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Title: Glaucoma and Cognitive Function Trajectories in a Population-Based Study: Findings from The Health and Retirement Study

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Abbreviations: HRS: The Health and Retirement Study. TICS: Telephone Interview for Cognitive Status. POAG: Primary Open Angle Glaucoma. NTG: Normal Tension Glaucoma. OAG: Open Angle Glaucoma. ACG: Angle Closure Glaucoma.

Key Words: Glaucoma, Vision, Ophthalmology, Cognitive Function, Aging

Key Points:

- Prior studies on the association of glaucoma and objectively measured cognitive function have been largely cross-sectional and reported mixed results.
- In this study of 7,073 US adults age ≥51 years, incident glaucoma was associated with higher cognitive function scores but steeper rates of cognitive score decline over a maximum follow-up time of 18 years.
- The observed associations between glaucoma and cognitive function were small and unlikely to be clinically meaningful.

Why Does This Matter? Identifying early risk factors for cognitive decline is an important research priority. Despite previous research to characterize the association of glaucoma with cognitive function, the present study suggests that such an association may be small or absent. Compared to prior studies on this topic, this investigation provides robust evidence based on its larger sample size, longitudinal follow-up, and repeated measures of cognitive function in a population-based sample.

Abstract

INTRODUCTION: Prior studies on the association of glaucoma and cognitive function have reported mixed results.

METHODS: The Health and Retirement Study (HRS) is a nationally representative panel survey of Americans age ≥51 years. HRS-linked Medicare claims data were used to identify incident glaucoma cases (by glaucoma type). Cognitive function was measured using the Telephone Interview for Cognitive Status (TICS), administered in each wave (every 2 years). Separate linear mixed models were fitted with either prevalent or incident glaucoma as a predictor of TICS trajectories and adjusting for age, race/ethnicity, educational attainment, gender, and medical history. Negative model estimates indicate associations of glaucoma with worse cognitive function scores or steeper per-year declines in cognitive function scores.

RESULTS: Analyses of prevalent glaucoma cases included 1,344 cases and 5,729 controls. Analyses of incident glaucoma included 886 cases and 4,385 controls. In fully-adjusted models, those with prevalent glaucoma had similar TICS scores to controls ($\beta = 0.01$; 95% Confidence Interval [CI]: -0.15, 0.18; p=0.86). However, in those with incident glaucoma, we detected a statistically significant association between glaucoma and lower TICS scores ($\beta = -0.29$; 95% CI: -0.50, -0.08; p=0.007). However, there was no statistically significant association between either prevalent or incident glaucoma and per-year rates of change in TICS scores. When categorizing glaucoma by type (primary open angle glaucoma, normal tension glaucoma, or other glaucoma), no significant associations were detected between either prevalent or incident glaucoma and levels of or rates of change in TICS scores in fully covariate adjusted models.

CONCLUSION: The observed associations between glaucoma and cognitive function were small and unlikely to be clinically meaningful. Compared to prior studies on this topic, this

investigation provides robust evidence based on its larger sample size, longitudinal follow-up, and repeated measures of cognitive function in a population-based sample.

BACKGROUND

Glaucoma, the leading cause of irreversible blindness, is a progressive optic neuropathy with incompletely understood pathogenesis that results in progressive vision loss, often beginning with peripheral visual field defects.[1–3] Glaucoma is as a neurodegenerative process associated with trans-synaptic degeneration in the brain, specifically in the lateral geniculate nucleus and visual cortex.[4,5] Some prior studies have suggested that the pathogenesis of primary open angle glaucoma (POAG) and normal tension glaucoma (NTG), specifically, may be part of a broad neurodegenerative mechanism with ocular and non-ocular manifestations. Moreover, there is considerable evidence that impaired vision is associated with a significant increase in the risk of accelerated cognitive decline and incident dementia.[6–8] Consequently, there is interest in assessing the association of glaucoma with neurodegenerative conditions like cognitive decline and dementia.[2,3,9–11] Understanding these association is important for devising surveillance and intervention strategies to optimize overall health and wellbeing for the growing population of older adults in the U.S. and worldwide.[12]

