The Association of Glaucoma with Cognitive Function in a Population Based Longitudinal Study of older U.S. Adults: Findings from The Health and Retirement Study

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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).

Prevalent Glaucoma Analysis:

Cases:

- 2 glaucoma claims (Claim A & Claim B) in a 1.5 year period.
- Claim A observed between 1/1/1997 and 6/30/2014. The date of Claim A is the index date. Claim B occurs after Claim A.
- Respondents were age ≥65 years at the time of each claim.
- Respondents had Fee For Service (FFS) Medicare Part A&B coverage in 90% of the months in the 1.5 years following Claim A.
- We use the first observed pair of claims that meet the above criteria.

Controls:

- No glaucoma diagnosis in claims.
- 1 eye exam claim (Claim A).
- Claim A observed between 1/1/1997 and 6/30/2014. The date of Claim A is the index date.
- Respondents were age ≥65 years at the time of the claim.
- Respondents had FFS Medicare Part A & B coverage in 90% of the months in the 1.5 years following Claim A.
- For each possible control, we selected one eligible claim at random.

Incident Glaucoma Analysis

Cases:

- 2 glaucoma claims (Claim A & Claim B) in a 1.5-year period, with no glaucoma claims in 2.5 years prior to Claim A.
- Claim A observed between 1/1/1997 and 6/30/2013. The date of Claim A is the index date. Claim B occurs after Claim A.

- Respondents were age ≥67.5 years at the time of each claim.
- Respondents had FFS Medicare Part A & B coverage in 90% of the months in the 2.5 years prior to Claim A and in the 1.5 years following Claim A.
- We use the first observed pair of claims that meet these criteria.

Controls:

- No glaucoma diagnosis in claims.
- 2 eye exam claims (Claim A & Claim B).
- Claim A observed between 1/1/1997 and 6/30/2013. The date of Claim A is the index date. Claim B occurs 2.5 years prior to 1.5 years post Claim A (effectively 2 eye exam claims in 2.5 years)
- Respondents were age ≥67.5 years at the time of each claim.
- Respondents had FFS Medicare Part A & B coverage in 90% of the months in the 2.5 years prior to Claim A and in the 1.5 years following Claim A.
- For each possible control, we selected one eligible claim pair at random.

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

Primary Open-Angle Glaucoma (POAG)

ICD-9: 365.11, 365.12

ICD 10: H40.11, H40.12

Secondary Open-Angle Glaucoma (OAG)

ICD-9: 365.1x, 365.3x, 365.52, 365.62, 365.65

ICD-10:H40.1x, H40.3x, H40.4x, H40.6x

Angle Closure Glaucoma (ACG)

