainty, when examining the association of ambient air pollution on GCIPL.[25]

Statistical Analysis

For this analysis, if both eyes of a patient were eligible for inclusion, one eye was randomly selected using STATA software (version 13; StataCorp LP, College Station, TX, USA). We examined the baseline characteristics of participants gathered over the period 2006 to 2010. Descriptive statistics for continuous variables are presented as means (standard deviation [SD]), whereas categorical variables are presented as numbers (percentage). The distribution of $PM_{2.5}$ was described as median (interquartile range [IQR]). We used multivariate regression models to examine the associations between air pollutant ($PM_{2.5}$) (independent variable) with self-reported glaucoma, IOP_{cc}, IOP_g, and thickness of GCIPL (dependent variables), adjusting for covariates using a forward stepwise model. Covariates included age, sex, race, Townsend depriva-

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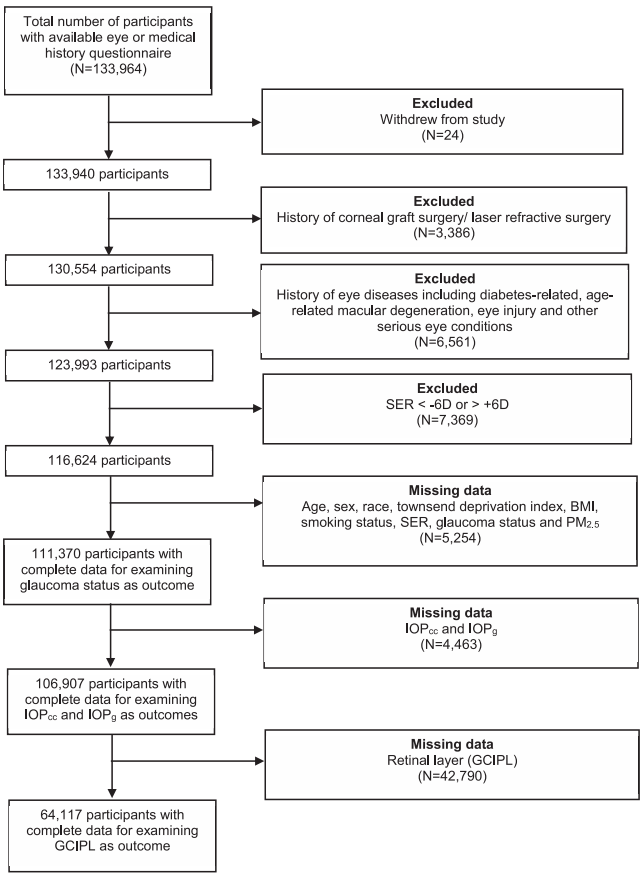

Figure. Flowchart of participants included in the study.

tion index, body mass index (BMI), smoking status, and SER. Systolic blood pressure (SBP) was additionally adjusted if IOP_{cc}/IOP_g were the outcome variables as blood pressure is related to both $PM_{2.5}$[26] and IOP.[27] IOP_{cc} was additionally adjusted if GCIPL was the outcome variable, in view of its relationship with retinal ganglion cell layer thickness, and as an etiological factor for glaucoma.[28] The effect estimates represent the change in self-reported glaucoma, IOP_{cc}/IOP_g, and GCIPL variables per IQR and quartile increment in $PM_{2.5}$ concentration.

Results

Of the 133,964 participants who completed ocular and medical questionnaires, 24 participants withdrew their consent. We further removed 17,316 participants according to the exclusion criteria (Figure), leaving data on 116,624 participants. There were complete data (age, sex, race, Townsend deprivation index, BMI, smoking status, refractive error, self-reported glaucoma, and $PM_{2.5}$) for 111,370 participants. Of the 111,730 participants, there were complete IOP measurements for 106,907 participants. The mean (SD) of IOP_{cc} and IOP_g were 16.0 mm Hg (3.7 mm Hg) and 15.8 mm Hg (3.6 mm Hg), respectively. Of the 106,907, there were complete GCIPL measures for 64,117 participants. The reason for this large number of exclusions for retinal layer analysis was that OCT imaging was introduced after the start of the UK Biobank, preventing imaging of the entire cohort.