Basic and translational research has provided supporting evidence and plausible mechanisms for a link between glaucoma and dementia.[13–23] For example, altered levels of amyloid beta (Aβ) and tau proteins are found both in the brain of those with Alzheimer's Disease (AD) and in the retinas of those with glaucoma.[13–18] Some clinic-based studies have reported an association of glaucomatous optic disc changes and visual field defects with dementia,[24–27] while others found no significant association.[28] Similarly, some epidemiological studies have reported high rates of co-occurrence of glaucoma and physician-diagnosed dementia[29–35] while others have not.[36–38] Compared to physician diagnosis of mild cognitive impairment or dementia, the

results of objective cognitive tests may provide a more sensitive tool for identifying differences and changes in cognition over time. Nevertheless, only cross-sectional studies have examined the association of glaucoma with objectively assessed cognitive function,[39–42] with some reporting an association[39,40] and others reporting no association.[41,42] However, to our knowledge, no prior study has provided evidence on whether glaucoma is associated with longitudinal changes in cognitive function in a representative sample.

In order to address this question, we used data from the Health and Retirement Study (HRS), a longitudinal national survey of U.S. adults age 51 years and older that began in 1992. Cognitive function is measured in the HRS every two years. In the current study, we sought to address the limitations of prior studies on the association of glaucoma and cognition, which have provided mixed results; these studies were largely cross-sectional, were not population-representative, and/or used less sensitive measures of cognitive health. We hypothesized that individuals with an incident or prevalent diagnosis of glaucoma have lower levels and steeper declines of cognitive function compared to individuals without glaucoma. Furthermore, we hypothesized that those with NTG and POAG are likely to experience the steepest rates of cognitive decline.

METHODS

Data Source

The HRS is a nationally-representative panel survey of Americans age ≥51 years conducted by the University of Michigan.[43] The study collects a wide array of sociodemographic, health, and economic data that is made publicly available

(hrsonline.isr.umich.edu). Participant data can also be linked to Medicare claims data from the Centers for Medicare and Medicaid Services. All respondents provided written informed consent for data linkage, and the HRS was approved by the institutional review board at the University of Michigan and conforms to the tenets of the Declaration of Helsinki.

Since 1998, the HRS has included approximately 20,000 adults, with a new cohort of participants age 51 to 56 years enrolled every 6 years. All participants are surveyed every 2 years. The current study used HRS survey data and linked Medicare claims from 1998 to 2016 from participants age ≥ 65 years at the time of glaucoma diagnosis. Prior research has identified associations between vision and cognition in both mid-life[44,45] and older adulthood[6], and identifying early risk factors for cognitive change is an important research priority.[46] Thus, we have included cognitive data from participants ≥ 51 years in this analysis, rather than limiting the analyses to cognitive function data from only later life.

Identification of Prevalent Glaucoma Cases, Incident Glaucoma Cases, and Controls

Inclusion criteria for cases and controls were: enrollment in Medicare Parts A and B for ≥90% of the months during the study period; and completion of the Telephone Interview for Cognitive Status (TICS) assessment at least one visit pre- and post- indexed date. In the analysis of prevalent glaucoma, controls with ≥1 eye exam claim were also eligible for inclusion. Further detail regarding the definition of glaucoma cases and controls for the prevalent and incident glaucoma analyses are presented in **Supplementary Appendix S1**.

Inclusion criteria for glaucoma cases also included ≥2 eye exams by an ophthalmologist or optometrist (identified by billing and provider taxonomy codes) within 18 months of the index

date. Using linked Medicare claims data, glaucoma cases were identified using International Classification of Disease, Ninth (ICD-9) and Tenth (ICD-10) edition codes. The ICD codes used to identify glaucoma by subtype are detailed in **Supplementary Appendix S2**. The strategy used to identify incident or prevalent glaucoma cases, identify controls, and assign cases to a glaucoma subtype is detailed in **Supplementary Appendix S3**.

Cognitive Assessment: Telephone Interview of Cognitive Status

Cognitive functioning in the HRS was measured using a modified version of the TICS, a standardized instrument used to test global cognitive functioning that has high specificity and sensitivity in differentiating common forms of dementia, such as AD, from normal cognitive status.[47] Using standardized scripts and procedures, the TICS was administered to participants during each wave of the HRS (every 2 years). Participants were asked to complete a 10 word immediate and delayed recall tests for verbal episodic memory, a serial 7s subtraction test for working memory, and a counting backwards test for attention and processing speed.. The scores range from 0-27 points, with higher scores indicating better cognitive performance.

