Fine Particulate Matter and Age-Related Eye Disease: The Canadian Longitudinal Study on Aging

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PURPOSE. To determine the relationship between fine particulate matter (PM2.5) and ocular outcomes such as visual impairment and age-related eye disease.

METHODS. Baseline data were used from the Canadian Longitudinal Study on Aging. The Comprehensive Cohort consisted of 30,097 adults ages 45 to 85 years. Annual mean PM2.5 levels (μg/m3) for each participant’s postal code were estimated from satellite data. Ozone, sulfur dioxide, and nitrogen dioxide levels were also estimated. Binocular presenting visual acuity was measured using a visual acuity chart. Intraocular pressure (IOP) was measured in millimeters of mercury using the Reichart Ocular Response Analyzer. Participants were asked about a diagnosis of glaucoma, macular degeneration, or cataract. Logistic and linear regression models were used.

RESULTS. The overall mean PM2.5 level was 6.5 μg/m3 (SD = 1.8). In the single pollutant models, increased PM2.5 levels (per interquartile range) were associated with visual impairment (odds ratio [OR] = 1.12; 95% confidence interval [CI], 1.02–1.24), glaucoma (OR = 1.14; 95% CI, 1.01–1.29), and visually impairing age-related macular degeneration (OR = 1.24; 95% CI, 1.10–2.09) after adjustment for sociodemographics and disease. PM2.5 had a borderline adjusted association with cataract (OR = 1.06; 95% CI, 0.99–1.14). In the multi-pollutant models, increased PM2.5 was associated with glaucoma and IOP only after adjustment for sociodemographics and disease (OR = 1.24; 95% CI, 1.05–1.46 and β = 0.24; 95% CI, 0.12–0.37).

CONCLUSIONS. Increased PM2.5 is associated with glaucoma and IOP. These associations should be confirmed using longitudinal data and potential mechanisms should be explored. If confirmed, this work may have relevance for revision of World Health Organization thresholds to protect human health.

Keywords: fine particulate matter, air pollution, glaucoma, eye disease, intraocular pressure, CLSA

Contaminated air increases the risk of disease and premature mortality. Prior research has identified consistent relationships between air pollution and lung cancer, stroke, hospital admission, and mortality.1–3 The effects of air pollution on the eye, which is directly exposed, are much less understood. It has been known for some time that smoking underlines the association between ambient air pollutants, such as fine particulate matter (PM2.5), and the risk of eye disease has not been widely studied. PM2.5, a consistent risk factor for mortality,4 is defined as having a mass median aerodynamic diameter of <2.5 μm. Common sources of PM2.5 include motor vehicles, smelters, power plants, industry, residential fireplaces and wood stoves, and forest fires.5 The World Health Organization has determined that long-term exposure to levels of PM2.5 >10 μg/m3 is associated with health hazards.6

Little epidemiological research exists examining the relationship between PM2.5 and eye disease. Relationships have been identified between PM2.5 and visual impairment,7 glaucoma,8,9 and AMD,10 but the results for cataract are unclear.14,15 To our knowledge, all of the existing studies have been done in east Asia or the United Kingdom with none being done in the United States or Canada. Some evidence indicates that these findings are biologically plausible.16,17 Using the baseline data from a large, population-based database called the Canadian Longitudinal Study on Aging (CLSA), we investigated the association between PM2.5 and four ocular outcomes: visual impairment, glaucoma, AMD, and cataract.

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METHODS

Study Population

Baseline data were used from the CLSA Comprehensive Cohort.\textsuperscript{18} We focused on the baseline data because not enough people have developed incident eye disease over the 3 years of follow-up completed thus far to be able to do a longitudinal analysis at this time. The CLSA Comprehensive Cohort consists of 30,097 people 45 to 85 years old who live near one of 11 data collection sites in seven Canadian provinces. The 11 CLSA data collection sites are located in Victoria, Vancouver, Surrey, Calgary, Winnipeg, Hamilton, Ottawa, Montreal, Sherbrooke, Halifax, and St. John’s. Stratified random sampling was done using provincial healthcare registration databases and random digit dialing of landline telephones. When sampling from provincial healthcare databases, people who were temporary visa holders or had transitional health coverage (when the information was available) were excluded. Non-permanent residents and non-Canadian citizens were excluded from both sampling frames. Further inclusion criteria were that participants had to be community dwelling, be cognitively unimpaired at baseline, speak English or French, and provide written informed consent. Full-time members of the Canadian Armed Forces, individuals residing on a federal First Nations reserve or settlement, and individuals living in nursing homes were excluded.