The characteristics of participants included in the study are shown in Table 1. Participants for the three outcomes had similar baseline characteristics such as age, sex, race, Townsend deprivation index, BMI, smoking status, and SBP. Compared to participants with the outcomes of self-reported glaucoma and IOP, those eligible for analysis of GCIPL thickness were slightly more myopic (0.04 D difference). The distributions of ambient $PM_{2.5}$ levels for each outcome-specific group are shown in Table 2. The mean GCIPL (SD) was 72.3 μm (7.2 μm). Of the 111,370 participants, 2040 (1.8%) reported being diagnosed with glaucoma. For each IQR of $PM_{2.5}$, there was a 6% (95% confidence interval [CI] = 1.01–1.12; $P = 0.02$) higher odds of self-reported glaucoma. There was no evidence of an association between smoking status and self-reported glaucoma.

Table 3 presents the relationship between $PM_{2.5}$ concentration with IOP_{cc} and IOP_g after adjustment for all covariates. A very small per IQR increase in $PM_{2.5}$ concentration increased the IOP_{cc} and IOP_g by 0.03 and 0.04 mm Hg, respectively. Compared with those in the lowest $PM_{2.5}$ concentration quartile, those in the highest quartile had a minimally higher IOP_{cc} ($\beta = 0.07$ mm Hg, $P = 0.04$) and IOP_g ($\beta = 0.13$ mm Hg, P

Table 1. Baseline Characteristics of Participants Included in the Study With Outcomes (Self-Reported Glaucoma, IOP, or GCIPL)

Characteristics	Mean (SD), *n* (%)		
	Self-Reported Glaucoma	IOP	GCIPL
Number of participants	111,370	106,907	64,117
Age, y	56.8 (8.0)	56.8 (8.0)	56.7 (8.0)
Sex			
Men	51,384 (46.1)	49,420 (46.2)	29,893 (46.6)
Women	59,986 (53.9)	57,487 (53.8)	34,224 (53.4)
Race			
White	101,228 (90.9)	97,268 (91.0)	59,087 (92.1)
Nonwhite	10,142 (9.1)	9,639 (9.0)	5,030 (7.9)
Townsend deprivation index*	−1.1 (3.0)	−1.1 (3.0)	−1.2 (2.9)
Body mass index, kg/m^2	27.3 (4.5)	27.3 (4.5)	27.2 (4.4)
Smoking status			
Never	62,046 (55.7)	59,468 (55.6)	35,834 (55.9)
Former	38,560 (34.6)	37,158 (34.8)	22,462 (35.0)
Current	10,764 (9.7)	10,281 (9.6)	5.821 (9.1)
Systolic blood pressure, mm Hg	139.9 (19.5)	139.9 (19.5)	139.7 (19.5)
Spherical equivalent refraction, D	−0.07 (2.1)	−0.08 (2.1)	−0.11 (2.1)

* Townsend deprivation index is an indication of the socioeconomic status; the higher and more positive the index, the more deprived an area.

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Table 2. Distribution of $PM_{2.5}$ ($\mu g/m^3$) for Each Specific Outcome Including Self-Reported Glaucoma, IOP, or GCIPL

Study Sample	Min	5%	25%	50%	75%	95%	Max	Mean (SD)	IQR
Within the self-reported glaucoma dataset	8.17	8.50	9.38	9.91	10.45	11.45	19.69	9.95 (0.90)	1.07
Within the IOP dataset	8.17	8.50	9.38	9.91	10.44	11.45	19.69	9.95 (0.90)	1.06
Within the GCIPL dataset	8.17	8.42	9.32	9.88	10.44	11.47	19.69	9.92 (0.93)	1.12

Max, maximum; Min, minimum.