Covariates:

Conceptually relevant covariates that may confound the association between glaucoma and cognitive function were included in the analyses. These include age at index enrollment, self-reported race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, Other), gender, educational attainment, and medical co-morbidities. Medical co-morbidities included separate dichotomous indicators for prior diagnosis of stroke, diabetes mellitus, systemic hypertension,

and cardiovascular disease, which were identified by self-report. Time invariant baseline values were used for all covariates.

Statistical Analysis

Baseline values for TICS scores and covariates by glaucoma status were characterized using descriptive statistics. To assess prevalent glaucoma as a predictor of levels of TICS scores, we used linear mixed models with random slopes and intercepts that account for repeated observations of cognitive function. TICS scores were modeled as a continuous variable. First, a model was constructed with diagnosis of any glaucoma (binary variable) as a predictor of TICS score, adjusted for age and baseline TICS score. Next, an interaction term between glaucoma and time (years since index) was added to the model to assess the association of glaucoma with rates of change in TICS scores. These models were repeated with full covariate adjustment for age, baseline TICS score, race/ethnicity, educational attainment, gender, and medical history.

To assess whether specific types of glaucoma were associated with cognitive performance, similar age-adjusted linear mixed models were constructed with categorical variables to represent glaucoma type. First, glaucoma was modeled with 4 categories (no glaucoma [reference category], POAG, NTG, other glaucomas) as a predictor of TICS scores. Next, since NTG may be considered a sub-type of POAG, the NTG and POAG categories were combined, yielding 3 categories of glaucoma.

Each analysis was repeated with incident glaucoma and glaucoma subtypes (instead of prevalent glaucoma) as the primary predictors. To account for each of these 10 tests, the p values generated by these models should be interpreted with a Bonferroni adjusted significance threshold of 0.005.

The above models used all available cognitive function measures in HRS for each participant, including measures from before and after the index date. This approach was chosen for the primary analysis, since if there were a unifying biological process (e.g., neurodegeneration, vasculopathy) underlying glaucoma and cognitive decline, one would expect this process to begin prior to a clinician diagnosis of glaucoma.[48] However, we also conducted a sensitivity analysis in which only cognitive function scores from after the incident enrollment date were included. We also conducted an exploratory analysis modeling glaucoma using six categories: no glaucoma [reference category], POAG, NTG, secondary OAG, ACG, other glaucomas). All statistical tests were two-sided and a significance threshold of $P < 0.05$ was used. Negative model parameter estimates indicate associations of glaucoma with worse cognitive function scores or steeper per-year declines in cognitive function scores. Data analysis was performed using Stata version 17.0 (StataCorp, College Station, TX).

RESULTS

Participant Characteristics

The full analytical sample included 1,344 cases with glaucoma (mean ± standard deviation (SD) age 72.6 ± 7.6 years, 64% female) and 5,729 controls (mean age 73.2 ± 7.2 years, 60% female). Analyses of prevalent glaucoma cases included 1,344 cases and 5,729 controls. Analyses of incident glaucoma included 886 cases and 4,385 controls. On average, these participants in were followed for a median (interquartile range) 6.8 (3.4-10.4) years in the glaucoma group and 4.5 (2.2-8.2) years in the control group. Maximum follow-up duration was 18 years. Among those with glaucoma, 772 had POAG, 62 had NTG, 253 had secondary OAG, 93 had ACG, and 164 had other glaucomas. Mean modified TICS score at study baseline was

14.4 (possible range: 0-27) for glaucoma cases and 14.7 for controls. Participant baseline characteristics by glaucoma status are presented in **Table 1** for the full analytical sample and in **Supplementary Appendix S4** for the subset used in the incident glaucoma analyses**.**

Glaucoma and Cognitive Function

The results of models assessing associations of prevalent and incident glaucoma with levels of and per-year rates of changes in TICS scores are summarized in **Table 2**. **Table 3** summarizes the results of covariate adjusted models using type of prevalent or incident glaucoma (no glaucoma, POAG, NTG, or other glaucoma) as a predictor of levels of and per-year rates of changes in TICS scores

Prevalent Glaucoma and Cognitive Function

No statistically significant associations between prevalent glaucoma and either levels of **(Figure 1)** or per-year rates of change **(Figure 2)** in TICS score. Results of these models are described in **Supplementary Appendix S5**.