Study Design

Data collection by CLSA staff consisted of a home visit and a visit to a data collection site.\textsuperscript{18} All CLSA staff collecting data underwent standardized training in order to collect data in a uniform way across all sites. Baseline assessments were done between December 2011 and July 2015. Written informed consent was obtained from all participants. Research Ethics Board approval was received in July 2010 from all affiliated sites. Ethics approval was received from the University of Ottawa for this analysis in May 2019.

Data Collection

Visual Impairment and Eye Disease. At the data collection sites, visual acuity was measured using an illuminated Early Treatment of Diabetic Retinopathy Study chart and its standard protocol.\textsuperscript{19} Scores were converted to the log of the minimum angle of resolution (logMAR). Visual acuity was evaluated at a distance of 2 meters using habitual distance correction (i.e., wearing normal corrective lenses for distance vision). Visual impairment (VI) was defined as presenting binocular acuity worse than 20/40 (0.301 logMAR), as is often used in North American research.\textsuperscript{20} Participants were asked to report if they have ever had a diagnosis of cataract, AMD, or glaucoma. To try to separate out those with late-stage AMD, we distinguished between those with a report of AMD without VI and those with a report of AMD with VI. Corneal-compensated intraocular pressure (IOP) was measured using the Reichart Ocular Response Analyzer (Reichart Technologies, Depew, NY, USA). The average IOP of the right and left eyes was used. If one eye had missing IOP data, then the IOP value of the other eye was used. If the person reported a diagnosis of glaucoma, we assumed that they were taking pressure-lowering eye drops. To estimate their pretreatment IOP, we imputed values by dividing their mean IOP by 0.7, which is the mean treatment effect of pressure-lowering eye drops.\textsuperscript{21} This approach has been used previously.\textsuperscript{22}

Air Pollution. Air pollution measures were provided by the Canadian Urban Environmental Health Research Consortium (CANUE) and were merged into the CLSA data.\textsuperscript{23} Ground-level PM\textsubscript{2.5} concentration levels were estimated by satellite by combining aerosol optical depth retrievals using the GEOS-Chem chemical transport model from the following National Aeronautics and Space Administration (NASA, Washington, DC, USA) instruments: Moderate Resolution Imaging Spectroradiometer, Multi-angle Imaging SpectroRadiometer, and Sea-viewing Wide Field-of-view Sensor. These measurements were subsequently calibrated to regional ground-based observations using geographically weighted regression. These 0.01° × 0.01° gridded surface datasets were used to assign values of annual mean concentration (µg/m\textsuperscript{3}) of PM\textsubscript{2.5} to the postal code of each CLSA participant.\textsuperscript{24–26}

Hourly ground-level ozone (O\textsubscript{3}) concentrations were estimated with the Global Environmental Multi-Scale Modelling Air Quality and Chemistry model by Environment and Climate Change Canada (Gatineau, QC, Canada) staff. Estimates incorporate ground-level observation data. These datasets were used to assign values of annual mean concentration of O\textsubscript{3} in parts per billion to the postal code of each CLSA participant.\textsuperscript{27–30}

Ground-level sulfur dioxide (SO\textsubscript{2}) concentrations were estimated from the Ozone Monitoring Instrument satellite data using SO\textsubscript{2} profiles from the Global Environmental Multiscale (GEM) model for air quality and chemistry over North America. These annual gridded datasets were aggregated to 3-year running averages and used by CANUE staff to assign values of annual mean concentration of SO\textsubscript{2} in parts per billion to the postal code of each CLSA participant.\textsuperscript{26,31–33}

Nitrogen dioxide (NO\textsubscript{2}) concentrations were estimated using data from national air pollution surveillance monitoring following methods reported in Hystad et al.\textsuperscript{34} Background and regional components were estimated with land use regression procedures using satellite-derived NO\textsubscript{2} estimates and geographic variables, and local scale variation was modeled using deterministic gradients. The model included road length within 10 km, satellite NO\textsubscript{2} estimates, area of industrial land use within 2 km, and summer rainfall.\textsuperscript{26,35}