$= 7.0 \times 10^{-5}$). Table 4 shows the association between $PM_{2.5}$ exposure and overall thickness of GC-IPL. Higher $PM_{2.5}$ concentration (per IQR increase) was associated with thinner GC-IPL ($\beta = -0.56$ µm, $P = 1.2 \times 10^{-53}$) (Table 4). There was a clear exposure–response relationship between higher levels of ambient $PM_{2.5}$ and thinner GCIPL ($P < 0.001$). Exposure to higher $PM_{2.5}$ was associated with thinner GCIPL thickness in the inner superior ($\beta = -0.65$ µm, 95% CI: −0.76, −0.53; $P = 7.4 \times 10^{-27}$) and inner inferior ($\beta = -0.61$ µm, 95% CI: −0.72, −0.50; $P = 1.8 \times 10^{-27}$) ETDRS subfields. The mean GCIPL (SD) thickness was significantly less in the inner inferior subfield among those with self-reported glaucoma compared to those without disease (83.4 µm [14.6 µm] vs. 92.2 µm [10.7 µm]; $P < 0.001$). Similarly, the inner superior subfield was also thinner among participants with self-reported glaucoma compared to those without (84.1 µm [14.8 µm] vs. 92.2 µm [11.5 µm]; $P < 0.001$). We observed a marginally lower mean GCIPL in the lower inner subfield compared with the upper inner subfield (83.4 µm [14.6 µm] vs. 84.1 µm [14.8 µm], $P = 0.027$) in people with self-reported glaucoma. Sensitivity analyses including only the participants with good SD OCT signal and image quality showed similar results ($n = 49{,}114$): Higher $PM_{2.5}$ concentration (per IQR increase) was associated with thinner GCIPL ($\beta = -0.50$ µm, 95% CI: −0.57, −0.42; $P = 1.3 \times 10^{-40}$).

Discussion

We have identified a novel association between greater exposure to ambient $PM_{2.5}$ and increased odds of self-reported glaucoma. We suggest that this is a meaningful association based on our finding that inner retinal changes, as seen in glaucoma, are greater in those exposed to higher levels of $PM_{2.5}$. Consistent with a previous report,[28,29] we found a subtle relationship between higher IOP and greater ambient $PM_{2.5}$, although the effect was too small to explain the higher risk of glaucoma associated with $PM_{2.5}$ exposure. On the basis that a 1 mm Hg change in IOP alters the risk of glaucoma by 10%,[30] we would expect changes in IOP 10-fold higher than those observed, if the glaucoma risk was solely mediated by raised IOP. These results suggest that exposure to $PM_{2.5}$ air pollutants may be an independent risk factor for glaucoma, possibly mediated by a neurotoxic or vascular mechanism rather than by elevation of IOP.

Air pollution exposure is associated with increased oxidative stress,[31] inflammation,[3] and hypercoagulation.[32] Exposure to polluted air has been associated with impaired cognitive function at all ages and increased risk of AD and other dementias in later life; this association is particularly notable with traffic-related pollutants.[33] Possible biological mechanisms include the provocation of oxidative stress[31] and systemic inflammatory responses,[3] disruption of the blood–brain barrier, precipitation of Aβ peptides, and microglial activation.[34,35] Exposure to ambient air pollution, especially $PM_{2.5}$, has been associated with higher rates of cardiovascular morbidity and mortality,[26,36] possibly due to its impact on microvascular function[37] as $PM_{2.5}$ can impair microvascular endothelium-dependent dilation.[38] The Multi-Ethnic Study of Atherosclerosis (MESA) study found that higher exposure to $PM_{2.5}$ was associated with narrower retinal arteriolar diameters in older individuals.[39] People with narrower retinal arteriolar diameters have increased risk of myocardial infarction, stroke, and cardiovascular mortality.[40–42] Very recently, Wang et al.[7] reported that higher average levels of $PM_{2.5}$ were associated with higher burden of glaucoma disability, using national-level data. Our analysis builds considerably on their outlined results, showing an association between air pollution and disease at the level of the individual.

Although raised IOP is the cardinal modifiable risk factor for primary open-angle glaucoma (POAG), around half of glaucoma patients present with IOP within the statistically "normal" range.[43] Some patients with glaucoma continue to experience disease progression despite lowering of IOP.[30] This suggests that other mechanisms are relevant, but these have remained elusive to date. Possible pressure-independent mechanisms relevant to glaucoma include oxidative stress, altered immunity, and impaired microcirculation.[44] The New England–based Normative Aging Study identified an association between black carbon exposure with IOP that was greater in individuals with a high oxidative stress allelic score.[29] The light absorbance of $PM_{2.5}$ filter samples has been used as a proxy measure for black carbon.[45] Oxidative stress may lead to impairment of secretion