Incident Glaucoma and Cognitive Function

This analysis included 886 individuals with incident glaucoma and 4,385 individuals with no glaucoma (this is slightly lower than the number of controls in the prevalent glaucoma analysis because inclusion in this analysis required ≥2 eyecare visits) (**Supplementary Appendix S4)**. In linear mixed models adjusted for age and baseline TICS score, those with incident glaucoma had similar age-adjusted TICS scores to controls ($\beta = 0.08$; 95% Confidence Interval [CI]: -0.11, 0.26; p=0.41). However, when also adjusting for sex, education,

race/ethnicity, and comorbid diseases, a significant association between glaucoma and higher TICS scores was observed (β = 0.27; 95% CI: 0.10, 0.44; p=0.002) **(Figure 1)**.

We also assessed associations of incident glaucoma with per-year rates of decline in cognitive scores by adding a glaucoma*time interaction term to our models. In both age-adjusted (β = -0.03; 95% CI: -0.05, -0.01; p=0.003) and fully adjusted (β = -0.030; 95% CI: -0.05, -0.01; p=0.004) models, participants with glaucoma had more rapid longitudinal declines in TICS scores than controls. The regression coefficients in these models represent the difference in per-year decline in TICS scores for glaucoma cases compared to controls. However, the intercept (baseline cognitive score) was higher for those with glaucoma compared to controls in in the fully-covariate adjusted model (β = 0.43; 95% CI: 0.23, 0.64; p<0.001) that compared trajectories, but not in the age-adjusted model (β = 0.24; 95% CI: 0.03, 0.45; p=0.11) **(Figure 2)**.

Glaucoma Type, Sensitivity, and Exploratory Analyses

No statistically significant associations between any glaucoma type and cognitive function were identified **(Table 3)**, including in the exploratory analysis including 6 categories of glaucoma. In a sensitivity analysis excluding TICS data that was collected prior to the incident diagnosis of glaucoma, results were similar to the primary analysis. The results of these analyses are further described in **Supplementary Appendix S5**.

DISCUSSION

In this longitudinal analysis of a population-based sample of U.S. adults, we found no evidence of a clinically significant association between prevalent or incident glaucoma and cognitive function. The statistically significant differences detected between those with and

without incident glaucoma were very small and are therefore unlikely to represent important inter-group differences. Similarly, when examining rates of cognitive decline by type of prevalent or incident glaucoma, we did not detect meaningful associations with cognitive trajectories. Based on the integration of administrative claims to identify glaucoma, rigorous longitudinal cognitive assessments, and a large population-based sample, this study provides evidence that a diagnosis of glaucoma alone may not be associated with substantial differences in levels or rates of decline of cognitive function.

Several basic science and translational studies have suggested possible mechanisms for a relationship between glaucoma and forms of dementia, particularly AD (see **Supplementary Appendix S6** for further detail).[13–23] Despite findings in the basic science and translational literature supporting a possible association of glaucoma with cognitive function or dementia, clinical and epidemiological research has provided mixed evidence. One prior small clinic based study reported an association of AD with glaucomatous changes of the optic nerve and retinal nerve fiber layer, as detected by confocal scanning laser tomography,[24] while a similar study did not.[28] While there is cross-sectional epidemiologic evidence of an association between glaucoma and dementia,[29–31] longitudinal studies have provided mixed evidence. Some have reported an association of glaucoma with dementia,[27,32,33] while others reported no association.[36–38] A recent meta-analysis found that five existing cohort studies reported no significant association between glaucoma and AD, whereas two case-control studies reported a pooled relative risk of 4.13 for AD in those with glaucoma, compared to controls.[34] Compared to cohort studies, case-control studies may be more susceptible to selection or recall bias, which could contribute to bias away from the null hypothesis (e.g., increased risk of a false positive result). The current study builds

on the prior literature by incorporating a large sample size, longitudinal follow-up, and robust repeated measures of cognitive function in a population-based sample.