Demographic, Health, and Lifestyle Data. Demographic data including age, sex, ethnicity, education, and income were obtained during the in-home visit using an interviewer-administered questionnaire. In order to assess household income, participants were asked, “What is your best estimate of the total household income received by all household members, from all sources, before taxes and deductions, in the past 12 months?” Participants were asked if they had ever received a physician diagnosis of several comorbid conditions including diabetes and hypertension. Blood pressure was measured six times using the BPTru BPM200 blood pressure monitor (Medaval, Dublin, Ireland). The first reading was discarded, and the average of the subsequent five readings was used. Hypertension was defined if a participant reported a physician diagnosis of hypertension or if the average systolic blood pressure was 130 mmHg or higher or diastolic blood pressure was 80 mmHg or higher.\textsuperscript{26} Smoking status was classified as current, never, or former based on
these interview questions: “Have you smoked at least 100 cigarettes in your life?” and “At the present time, do you smoke cigarettes daily, occasionally (at least once in last 30 days), or not at all (not in last 30 days)?” A current smoker was defined as a person who reported smoking at least 100 cigarettes and currently smokes daily or occasionally, whereas a former smoker was someone who reported smoking at least 100 cigarettes in life but had not smoked in the last 30 days.

**Statistical Analysis.** Mean values of PM$_{2.5}$ and their standard deviations were given by categorical demographic, health, lifestyle, and ocular variables. Pearson's correlation coefficient was calculated between PM$_{2.5}$ and IOP. IOP values greater than 60 were excluded, as these were considered probable measurement errors. Relationships between PM$_{2.5}$ and categorical ocular variables were tested by linear regression.

In separate multivariable analyses, logistic regression was used to determine the relationship between PM$_{2.5}$ and VI, glaucoma, and cataract; multinomial regression was used for the three-category AMD variable; and linear regression was used for IOP. These regression models were first adjusted for potentially confounding variables such as age, sex, education, household income, ethnicity, diabetes, hypertension, smoking, and province. In a second phase of adjustment, models were also adjusted for other pollutants including O$_3$, SO$_2$, and NO$_2$. The correlation between PM$_{2.5}$ and the other pollutants was checked to guard against multicollinearity. Variance inflation factors were checked, as well. Sampling weights and strata variables were incorporated into all analyses using the SVY commands in Stata/SE 16 (StataCorp, College Station, TX, USA). The Venn diagram was produced in R 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria) with the limma 3.46.0 package. The Venn diagram

**Table 1.** Average Levels of PM$_{2.5}$ by Demographic, Smoking, or Health ($N$ = 29,147)

| Variable* | Fine Particulate Matter ($\mu g/m^3$) Mean (SD) |
|-----------|-----------------------------------------------|
| Age group (y) |                                             |
| 45–54 ($n$ = 7405) | 6.4 (1.4)                                     |
| 55–64 ($n$ = 9575) | 6.5 (1.9)                                     |
| 65–74 ($n$ = 7107) | 6.6 (2.1)                                     |
| 75–85 ($n$ = 5060) | 6.7 (2.1)                                     |
| Sex |                                             |
| Female ($n$ = 14,830) | 6.5 (1.8)                                     |
| Male ($n$ = 14,317) | 6.5 (1.8)                                     |
| Ethnic or racial background |                                           |
| White ($n$ = 27,467) | 6.5 (1.8)                                     |
| Black ($n$ = 255) | 6.9 (1.8)                                     |
| Asian ($n$ = 663) | 6.5 (1.5)                                     |
| Aboriginal ($n$ = 347) | 6.3 (1.7)                                     |
| Other ($n$ = 415) | 6.8 (1.7)                                     |
| Education |                                             |
| More than bachelor's degree ($n$ = 6223) | 6.5 (1.7)                                     |
| Bachelor's degree ($n$ = 6862) | 6.6 (1.7)                                     |
| Less than bachelor's degree ($n$ = 16,010) | 6.5 (1.8)                                     |
| Annual household income |                                      |
| ≥$150,000 ($n$ = 10,003) | 6.4 (1.6)                                     |
| $50,000–$100,000 ($n$ = 9564) | 6.5 (1.8)                                     |
| $20,000–$50,000 ($n$ = 6167) | 6.7 (1.9)                                     |
| <$20,000 ($n$ = 1525) | 7.0 (2.0)                                     |
| Refused/don't know ($n$ = 1888) | 6.6 (1.9)                                     |
| Smoking |                                             |
| Never ($n$ = 13,812) | 6.5 (1.7)                                     |
| Former ($n$ = 12,723) | 6.5 (1.8)                                     |
| Current ($n$ = 2511) | 6.8 (1.8)                                     |
| Diabetes |                                             |
| None ($n$ = 23,909) | 6.5 (1.8)                                     |
| Type 1 ($n$ = 170) | 6.7 (1.6)                                     |
| Type 2 ($n$ = 2694) | 6.5 (1.9)                                     |
| Suspect/neither type ($n$ = 2032) | 6.3 (1.7)                                     |
| Hypertension |                                           |
| No | 6.5 (1.7)                                     |
| Yes | 6.5 (1.8)                                     |
| Province |                                           |
| Alberta ($n$ = 2949) | 7.8 (1.9)                                     |
| British Columbia ($n$ = 5509) | 5.8 (1.3)                                     |
| Manitoba ($n$ = 3110) | 6.1 (1.1)                                     |
| Newfoundland and Labrador ($n$ = 2124) | 5.7 (1.8)                                     |
| Nova Scotia ($n$ = 3043) | 5.0 (1.2)                                     |
| Ontario ($n$ = 6355) | 7.0 (1.8)                                     |
| Quebec ($n$ = 6057) | 7.2 (1.6)                                     |