Table 3. Multivariable Linear Regression of $PM_{2.5}$ With IOP_{cc} and IOP_g*

	IOP_{cc}			IOP_g		
Particulate Matter With an Aerodynamic Diameter < 2.5 µm	**β†**	**(95% CI)**	***P* Value**	**β**	**(95% CI)**	***P* Value**
Per IQR, 1.06 $\mu g/m^3$ increase	0.03	(0.0003–0.06)	0.05	0.04	(0.02–0.07)	0.0004
Quartiles of $PM_{2.5}$, $\mu g/m^3$						
Q1, 8.17–9.38	Ref			Ref		
Q2, 9.39–9.91	−0.02	(−0.08, 0.05)	0.62	0.04	(−0.02, 0.10)	0.22
Q3, 9.92–10.45	−0.01	(−0.07, 0.05)	0.73	0.06	(−0.004, 0.13)	0.06
Q4, 10.46–19.69	0.07	(0.005–0.14)	0.04	0.13	(0.07–0.20)	7.0×10^{-5}

* Initial covariates entered into stepwise forward regression model: $PM_{2.5}$, age, sex, race, Townsend index, BMI, smoking status, SER, and SBP. For outcome IOP_{cc}, the final covariates chosen by the model include age, SBP, SER, sex, smoking status, and race. For outcome IOP_g, the final covariates chosen by the model include SBP, SER, race, age, smoking status, BMI, $PM_{2.5}$, and sex. Age (years), BMI (kg/m^2), IOP_{cc} and IOP_g (mm Hg), SER (diopters), SBP (mm Hg), and $PM_{2.5}$ ($\mu g/m^3$).

† The beta coefficients (β) represent the effect size for IOP_{cc} and IOP_g per IQR (1.06 $\mu g/m^3$) increase in $PM_{2.5}$.

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Table 4. Multivariable Linear Regression of $PM_{2.5}$ With Overall Average Thickness of GCIPL*

Particulate Matter With an Aerodynamic Diameter < 2.5 μm	β†	GCIPL (95% CI)	*P* Value
Per IQR, 1.12 μg/m^3 increase	−0.56	(−0.63, −0.49)	1.2×10^{-53}
Quartiles of $PM_{2.5}$, μg/m^3			
Q1, 8.17–9.38	Ref		
Q2, 9.39–9.92	−0.18	(−0.35, −0.02)	0.03
Q3, 9.93–10.46	−0.48	(−0.65, −0.30)	6.2×10^{-8}
Q4, 10.47–19.69	−1.25	(−1.43, −1.07)	4.7×10^{-42}
P for trend			<0.001

* Initial covariates entered into stepwise forward regression model: $PM_{2.5}$, age, sex, race, Townsend deprivation index, BMI, smoking status, refractive error, and IOP_{cc}. Final covariates chosen by the model include age, SER, IOP_{cc}, $PM_{2.5}$, Townsend deprivation index, sex, BMI, smoking status. Age (years), BMI (kg/m^2), IOP_{cc} (mm Hg); SER (diopters), and $PM_{2.5}$ (μg/m^3).

† The beta coefficients (β) represent the effect size for GCIPL (μm) per IQR (1.12 μg/m^3) increase in $PM_{2.5}$.

of vasoregulatory factors from endothelial cells, namely nitric oxide (NO) and endothelin-1 (ET-1), affecting ocular vascular smooth muscle tone or endothelial dysfunction, and reducing ocular blood flow.[46]

Air pollution is the most prevalent source of environmentally induced inflammation. Neuroinflammation has been identified as a mechanism underlying glaucoma.[47] Glaucoma is an optic neuropathy characterized by degeneration of retinal ganglion cells (RGC), and previous studies have reported thinning of GCIPL in glaucoma.[48,49] GCIPL thickness has shown higher diagnostic utility than peripapillary RNFL thickness in early glaucoma and similar diagnostic ability for moderate and severe glaucoma.[50,51] Our results show that higher $PM_{2.5}$ exposure is associated with a thinner GCIPL, which may reflect structural changes related to glaucoma. Vascular mechanisms may also increase the risk of glaucoma, which is supported by the findings on the associations between glaucoma and systemic blood pressure,[52] vasospasm,[53] or diseases with vascular manifestations, such as diabetes[54] and migraine.[55] The Blue Mountains Eye Study reported that generalized retinal arteriolar narrowing was associated with POAG.[56,57] Loss of retinal ganglion cells may lead to decrease in retinal vessel diameter via the autoregulatory mechanism responding to a reduction in oxygen demand.[56]