While several studies have assessed associations between glaucoma and dementia, relatively few have studied the relationship between glaucoma and cognitive function. To the best of our knowledge, the present study provides the first longitudinal evidence regarding the association of glaucoma with objectively measured cognitive function. Some cross-sectional studies have reported an significant association between glaucoma and cognitive function scores,[39,40,49,50] while others found no such association.[41,42] Among prior cross-sectional studies, the most robust evidence comes from a study of 3,127 participants in the Beijing Eye Study, in which those with ACG had cognitive function scores that were 0.07 standard deviations lower than those without ACG, though no association was found between POAG and cognitive function in that study.[50] The present study builds on this prior work by longitudinally following more than 5,000 individuals from a population-based cohort for up to 18 years. Accordingly, our investigation provides robust evidence on the association between glaucoma and changes in cognitive function, suggesting that a clinically significant association may not be present.

In addition to incorporating longitudinal follow-up, our study also has a larger sample size than prior studies on this topic. This large sample size allowed us to examine specific types of glaucoma. This is particularly noteworthy given recent interest in assessing associations between NTG and dementia, which may share common etiologies (e.g., vascular deregulation, cerebrospinal fluid abnormalities, or genetic mutations in the *OPTN* or *TBK1* gene).[41] However, evidence for an association between NTG and dementia has been limited, with the strongest evidence coming from a cross-sectional case-control study of 290 participants that reported a 2-fold increase in prevalence of cognitive impairment among those with NTG, compared to

POAG.[41] However, that study defined NTG and POAG based on highest recorded IOP (≤21 mmHg vs ≥25 mmHg; excluding those with highest IOP 22-24 mmHg from the analysis) and did not compare NTG or POAG to non-glaucomatous controls. In contrast, our study provides no evidence for a clinically significant association between NTG and either levels or trajectories of cognitive function.

While we found no evidence of a clinically meaningful association of glaucoma with cognitive function, there is a well-characterized association between vision impairment and cognitive function. In fact, in a meta-analysis, vision impairment was significantly associated with cognitive decline and a greater than 2-fold increased odds of dementia among longitudinal studies that objectively assessed vision.[6] Several mechanisms have been proposed for this association. Those with poor vision may: have decreased afferent sensory input causing direct alterations to the brain; engage in less cognitively stimulating activity; experience decreased social and/or physical activity that mediates this association; and/or struggle with increased cognitive load.[51] Thus, it is possible that, while glaucoma itself is not associated with cognitive trajectories, vision impairment due to glaucoma could be related to changes in cognition. While one study has reported that severity of glaucoma was not associated with risk of dementia,[37] a recent cross-sectional study found 2.6 times greater odds of mild cognitive impairment in those with severe glaucoma compared to those with mild glaucoma.[52] Moreover, a study of 115 people found that those with longitudinal declines in cognitive function scores had higher variability in their visual field testing results.[53] Further research with larger sample sizes and robust measures of cognitive function are needed to characterize this relationship more fully.

The results of this study should be interpreted in the context of the following limitations. First, this study used administrative claims to determine glaucoma diagnoses. Thus, there could

be misclassification bias due to systematic over-reporting or underreporting of certain types of glaucoma. Nevertheless, we sought to reduce the likelihood of this by only including individuals who had at least two visits with an ophthalmologist or optometrist. Moreover, we addressed this limitation by categorizing glaucomas using an algorithm designed to minimize misclassification of the type of glaucoma (e.g., POAG, ACG, etc.) **(Appendix 2)**. Prior studies have suggested high accuracy of administrative claims ICD diagnosis codes to identify subjects with glaucoma.[54,55] However, the accuracy of ICD codes to identify glaucoma subtypes is unknown. Second, while we adjusted for several covariates, including age, baseline TICS score, sex, self-reported race, educational attainment, and comorbid diseases, residual confounding is possible in analyses of observational data. For example, we did not adjust for glaucoma treatment. Adjustment for such factors would be expected to bring model estimates closer to the null hypothesis, and thus would be unlikely to change the conclusions of this study. Third, this study only includes Medicare eligible participants (age ≥67.5 in the present study). Moreover, selection bias is possible in the sample since it only includes those who receive eye care. Some groups (e.g., Black race or Hispanic ethnicity) who are at disproportionately high risk for glaucoma and dementia are also more likely than others to not have access to eye care. Further research is needed to assess associations of glaucoma with cognitive function earlier in the life-course and among those who have limited access to outpatient care. Fourth, data on clinical severity of glaucoma was not available from ICD-9 codes, and clinical metrics like visual acuity or visual fields were not captured in this study. Thus, we were unable to test whether those with more severe glaucoma are likely to experience accelerated cognitive decline. Finally, individuals with only one ICD code diagnosis of glaucoma are excluded from the analysis. While this increases the specificity of our glaucoma definition, it may exclude some cases of glaucoma. In turn, this