*The following variables have missing data: education ($n$ = 52), smoking ($n$ = 101), diabetes ($n$ = 342), and hypertension ($n$ = 1).
was produced for those who had non-missing values for all four ocular outcomes and non-missing PM$_{2.5}$ data ($n = 27,864$).

**RESULTS**

Ninety-seven percent of CLSA participants ($n = 29,147$) had a non-missing value for PM$_{2.5}$. The 950 people who were missing data on PM$_{2.5}$ were almost all from British Columbia (78%). Those missing PM$_{2.5}$ data were also older, more likely to be female, and more likely to have VI and cataract than those who had PM$_{2.5}$ data.

Certain people lived in postal codes that had higher mean levels of PM$_{2.5}$ (Table 1). These included older people, certain ethnic groups, people who had lower incomes, current smokers, and people with type 1 diabetes. PM$_{2.5}$ levels also differed by province, with higher levels in Alberta, Ontario, and Quebec than in the other provinces. Also, people who reported AMD, glaucoma, or cataract lived in areas with higher mean PM$_{2.5}$ levels ($P < 0.05$) (Table 2). There is some overlap among those affected by our four ocular outcomes (VI, AMD, glaucoma, and cataract). In the Venn diagram shown in the Figure, for example, 5790 have only cataract, 661 have cataract and glaucoma, 720 have

| Table 2. Average Levels of PM$_{2.5}$ by Visual Impairment or Eye Disease ($N = 29,147$) |
|-----------------------------------------|----------------|---------|
| **Variable**                           | **Fine Particulate Matter (µg/m$^3$) Mean (SD)** | **$P$** |
| Visual impairment                      |               |         |
| No ($n = 26,655$)                      | 6.5 (1.8)     | 0.780   |
| Yes ($n = 2,067$)                      | 6.5 (2.0)     |         |
| Glaucoma                               |               |         |
| No ($n = 27,525$)                      | 6.5 (1.8)     |         |
| Yes ($n = 1,467$)                      | 6.7 (2.0)     | $<0.001$|
| Age-related macular degeneration       |               |         |
| No ($n = 27,715$)                      | 6.5 (1.8)     |         |
| Yes but not visually impaired ($n = 948$) | 6.6 (1.9)  | 0.014   |
| Yes and visually impaired ($n = 237$)  | 6.8 (2.2)     | 0.011   |
| Cataract                               |               |         |
| No ($n = 20,264$)                      | 6.5 (1.7)     |         |
| Yes ($n = 8,286$)                      | 6.6 (2.0)     | $<0.001$|

*Note that 425 were missing data on visual impairment, 155 were missing data on glaucoma, 247 were missing data on AMD, and 597 were missing data on cataract.*

**Figure.** Venn diagram to illustrate the overlap in the number of people affected by ocular outcomes.
There was no relationship between PM$_{2.5}$ and IOP in areas with higher PM$_{2.5}$ levels (per interquartile range $β$ = 0.15; 95% CI, 0.09–0.21). In the multi-pollutant model, neither PM$_{2.5}$ nor O$_3$ were associated with IOP ($β$ = 0.07; 95% CI, 0.04–0.10) adjusted for age, sex, ethnicity, education, household income, smoking, diabetes, hypertension, and province. In single-pollutant models, higher values of PM$_{2.5}$ were associated with glaucoma (OR = 1.06; 95% CI, 0.99–1.14). There was no relationship between PM$_{2.5}$ and IOP ($β$ = -0.00; 95% CI, -0.10–0.09) in the single-pollutant model.