Our results did not suggest a clinically meaningful relationship between ambient $PM_{2.5}$ with IOP_g/IOP_{cc}. From this, we infer that the effect of $PM_{2.5}$ exposure on glaucoma is not primarily mediated by IOP.[44] Corneal biomechanics influence IOP measurements, where the arrangement of collagen fibers determines the corneal elasticity, viscosity, and energy damping.[58] Compared to IOP_g, IOP_{cc} is thought to be a more accurate assessment of the "true" IOP and less affected by corneal biomechanics (Luce D. *IOVS* 2006;47:ARVO E-Abstract 2266). The effect estimate of $PM_{2.5}$ concentration (highest quartile) was greater on IOP_g compared to IOP_{cc}, suggesting that the $PM_{2.5}$ exposure may influence the connective tissue biomechanical properties of the cornea.

We used self-reported glaucoma as an outcome measure. While this is an imperfect tool to identify cases and differentiate between the different types of glaucoma, we consider it a valid measure as a recent genome-wide analysis (GWAS) found that many SNPs known to be associated with glaucoma were present in self-reported disease in UK Biobank participants.[5] In addition, the SNPs had a remarkable correlation between the effect sizes for IOP and POAG. In our cohort, 1.8% of participants self-reported a diagnosis of glaucoma. A meta-analysis showed that the global prevalence of glaucoma in Europeans aged 40 to 80 years old was 2.93%,[59] while another meta-analysis reported that the prevalence of POAG among whites was 2.1%.[60] However, as glaucoma prevalence increases exponentially with age, and is more common among men, we used age- and sex-specific rates of glaucoma from the EPIC-Norfolk Eye Study, and applied them to the age- and sex-specific numbers of participants in UK Biobank, to project the expected rate of glaucoma in our cohort. Our calculations suggested that we should see 1.6% of people with glaucoma, in line with the 1.8% we observed. In the EPIC-Norfolk study, 66.6% of participants with POAG had previously been diagnosed.[43] Compared with the United Kingdom, 49% were previously diagnosed in the Blue Mountains Eye Study,[61] 47% in the Rotterdam Eye Study,[62] and 50% among white people in the Baltimore Eye Study.[63] The higher rate of previously diagnosed cases of glaucoma in the United Kingdom may reflect better access to health care in the United Kingdom, with universal access and free eye tests for those above 60 years old.[43] In the United Kingdom, people are examined by optometrists and those with suspected glaucoma are referred to ophthalmologists for definitive diagnosis and management. The access to and use of eye care services for glaucoma may differ between participants living in urban areas compared to those living in rural areas. Among the 101,702 participants living in urban areas, the proportion of participants with self-reported glaucoma (n = 1888 [93.5%]) was slightly higher compared to those without self-reported glaucoma (n = 99,814 [92.1%]; P = 0.026). We therefore adjusted for population density (urban versus rural) in the multivariate regression model, and $PM_{2.5}$ was associated with a 6% (95% CI: 1.01–1.11; P = 0.017; per IQR increase) higher odds of self-reported glaucoma.