may bias our results away from the null hypothesis (i.e., towards a false positive result). Because we report no clinically meaningful differences in TICS between those with and without glaucoma, inclusion of individuals with only one ICD diagnosis of glaucoma would not be expected to change the conclusions of this study.

Compared to prior research on this topic, which has provided mixed results, this study has a number of noteworthy strengths. First, this study provides longitudinal evidence from a large, population based sample, whereas prior studies either had relatively small samples and/or used cross-sectional data.[39–42] Second, given the relatively large sample size, we were able to categorize participants based on the type of glaucoma that they had (e.g., POAG, ACG, etc.); this permitted us to assess associations between specific types of glaucoma and cognitive function. Third, prior studies have commonly used dichotomous indicators of cognitive impairment or dementia,[27,32,33,35–37] and thus were not designed to study cognitive trajectories, as we were able to do in the current investigation.

In conclusion, in this large population-based study of older U.S. adults, we detected some small statistically significant associations between incident glaucoma and cognitive function. However, based on the magnitude of these associations, they are unlikely to be clinically meaningful. Compared to prior studies on this topic, this study provides robust evidence based on its larger sample size, longitudinal follow-up, repeated measured of cognitive function, and a population-based sample. Based on the documented consistent association between vision impairment, cognitive decline, and dementia[6] one possibility is that glaucoma-related vision loss could be a risk factor for adverse cognitive outcomes. Thus, additional research is needed to determine whether the magnitude of glaucomatous vision loss and/or specific types of visual loss due to glaucoma (e.g., visual field, contrast sensitivity) are associated with cognitive outcomes.

Given the large and growing population of older adults in the U.S. and globally, a more complete understanding of the relationship between glaucoma and cognitive health is needed to promote wellbeing and healthy aging.

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Supplementary Material

Supplementary Appendix S1: Definitions of Glaucoma Cases and Controls for the Analyses of Prevalent and Incident Glaucoma (cases were defined using Medicare claims as described in Appendix 2).

Supplementary Appendix S2: International Classification of Disease, Ninth (ICD-9) and Tenth (ICD-10) edition codes used for the categorization of glaucoma.

Supplementary Appendix S3: Strategy for Identifying Prevalent and Incident Glaucoma Cases and Controls, and Algorithm for Sub-Categorization of Glaucoma

Supplementary Appendix S4: Baseline Characteristics of 5,271 Older Adults in the United States, with Incident Glaucoma or No Glaucoma During the Study Period

Supplementary Appendix S5: Supplementary Results; Prevalent Glaucoma and Cognitive Function; Glaucoma Type and Cognitive Function; Sensitivity and Exploratory Analyses

Supplementary Appendix S6: Basic science studies reporting proposed mechanisms for an association of glaucoma with cognitive function, particularly Alzheimer's Disease

Table 1: Baseline Characteristics of 7,073 Older Adults in the United States, by Glaucoma Status

Characteristic	Any Glaucoma (n=1,344)	No Glaucoma (n=5,729)	p-value, glaucoma vs no glaucoma
Age at baseline, mean (SD)	72.6 (7.6) years	73.2 (7.2) years	<0.01 (1)
Women, n (%)	856 (63.7%)	3,446 (60.1%)	0.017 (2)
Years of Formal Education			0.18 (2)
0-11 Years, n (%)	361 (26.9%)	1,395 (24.3%)	
12 Years, n (%)	446 (33.2%)	2,045 (35.7%)	
13-15 Years, n (%)	263 (19.6%)	1,105 (19.3%)	
≥16 Years, n (%)	274 (20.4%)	1,184 (20.7%)	
Ethnicity			<0.001 (2)
Non-Hispanic White	937 (69.7%)	4,851 (84.7%)	
Non-Hispanic Black	261 (19.4%)	507 (8.9%)	
Hispanic	116 (8.6%)	279 (4.9%)	
Other	30 (2.2%)	92 (1.6%)	
Comorbid Disease (self-reported)			
Hypertension	863 (64.2%)	3,541 (61.8%)	0.10 (2)
Type 2 Diabetes Melitus	337 (25.0%)	1,277 (22.3%)	0.03 (2)
Cardiovascular Disease	334 (24.9%)	1,855 (32.4%)	<0.001 (2)
Stroke	100 (7.4%)	489 (8.5%)	0.19 (2)