ICD-9: 365.2x

ICD-10: H40.2x

Normal Tension Glaucoma

ICD-9: 365.12

ICD-10: H40.1290

Glaucoma Suspect

ICD-9: 365.0

ICD-10: H40.0

All Other Glaucoma

ICD-9: All other 365.xx codes except 365.0x

ICD-10: All other H40.xx codes except H40.0x

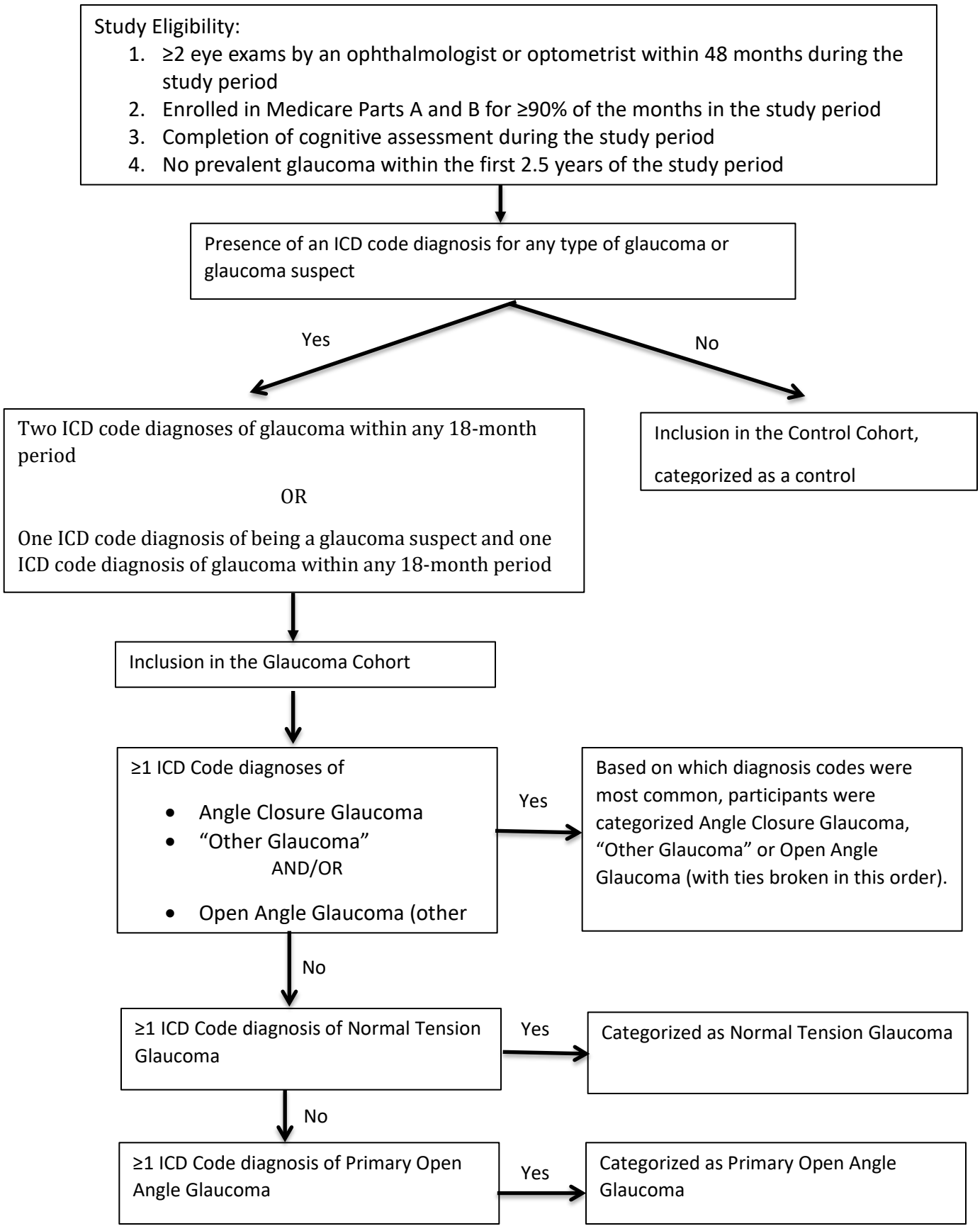
Supplementary Appendix S3: Strategy for Identifying Prevalent and Incident Glaucoma Cases and Controls, and Algorithm for Sub-Categorization of Glaucoma

Glaucoma was categorized as either 1) two ICD code diagnoses of glaucoma within any 18-month period; or 2) one ICD code diagnosis identifying glaucoma suspect and one identifying a diagnosis of glaucoma within any 18-month period. Individuals categorized as having glaucoma at any time point were included in the prevalent glaucoma cohort. To categorize incident glaucoma, a 2.5-year look-back period was used to evaluate whether individuals had prevalent glaucoma at the time of study enrollment. Those with a diagnosis of glaucoma or glaucoma suspect during the look-back period were excluded from the incident glaucoma cohort. Index date for both incident and prevalent glaucoma cases was the time of the first ICD code diagnosis of glaucoma (not including glaucoma suspect).

