Inverse Association of APOE ε4 and Glaucoma Modified by Systemic Hypertension: The Canadian Longitudinal Study on Aging

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Purpose. Studies examining the apolipoprotein E (*APOE*) ε4 allele and glaucoma are inconsistent, which could be due to interactions with other factors. We examined the relationship between the *APOE ε4* allele and glaucoma and intraocular pressure in a large, population-based random sample and explored whether the *APOE ε4* allele interacted with systemic hypertension.

Methods. Data came from the Canadian Longitudinal Study on Aging, a population-based study that included 24,655 adults ages 45 to 85 years old in the European ancestry cohort. *APOE* genotypes were derived from single-nucleotide polymorphisms rs429358 and rs7412. Participants were asked about a prior diagnosis of glaucoma from a doctor. Corneal compensated intraocular pressure (IOP) was measured using the Reichart Ocular Response Analyzer.

Results. Having an *APOE ε4* allele was associated with a lower odds of glaucoma after adjusting for age, sex, IOP, and the top 10 population structure principal components (odds ratio [OR] = 0.83; 95% confidence interval [CI], 0.69-0.98; $P = 0.033$). A novel statistically significant interaction was found in that having an *APOE ε4* allele was only associated with glaucoma in those without systemic hypertension (OR = 0.62; 95% CI, 0.46-0.85) although it was not associated in those with it (OR = 0.97; 95% CI, 0.79-1.21) (interaction term P value = 0.017). *APOE ε4* was not associated with IOP ($\beta = -0.01$; 95% CI, −0.13 to 0.10).

Conclusions. Evidence increasingly points to the *APOE ε4* allele having protective benefits against glaucoma, but this association was limited to those without systemic hypertension. Further research is needed to understand the biological mechanisms for these findings and the treatment potential they hold.

Keywords: apolipoprotein, glaucoma, intraocular pressure, CLSA, hypertension

Although the heritability of glaucoma and intraocular pressure is well established,[1] the search for genetic variants that explain more than a small fraction of that heritability continues. The apolipoprotein E ε4 variant (*APOE ε4*) is a well-known and common risk factor for late-onset Alzheimer's disease.[2,3] Some researchers have found that people with glaucoma are more likely to have Alzheimer's disease or worse cognitive performance[4–6] and have considered common biological mechanisms between Alzheimer's disease and glaucoma, including genetic factors such as *APOE ε4*.[7] Studies evaluating *APOE ε4* and glaucoma have been conflicting because they have shown positive,[8] negative,[9–11] and null results.[12–14]

Some research has noted that a positive association between *APOE ε4* and glaucoma may be limited to those of Asian ethnicity[15,16] indicating possible interaction by other genetic or environmental factors. Systemic hypertension is a well-established risk factor for glaucoma.[17] It is possible that the impact of *APOE ε4* is modified by the presence of systemic hypertension, an extremely prevalent condition of aging.[18] Indeed, several studies have reported that *APOE ε4* and systemic hypertension interact synergistically in their relationship with cognitive function and Alzheimer's disease.[19–22] Using cross-sectional data from a very large Canadian population-based study, we sought to determine whether *APOE ε4* was associated with glaucoma and whether this association was modified by systemic hypertension.

Methods

Study Population

Baseline data were used from the Comprehensive Cohort of the Canadian Longitudinal Study on Aging, which consisted

of 30,097 adults ages 45 to 85 years old.[23] We focused on the baseline data because not enough people had yet developed incident glaucoma with only three years of follow-up data. Participants in the Comprehensive Cohort had to live near one of 11 data collection sites in seven Canadian provinces (Victoria, Vancouver, Surrey, Calgary, Winnipeg, Hamilton, Ottawa, Montreal, Sherbrooke, Halifax, and St. John's). Stratified random sampling was conducted using provincial healthcare registration databases and random digit dialing of landline telephones. Non-permanent residents and non-Canadian citizens were excluded from both sampling frames. When sampling from provincial healthcare databases, temporary visa holders or those who had transitional health care coverage were excluded. Also excluded were full-time members of the Canadian Armed Forces, individuals residing on a federal First Nations reserve or settlement, and individuals living in nursing homes. Inclusion criteria were that participants had to be community-dwelling, cognitively unimpaired at baseline, speak English or French, and provide written informed consent.