1. **Two-sample t-test**
2. **Pearson chi square test**

Table 2: Associations of Prevalent and Incident Glaucoma with Levels and Rates of Change in

Predictor	Between Group Difference for Glaucoma Cases compared to Controls (1)	Age-Adjusted Model			Fully Covariate Adjusted Model (2)		
		β	95% CI	p	β	95% CI	p
Prevalent Glaucoma (n=7,073)	Levels of Cognitive Function Scores	0.01	-0.15, 0.18	0.86	0.14	-0.02, 0.30	0.08
	Rate of Change in Cognitive Function Scores (per year) (3)	0.01	-0.02, 0.02	0.65	0.007	-0.02, 0.04	0.65
Incident Glaucoma (n=5,271)	Levels of Cognitive Function Scores	0.077	-0.11, 0.26	0.41	0.27	0.10, 0.44	0.002
	Rate of Change in Cognitive Function Scores (per year) (3)	-0.031	-0.05, -0.01	0.003	-0.03	-0.05, -0.01	0.004

Telephone Interview for Cognitive Status (TICS) Scores in Linear Mixed Models

1. Negative model parameter estimates indicate associations of glaucoma with worse cognitive function scores or steeper per-year declines in cognitive function scores.
2. Both models adjusted for age and baseline TICS score. The fully covariate adjusted model included adjustment for sex, education, self-reported race, and history of hypertension, type 2 diabetes melitus, cardiovascular disease, and stroke.
3. The parameter estimate for the glaucoma*time interaction term is presented in the table.

Table 3: Covariate Adjusted Linear Mixed Models of Prevalent and Incident Glaucoma Type as a Predictor of Levels and Rates of Change of Cognitive Function Scores

Predictor:		Prevalent Glaucoma			Incident Glaucoma		
Glaucoma Category	Cognitive Function Outcome	β (1)	95% CI	p (2)	β (1)	95% CI	p (2)
No Glaucoma	-	ref.	ref.	ref.	ref.	ref.	ref.
POAG	Level of TICS Score	0.14	-0.06, 0.34	0.17	0.17	-0.08, 0.42	0.18
	Rate of Change in TICS Score (per year)	0.003	-0.03, 0.04	0.87	-0.01	-0.08, 0.02	0.19
NTG	Level of TICS Score	0.33	-0.33, 1.00	0.46	0.16	-0.31, 1.24	0.24
	Rate of Change in TICS Score (per year)	-0.02	-0.14, .10	0.77	0.06	-08, 0.20	0.39
Other Glaucoma (3)	Level of TICS Score	0.12	-0.12, 0.36	0.33	0.22	-0.08, 0.52	0.15
	Rate of Change in TICS Score (per year)	0.02	-0.02, 0.06	0.48	-0.01	-0.07, 0.05	0.77

Abbreviations: TICS: Telephone Interview for Cognitive Status. POAG: Primary Open Angle Glaucoma. NTG: Normal Tension Glaucoma.

1. Negative model parameter estimates indicate associations of glaucoma with worse cognitive function scores or steeper per-year declines in cognitive function scores. Models included adjustment for age, baseline TICS score, sex, education, self-reported race, and history of hypertension, type 2 diabetes melitus, cardiovascular disease, and stroke.
2. The results of these models should be interpreted using a Bonferroni adjusted significance threshold of p=0.005 to account for 10 multiple comparisons (Presented in the table: POAG vs no glaucoma, NTG vs no glaucoma, other glaucoma vs no glaucoma; presented in text only: POAG or NTG vs no glaucoma; other glaucoma vs no glaucoma).
3. Other Glaucoma includes Secondary Open Angle Glaucoma, Angle Closure Glaucoma and "Other Glaucoma" ICD diagnosis codes.