Although the $PM_{2.5}$ concentration in our analyses was within the WHO ambient air quality guidelines of annual means of 10 μg/m^3, it was sufficient to cause a 6% increased odds of self-reported glaucoma per IQR increase in $PM_{2.5}$. The WHO reported that in 98% of cities in low- and middle-income countries, air pollution levels exceeded recommended limits.[64] For example, $PM_{2.5}$ concentrations for Qatar (107.3 μg/m^3), Saudi Arabia (106.2 μg/m^3), Bangladesh (89.4 μg/m^3), and India (74.3 μg/m^3) are high,[2] and in China they ranged from 11 to 157 μg/m^3.[64] Studies of the concentration–response function in cardiovascular and respiratory disease have identified no well-delineated effects threshold. The best evidence suggests that PM concentration-morbidity can reasonably be modeled as linear.[37] From a public policy perspective, this is good news because moderate improvements in air quality should result in corresponding reductions in disease risk. However, the WHO data suggest that disease risk in the most polluted areas of the world may be higher than observed in the United Kingdom by a factor of 10. In addition, the level of $PM_{2.5}$ concentration in our study is based on outdoor levels at participants' home address, which would not account for indoor pollution or workplace exposure. Cigarette smoke may also contribute to particulate matter air pollution.[65] Hence, we examined the association between smoking status of participants with self-reported glaucoma, but did not identify a significant association. This suggests that the relationship between $PM_{2.5}$ and self-reported glaucoma is not mediated by cigarette smoke. Household air pollution is one of the leading causes of disease and premature death in the developing world, and sources include burning fuels such as wood and coal in inefficient stoves of open hearths.[66] Americans, on average, spend approximately 90% of their time

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indoors,[67] where the concentrations of some pollutants are often two to five times higher than typical outdoor concentrations.[68] It is likely that the biases and inadequacies that affect our analysis will skew the effect toward the null. Our participants will have been exposed to higher levels of $PM_{2.5}$ than the ambient residential figures indicate; hence, we may have identified only the "tip of the iceberg."

The strengths of this study include its large sample size, and the highly accurate and reproducible measurements of the SD OCT retinal thickness. This is the first large study to evaluate the association of ambient air pollution with two glaucoma endophenotypes and self-reported disease using a combination of epidemiologic and retinal imaging techniques. The limitations of the study include the low response rate of 5.5% in UK Biobank. Since air pollution was estimated using the participants' home address, this would not have accounted for individual activities, indoor air pollution, and workplace exposure,[69] thereby increasing the risk of misclassification bias. However, it is likely that the individual exposure to air pollution will be higher and probably nondifferential between cases and controls. Hence, our risk estimates may have been underestimated. The status of self-reported glaucoma was obtained from questionnaire and lacked detailed information to differentiate the different types of glaucoma. Information collected through questionnaire is subject to misclassification. However, a recent study by Khawaja et al.[5] demonstrated that people who self-report a diagnosis of glaucoma have a genetic makeup that is consistent with a glaucoma diagnosis. The prevalence of self-reported glaucoma may have been low (1.8%) and may not be fully representative of the local or national population. Lack of precision in diagnosing glaucoma may have reduced the power of the study. This will have diminished our ability to identify a true association. Participants who had self-reported ocular diseases were excluded from the study. The discrepancy between self-reported ocular conditions and clinically diagnosed ocular diseases could have well-recognized impacts on the retinal layer thickness or IOP measurements. However, because the participants were unlikely to be aware of their OCT measures, it is most likely to be nondifferential misclassification bias between those who reported or did not report a diagnosis of eye disease. Out of the 111,370 participants with data on self-reported glaucoma, 106,907 participants had IOP data and 64,117 participants had measurements on GC IPL. However, the baseline characteristics (Table 1) across the three glaucoma-associated outcome groups are similar in most aspects with the exception of refractive error. The cross-sectional design of our study also limits any determination of the cause and effect of the relationship between $PM_{2.5}$ concentration and glaucoma-associated outcomes.

In this study of a large, middle-aged UK population, we found a significant association between higher current $PM_{2.5}$ exposure and both a higher risk of self-reported glaucoma and thinner macular GCIPL. The association appears independent of IOP. These findings require replication in other cohorts. It is possible that the structural features observed may result from a condition similar to, but distinct from, glaucoma and that thinning of the GCIPL may be a "pollution retinopathy." However, the direction of the relationships between $PM_{2.5}$ and both glaucoma and associated retinal layer thicknesses indicates that higher exposure to $PM_{2.5}$ may make the GCIPL more vulnerable and increase the risk of glaucoma. Further, longitudinal research will be required to determine if exposure to pollution causes development or progression of glaucoma, or possibly that there exists a clinically similar condition—"particulate pollution-induced retinopathy." Our findings add to evidence for the damaging effects of ambient air pollution, even at relatively low levels of mean $PM_{2.5}$ exposure. Further research into the effects of fine particulate air pollution on both RGC physiology and retinal vasculature may help in the identification of an underlying pathological mechanism.

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Appendix

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