Study Design

All Canadian Longitudinal Study on Aging (CLSA) staff collecting data underwent standardized training to collect data in a uniform way. Data collection required both a home visit and a visit to a data collection site. Baseline assessments were completed 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 from the University of Ottawa was received for this analysis.

Data Collection

Eye Disease and IOP. Participants were asked about a previous diagnosis of glaucoma. Although self-report of glaucoma may lead to misclassification, deBoever et al.[24] showed that self-reported glaucoma and medical-record-identified glaucoma revealed almost the exact same genetic effects with a correlation between 0.9 and 1.0. The Reichart Ocular Response Analyzer was used to measure corneal-compensated intraocular pressure (IOP). Contraindications included eye surgery in the last three months, a detached retina, or an eye infection. The average IOP of the right and left eyes was used. If only one eye had IOP data, then the IOP value of that eye was used alone. To estimate pretreatment IOP, for those who currently had a prescription of pressure-lowering eye drops, we divided their mean IOP by 0.7, which is the mean treatment effect.[25] This approach has been used previously.[26]

Systemic Hypertension. Blood pressure was measured six times using the BpTRU BPM200 Blood Pressure Monitor (BpTRU Medical Devices Headquarters, Coquitlam, BC, Canada). 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 mm Hg or higher or diastolic blood pressure was 80 mm Hg or higher.[27] Questions were also asked about the age of onset and the use of medications to control systemic hypertension.

Genotyping. Nonfasting blood samples were taken from consenting participants. Whole blood from EDTA tubes was stored on Whatman paper in microwell plates at room temperature, which were shipped to the Biorepository and Bioanalysis Centre. The Affymetrix UK Biobank Axiom array was used to genotype the samples, resulting in 794,409 single nucleotide polymorphisms (SNP) from 26,622 participants who provided genetic data.[28,29] We used Release 3 of the CLSA genomic data. Extensive marker-based quality control was performed by the CLSA according to standard procedures, including checks for genotype consistency across genotyping batch, participant chromosomally defined sex, Hardy-Weinberg equilibrium, and discordance of genotyping across control replicates.[28,29] Sample-based quality control included checking for relatedness, heterozygosity and genotype missingness.[28,29] We excluded 15 individuals with extreme values of heterozygosity and genotype missingness and 1666 related individuals. We used chromosomally defined sex in our analysis and excluded 15 individuals for whom sex could not be determined from the genotype data. To control for population structure, we limited our analysis to the CLSA European ancestry subset, which was determined using principal components analysis.[28,29] This subset contains the large majority (93% n = 24,658) of CLSA individuals genotyped.

The Affymetrix UK Biobank Axiom array includes the two single nucleotide polymorphisms (rs429358 and rs7412) whose haplotypes define the *APOE* alleles *ε2, ε3*, and *ε4*. The rs429358-rs7412 haplotypes T-T, T-C, and C-C correspond to alleles *ε2, ε3*, and *ε4*, respectively. Unambiguous haplotypes can be obtained from the rs429358 and rs7412 genotypes except for the double heterozygotes, which could be *ε2/ε4* or *ε1/ε3*. However, because the *ε1* allele is extremely rare, the double heterozygotes were assigned to *ε2/ε4*. The *APOE* genotypes were then categorized by *ε4* or *ε2* status (i.e., as including an *ε4* allele or not, or including an *ε2* allele or not).