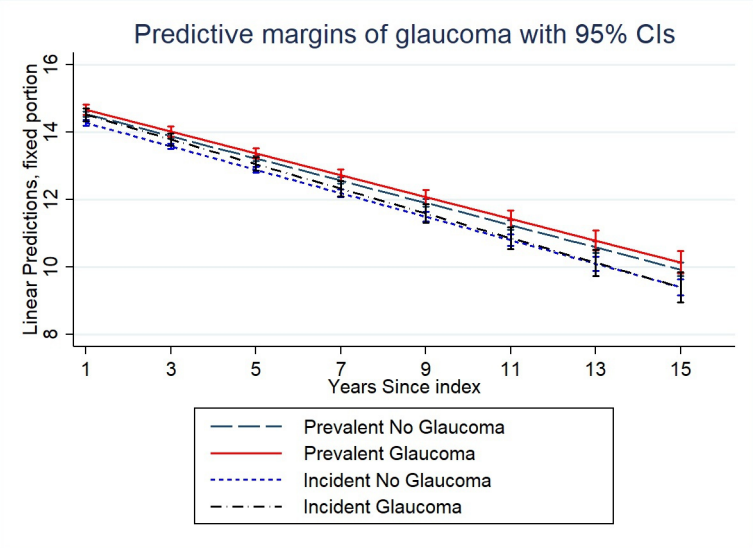
Figure Legend:

Figure 1: Associations of Prevalent and Incident Glaucoma with Levels and Rates of Change in Telephone Interview for Cognitive Status (TICS) Scores in Linear Mixed Models

TICS: Telephone Interview for Cognitive Statua. Negative model parameter estimates indicate associations of glaucoma with worse cognitive function scores or steeper per-year declines in cognitive function scores. Both models adjusted for age and baseline TICS score. The fully covariate adjusted model included adjustment for sex, education, self-reported race, and history of hypertension, type 2 diabetes melitus, cardiovascular disease, and stroke.
(1) The parameter estimate for the glaucoma*time (in years) interaction term is presented in the figure, so this estimate represents differences in per-year rates of decline in TICS scores.

Figure 2: Model Predicted Telephone Interview for Cognitive Status Trajectories for Individuals With and Without Prevalent and Incident Glaucoma

Overall, levels and rates of change in Telephone Interview for Cognitive Status scores were similar in the glaucoma an no glaucoma groups.



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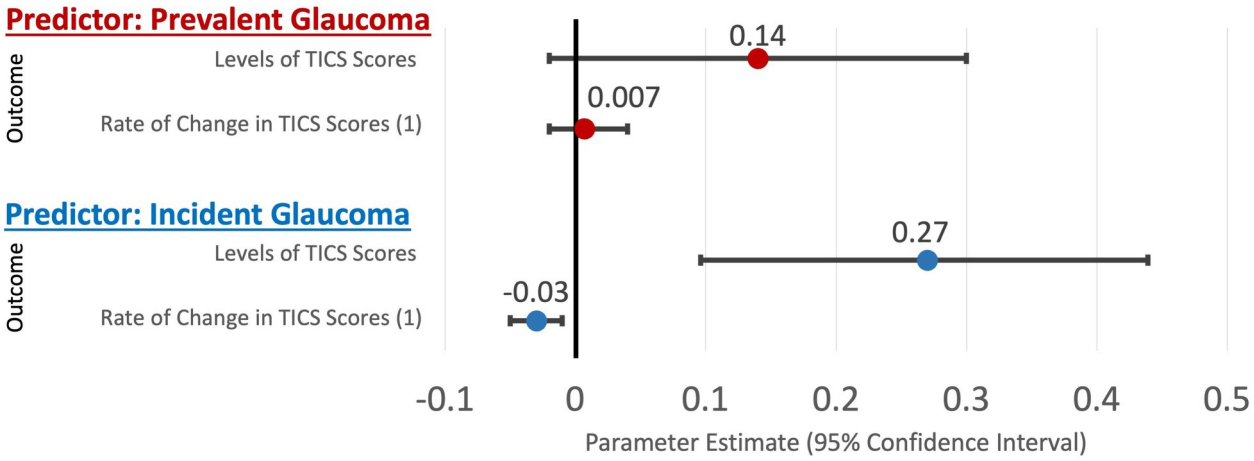

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