PM$_{2.5}$ was somewhat correlated with other pollutants such as O$_3$ ($r$ = -0.08), SO$_2$ ($r$ = -0.12), and NO$_2$ ($r$ = 0.20) ($P = 0.001$). When these three other pollutants were entered into the model, PM$_{2.5}$ became more associated with glaucoma (OR = 1.24; 95% CI, 1.05–1.46) (Table 4). Higher levels of both PM$_{2.5}$ and O$_3$ were associated with IOP with the other three pollutants in the model ($β$ = 0.24; 95% CI, 0.12–0.37 and $β$ = 0.39; 95% CI, 0.28–0.50, respectively). Higher PM$_{2.5}$ levels only had a borderline association with visually impairing AMD (OR = 1.41; 95% CI, 0.96–2.08; $P = 0.08$). Higher O$_3$ levels were inversely associated with cataract (OR = 0.92; 95% CI, 0.85–0.99), and NO$_2$ was inversely associated with VI (OR = 0.86; 95% CI, 0.74–0.99; $P = 0.042$).

Given that we calculated imputed IOP for people with glaucoma to account for presumed treatment effects, we did a sensitivity analysis excluding people with glaucoma to further investigate the relationships between air pollution and IOP. The results from the sensitivity analysis were consistent with our main results. Specifically, in the single pollutant model, PM$_{2.5}$ was not associated with IOP ($β$ = -0.07; 95% CI, -0.15–0.02). In the multi-pollutant model, PM$_{2.5}$ and O$_3$ were associated with IOP ($β$ = 0.15; 95% CI, 0.04–0.26 and $β$ = 0.40; 95% CI, 0.29–0.50, respectively).

In the multi-pollutant models, the variance inflation factors, which can indicate problems with collinearity, were less than 2.5 except for O$_3$, which had a variance inflation factor of 2.6. When we ran the models without O$_3$ in a sensitivity analysis, PM$_{2.5}$ remained statistically significantly associated with glaucoma (OR = 1.21; 95% CI, 1.04–1.42), but the relationship with IOP was attenuated and had borderline significance ($β$ = 0.11; 95% CI, -0.01–0.23; $P = 0.067$).

### DISCUSSION

In single-pollutant models, higher values of PM$_{2.5}$ were associated with an increased odds of visual impairment, visually impairing AMD, and glaucoma. In multi-pollutant models, higher values of PM$_{2.5}$ were associated with glaucoma and IOP. The relationship between PM$_{2.5}$ and glaucoma is biologically plausible. Emerging evidence from mouse models suggests that PM$_{2.5}$ exposure may contribute to glaucoma and ocular hypertension. A study by Li et al. in mice found that exposure of the ocular surface and trabecular meshwork to PM$_{2.5}$ resulted in increases in IOP and upregulation of the nucleotide-binding domain, leucine-rich containing family, pyrin domain-containing-3.
an endophenotype for glaucoma, was measured, and the results with glaucoma and IOP were consistent in that both were related to PM$_{2.5}$. Second, our data are cross-sectional, so we cannot establish the temporality of the exposure to air pollution and the presence of glaucoma. Although the CLSA is longitudinal, at this time there has only been one wave of 3-year follow-up data released, and there is insufficient power to conduct a longitudinal analysis. Finally, the air pollution data are based on the postal code of the residence of the participant, so if a person does not spend much time at their residence or they recently moved to that residence, there would be misclassification of exposure. This misclassification, though, would likely be nondifferential by glaucoma status, which would result in an underestimation of the true effect.

To conclude, increased PM$_{2.5}$ was associated with glaucoma and IOP. These associations should be confirmed using longitudinal data, and potential mechanisms should be explored. The mean long-term exposure levels of PM$_{2.5}$ in this study were below the World Health Organization threshold of 10 μg/m$^3$ and the Canadian threshold of 8.8 μg/m$^3$. Therefore, if confirmed, this work may have relevance for revised thresholds to protect human health.

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