Statistical Analysis

Our main outcomes were glaucoma and current IOP. People with and without glaucoma were classified by *APOE* genotype and by *APOE ε4* or *ε2* status. Differences were tested by χ^2 testing. Mean IOP levels were also tested by *APOE* genotype and by *APOE ε4* status. Differences were tested by linear regression. To determine the relationship between *APOE ε4* and glaucoma, logistic regression was used. Age, chromosomal sex, and IOP (for glaucoma only) were included in regression analyses. We also adjusted for the top 10 principal components from the principal components analysis of the CLSA European ancestry subset to control for residual population structure as is recommended.[30–32] Age was best modeled by including a main effect and a squared term. In a sensitivity analysis to address potential survival bias, we examined whether our results were similar in both older adults and middle-aged adults. Another sensitivity analysis examined an estimate of the pretreatment IOP as a secondary outcome. Multiplicative interaction between *APOE ε4* and systemic hypertension was first examined by stratification and then by entering a product term into the regression model. The complex survey design was accounted for in all analyses. Stata/SE Version 16.1 was used.

Results

Of the 26,622 people in the CLSA who had genotyping data, 24,655 had European ancestry. Our analyses are limited to this group to reduce the risk of population stratification bias.

Investigative Ophthalmology & Visual Science

Table 1. Key Characteristics of Those With and Without Glaucoma (n = 22,761)

	Glaucoma %	No Glaucoma %	*P* Value
Age, years	68.0 (11.4)	59.2 (9.6)	<0.001
APOE Genotype			
ε2/ε2 (n = 142)	0.5	0.6	0.104
ε2/ε3 (n = 2938)	14.9	12.8	
ε2/ε4 (n = 486)	2.1	2.1	
ε3/ε3 (n = 13,747)	62.3	60.1	
ε3/ε4 (n = 5008)	18.4	22.5	
ε4/ε4 (n = 440)	1.8	1.9	
APOE ε4 status			
No *ε4* allele (n = 16,827)	77.7	73.4	0.006
≥1 *ε4* allele (n = 5934)	22.3	26.6	
APOE ε2 status			
No *ε2* allele (n = 19,195)	82.5	84.5	0.124
≥1 *ε2* allele (n = 3566)	17.5	15.5	
Current IOP, mm Hg (n = 21,894)	17.8 (5.3)	15.8 (3.5)	<0.001
Corrected IOP, mm Hg (n = 21,894)	20.4 (7.2)	15.8 (3.5)	<0.001
Systemic Hypertension (n = 22,761)	62%	51%	<0.001

Table 2. Logistic Regression Model of Association Between *APOE ε4* and Glaucoma

APOE	Odds Ratio* (n = 21,778)	95% CI
0 *APOE ε4* alleles	1.00	Reference
≥1 *APOE ε4* allele	0.83	0.69–0.98

* Adjusted for age, sex, IOP, and the top 10 population structure principal components.

Table 3. Logistic Regression Model of Association Between *APOE ε4* and Glaucoma in People Stratified by Systemic Hypertension Status

Strata	*APOE ε4*	Glaucoma OR*,†	95% CI
No HBP (n = 9697)	0 *ε4* alleles	1.00	Reference
	≥1 *ε4* allele	0.62	0.46–0.85
HBP (n = 12,081)	0 *ε4* alleles	1.00	Reference
	≥1 *ε4* allele	0.97	0.79–1.21

HBP, high systemic blood pressure.
* Adjusted for age, sex, IOP, and the top 10 population structure principal components.
† Interaction term *P* value = 0.017.

After the exclusions for sample quality control and missing data for glaucoma and *APOE*, 22,761 people remained. In this cohort, 1093 people reported glaucoma. The prevalence of glaucoma by each *APOE* genotype and by the presence of the ε4 or ε2 allele is shown in Table 1. People who had at least 1 *ε4* allele were less likely to report glaucoma ($P = 0.006$). People with glaucoma were older and had higher current IOP and higher corrected IOP (estimate of pretreatment IOP) ($P < 0.001$). They were also more likely to have systemic hypertension ($P < 0.001$). Of those with a prior physician diagnosis of high blood pressure, the average age of onset was 53 years old (SD = 13).