Some individuals had ICD code diagnoses for multiple subtypes of glaucoma. First, if individuals had ≥1 claim for angle-closure glaucoma (ACG), other glaucomas, or a secondary open-angle glaucoma (OAG), they were assigned to whichever diagnosis was most common. Ties were broken in this order: ACG, other glaucoma, OAG. Second, among those without diagnosis codes of secondary OAG, ACG, or other glaucoma, individuals with diagnosis codes for NTG were assigned to NTG. Third, individuals with diagnosis codes for POAG (without diagnosis codes for any other glaucoma type) were assigned to POAG. This strategy was designed with the intention of minimizing misclassification bias in the presence of conflicting ICD code diagnoses. For example, some individuals with less common types of glaucoma (e.g.,

NTG, pseudoexfoliation glaucoma, etc.) could also receive diagnoses of POAG (e.g., via misdiagnosis, coding error, as a provisional diagnosis while further workup was pending, etc.). Thus, participants were only categorized as having POAG if they did not have diagnosis codes for any other glaucoma subtype. Using this approach, we identified 1,271 glaucoma cases with mean age at index enrollment of 77.6 years. The algorithm is depicted in the figure below.

To select controls to match the prevalent glaucoma cohort, individuals with ≥1 eye exam claim were eligible for inclusion in the control cohort. To select controls to match the incident glaucoma cohort, individuals with ≥2 eye exams with an ophthalmologist or optometrist within a 48-month period were eligible for inclusion in the control cohort. Among these individuals, those without any ICD diagnosis code for any type of glaucoma or glaucoma suspect were included in the control cohort. Index date for each control was randomly selected from the dates of his or her eye examinations.


Study Eligibility:
1. ≥2 eye exams by an ophthalmologist or optometrist within 48 months during the study period
2. Enrolled in Medicare Parts A and B for ≥90% of the months in the study period
3. Completion of cognitive assessment during the study period
4. No prevalent glaucoma within the first 2.5 years of the study period
Presence of an ICD code diagnosis for any type of glaucoma or glaucoma suspect
Yes
No
Two ICD code diagnoses of glaucoma within any 18-month period
OR
One ICD code diagnosis of being a glaucoma suspect and one ICD code diagnosis of glaucoma within any 18-month period
Inclusion in the Control Cohort, categorized as a control
Inclusion in the Glaucoma Cohort
≥1 ICD Code diagnoses of
Angle Closure Glaucoma
"Other Glaucoma"
AND/OR
Open Angle Glaucoma (other
Yes
Based on which diagnosis codes were most common, participants were categorized Angle Closure Glaucoma, "Other Glaucoma" or Open Angle Glaucoma (with ties broken in this order).
No
≥1 ICD Code diagnosis of Normal Tension Glaucoma
Yes
Categorized as Normal Tension Glaucoma
No
≥1 ICD Code diagnosis of Primary Open Angle Glaucoma
Yes
Categorized as Primary Open Angle 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

Characteristic	Glaucoma (n=886)	No Glaucoma (n=4,385) (1)	p-value, glaucoma vs no glaucoma
Age, mean (SD)	69.4 (7.8) years	67.8 (8.5) years	<0.001 (2)
Women, n (%)	561 (63.3%)	2,654 (60.5%)	0.12 (3)
Years of Formal Education			0.31 (3)
0-11 Years, n (%)	230 (26.0%)	1,030 (23.5%)	
12 Years, n (%)	300 (33.9%)	1,595 (36.4%)	
13-15 Years, n (%)	178 (20.1%)	848 (19.3%)	
≥16 Years, n (%)	178 (20.1%)	912 (20.8%)	
Ethnicity			<0.001 (3)
Non-Hispanic White	649 (73.3%)	3,845 (87.7%)	
Non-Hispanic Black	135 (15.2%)	305 (7.0%)	
Hispanic	77 (8.7%)	173 (4.0%)	
Other	62 (1.4%)	25 (2.8%)	
Comorbid Disease (self-reported)			
Hypertension	451 (50.9%)	2113 (51.8%)	0.14 (3)
Type 2 Diabetes Melitus	150 (16.9)	585 (13.3%)	0.005 (3)
Cardiovascular Disease	169 (19.1%)	933 (21.3%)	0.14 (3)
Stroke	57 (6.4%)	252 (5.8%)	0.42 (3)