APOE ε4 heterozygotes made up 24% of the sample whereas *ε4* homozygotes made up 2% of the sample. Having an *APOE ε4* allele was inversely associated with a report of glaucoma after adjustment for age, sex, IOP, and the top 10 population structure principal components (odds ratio [OR] = 0.83; 95% confidence interval [CI], 0.69–0.98; $P = 0.033$) (Table 2). In a sensitivity analysis, we examined whether our results were similar in both older adults and in middle-aged adults. *APOE ε4* was inversely associated with glaucoma in both adults aged 65 to 85 years (OR = 0.83; 95% CI, 0.68–1.02) and in adults aged 45 to 65 years (OR = 0.81; 95% CI, 0.59–1.11) respectively.

Stratified results indicated that the *APOE ε4* allele was only associated with a report of glaucoma in those without systemic hypertension (OR = 0.62; 95% CI, 0.46-0.85) but not in those with systemic hypertension (OR = 0.97; 95% CI, 0.79–1.21) after adjustment for age, sex, IOP, and the top 10 population structure principal components (Table 3). An interaction term between systemic hypertension and *APOE ε4* was statistically significant in a model including *APOE ε4*, systemic hypertension, their interaction term, age, sex, IOP and the top 10 population structure principal components ($P = 0.017$). The reciprocal of this interaction is shown in Table 4. Those with systemic hypertension were more likely to have glaucoma but only if they had an *APOE ε4* allele (OR = 1.47; 95% CI, 1.05–2.08). There was no association with systemic hypertension if they did not have an *APOE ε4* allele (OR = 0.94; 95% CI 0.79, 1.11). The interaction did not vary by the age of onset or duration of the systemic hypertension or by whether people were taking medication to control the systemic hypertension (data not shown).

Table 4. Logistic Regression Model of Association Between Systemic Hypertension and Glaucoma in People Stratified by *APOE ε4* Status

Strata	Systemic Hypertension	Glaucoma OR*,†	95% CI
No *APOE ε4* (n = 16,109)	No	1.00	Reference
	Yes	0.94	0.79–1.11
APOE ε4 (n = 5669)	No	1.00	Reference
	Yes	1.47	1.05–2.08

* Adjusted for age, sex, IOP, and the top 10 population structure principal components.
† Interaction term *P* value = 0.017.

Investigative Ophthalmology & Visual Science

Having an *APOE ε4* allele was not associated with IOP ($\beta = -0.01$; 95% CI, −0.13 to 0.10). Having an *APOE ε2* allele was not associated with either glaucoma (OR = 1.14; 95% CI, 0.94-1.39) or IOP ($\beta = -0.02$; 95% CI, −0.17 to 0.12). In sensitivity analyses, neither *APOE ε4* ($\beta = -0.03$; 95% CI, −0.15 to 0.09) nor *APOE ε2* ($\beta = -0.03$; 95% CI, −0.17 to 0.14 = 2) were associated with an estimate of pretreatment IOP.

Discussion

Our results confirm prior findings of an inverse association between *APOE ε4* and glaucoma.[9–11] In addition, for the first time, we report an interaction between *APOE ε4* and systemic hypertension such that the inverse association with glaucoma was only found in those without systemic hypertension.

Because *APOE ε4* was not associated with IOP, the mechanism through which *APOE ε4* might protect against glaucoma is thought to be pressure-independent. The mechanism by which *APOE ε4* might protect against glaucoma may be related to microglia, the immune cells of the central nervous system, which have previously been found to be related to glaucoma.[33] In two mouse models of glaucoma, after IOP elevation, *APOE* was upregulated and controlled a process by which microglia were shown to transition from a homeostatic state to a chronic inflammatory, neurodegenerative phenotype.[34] Furthermore, Margeta et al.[34] showed that compared to *APOE ε3* microglia, *APOE ε4* microglia were more likely to remain in homeostasis and fewer retinal ganglion cells were lost despite elevation of IOP. This work may have treatment implications because the authors found that a protein called Galectin-3 was upregulated in both mouse models and was regulated by *APOE.*[34] *APOE ε4* mice had less upregulation of Galectin-3. Pharmacological inhibition of Galectin-3 was protective against retinal ganglion cell loss.[34]

In addition, we found that the inverse association with *APOE ε4* was only found in those without systemic hypertension. The results were not significantly different depending on the age of onset or duration of the hypertension or by whether the hypertension was treated by medication or not. Perhaps *APOE ε4* can protect against upregulation of Galectin-3 in the face of elevated IOP but it cannot protect retinal ganglion cells in the face of concurrent or past systemic hypertension. It has been hypothesized that systemic hypertension leads to vascular dysregulation, impaired blood flow to the optic nerve, oxidative stress, and apoptosis of retinal ganglion cells.[35] This interaction should be confirmed and further explored. An interaction between *APOE ε4* and systemic hypertension has previously been reported for cognitive function and Alzheimer's disease.[19–22]

Our findings are consistent with other studies that have found a protective effect of *APOE ε4*. Our odds ratio is remarkably consistent with the findings of Margeta et al.[9] who also reported an odds ratio of 0.83, 95% CI 0.74, 0.94. Our odds ratio is more attenuated than that found in a Chinese population in which the odds ratio was 0.36 (95% CI, 0.17–0.79) in those with normal tension glaucoma and 0.72 (95% CI, 0.46–1.13) in those with high tension glaucoma.[10] Interestingly, studies have also reported that *APOE ε4* is inversely associated with age-related macular degeneration.[36] The inverse associations of *APOE ε4* with glaucoma and age-related macular degeneration stand in contrast to the positive association between *APOE ε4* and Alzheimer's disease.[2,3] Margeta et al. have speculated that the reason for these opposing associations is that *APOE ε4* microglia that are less reactive may benefit the retina but be harmful to the Alzheimer's brain, which is characterized by amyloid plaques and neurofibrillary tangles that must be controlled by the immune system.[9]

The major strength of this work is that we used a very large, population-based dataset of over 21,000 people. This work does have some limitations. First, glaucoma was self-reported, which may have led to misclassification. However, deBoever et al.[24] found a very strong correlation (>0.9) between genetic associations with glaucoma that relied on self-report of the phenotype and those that relied on a phenotype obtained via medical records. Furthermore, our results are remarkably consistent with Margeta et al.[9] in which glaucoma was identified via a standardized clinical examination. Second, we had no data on the type of glaucoma. Given this analysis was limited to the European ancestry cohort, we can speculate that most of the glaucoma was primary open-angle glaucoma. Margeta et al.[9] found a stronger inverse association in those with normal-tension glaucoma compared to those with high-tension glaucoma. We are unable to reliably distinguish between these subtypes of glaucoma. Third, the generalizability of our results may be limited to those of European ancestry. Of those with genetic data, the CLSA population was almost entirely of European ancestry (93%) giving us very little statistical power to examine the association in other ethnic backgrounds. Finally, we cannot exclude the possibility of survival bias such that those who had *APOE ε4* and glaucoma may have been less likely to participate in the CLSA because of death, dementia, or other disability. However, if true, we would expect this bias to have more of an effect on older participants than in younger participants yet the odds ratios were very similar to one another making survival bias less of a concern. The use of longitudinal data in conjunction with a competing risks analysis could further investigate this potential bias.

Using a large population-based cohort, we have confirmed that *APOE ε4* has an inverse association with glaucoma and we report for the first time an interaction between *APOE ε4* and systemic hypertension that should be confirmed. The possibility of targeting the microglial transition controlled by *APOE* and Galectin-3 should be further investigated.

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