1. **The number of individuals with no glaucoma is lower in this subset, since**
2. **Two-sample t-test**
3. **Pearson chi square test**

Supplementary Appendix S5: Supplementary Results

Prevalent Glaucoma and Cognitive Function

In linear mixed models adjusted for age and baseline TICS score, those with glaucoma had similar age-adjusted TICS scores to controls (β = 0.01; 95% Confidence Interval [CI]: -0.15, 0.18; p=0.86). Results were nearly identical when also adjusting for sex, education, race/ethnicity, and comorbid diseases (β = 0.14; 95% CI: -0.02, 0.30; p=0.082) **(Figure 1)**.

We assessed associations of prevalent 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 = 0.01; 95% CI: -0.02, 0.04; p=0.65) and fully adjusted (β = 0.007; 95% CI: -0.02, 0.04; p=0.65) models, participants with glaucoma similar longitudinal declines in TICS scores compared to controls. The regression coefficients in these models represent the difference in per-year decline in TICS scores for glaucoma cases compared to controls. Moreover, the intercept (baseline cognitive score) was also similar for those with glaucoma vs no glaucoma in both models. Predicted TICS trajectories over time for individuals with and without glaucoma are depicted in **Figure 2**.

<u>Glaucoma Type and Cognitive Function</u>

First, glaucoma was modeled using four categories: no glaucoma, POAG, NTG, and other glaucoma. With this categorization, there were no statistically significant differences between any glaucoma type and controls in levels or per-year declines of TICS scores **(Table 3).** This finding was consistent in models using both prevalent glaucoma and incident glaucoma as predictors and in both age-adjusted and fully covariate adjusted models (**Table 3)**. When modeling prevalent or incident glaucoma using three categories

(no glaucoma, POAG or NTG, or other glaucoma), there were also no statistically significant differences detected.

Sensitivity and Exploratory Analyses

In a sensitivity analysis excluding TICS data that was collected prior to the incident diagnosis of glaucoma, results were similar to the primary analysis. While some statistically significant findings were observed, no clinically significant associations were detected between glaucoma and TICS scores or between glaucoma and rates of decline in TICS scores. In an exploratory analysis modeling glaucoma using 6 categories (no glaucoma [reference category], POAG, NTG, secondary OAG, ACG, other glaucomas), no statistically significant associations of any glaucoma subtype with TICS were identified.

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

The pathogenesis of Alzheimer's Disease (AD) involves loss of neurons in the hippocampus and cerebral cortex resulting from the abnormal accumulation of misfolded amyloid beta (Aβ) and tau proteins in the brain.[1] Aβ neurotoxicity may be involved in the development of retinal abnormalities and glaucomatous retinal ganglion cell death.[2–4] Furthermore, altered Tau levels have been detected in the retina and optic nerve of patients with glaucoma and may be associated with visual dysfunction.[5–7] Other proposed theories for the glaucoma-dementia relationship include: insufficient clearance of neurotoxins including Aβ in the glymphatic system;[8] presence of optineurin (a contributory gene to adult-onset primary open angle glaucoma) in the neurofibrillary tangles and dystrophic neurites characteristic of AD;[9] involvement of calcineurin in the inflammatory processes of AD as well as glaucomatous RGC degeneration;[10,11] and autophagic dysregulation.[12] While this prior work has suggested possible mechanisms for an association of glaucoma with changes in cognitive function, the present study suggests that such an association with receiving a diagnosis of glaucoma may not exist. Further research is therefore needed to characterize the relationships between AD, cognitive decline and severity of glaucoma and glaucoma-related vision loss.

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