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Glaucoma, Alzheimer's Disease and Other Dementia: A Longitudinal Analysis

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Abstract

Purpose—To evaluate the risk of developing Alzheimer's disease (AD) or other dementia in patients diagnosed with open-angle glaucoma (OAG) in a nationally representative longitudinal sample of elderly persons.

Methods—This is a longitudinal retrospective cohort study (January 1, 1994 – December 31, 2007) that used Medicare 5% claims data. We identified beneficiaries aged 68+ years who had at least 2 claims with diagnoses of OAG and no Alzheimer's or other dementia in 1994, using a 3 year look-back period between 1991–1993 ($n = 63,235$) and beneficiaries matched on age, sex, race, and Charlson index without a diagnosis of OAG throughout the observational period ($n = 63,235$) using propensity score matching. Using a Cox Proportional Hazards model, we analyzed time to Alzheimer's disease diagnosis and time to Alzheimer's disease or other dementia diagnosis.

Results—Elderly individuals diagnosed with OAG did not have an increased rate of AD and other dementia diagnosis compared to those without OAG during a 14-year follow-up period, even after controlling for relevant covariates present at baseline.

Conclusions—Individuals aged 68+ years diagnosed with OAG have a decreased rate of AD or other dementia diagnosis compared to control patients without an OAG diagnosis. Although OAG and AD are both age-related neurodegenerative diseases, our findings do not support a positive association.

Introduction

Glaucoma is a group of optic neuropathies that have in common a degeneration of retinal ganglion cells and their axons, resulting in a characteristic optic nerve appearance and corresponding visual field defects.¹ Open-angle glaucoma (OAG) is the most common glaucoma type. Without treatment, glaucoma can cause visual disability and eventually blindness.¹ Currently intraocular pressure (IOP) is the only proven treatable factor but increasing attention is being paid to neuroprotection as a treatment approach.²

Alzheimer's disease (AD) is the most common cause of dementia in the elderly.³ It is an acquired progressive neurodegenerative disorder characterized clinically by gradual cognitive decline and behavioral impairment.⁴ Pathologically, hallmarks of AD include

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extracellular β -amyloid ($A\beta$) senile plaques and intracellular neurofibrillary tangles composed of abnormally phosphorylated tau protein.^{5,6} A major genetic risk factor for late-onset AD is the epsilon 4 allele of apolipoprotein E (*APOE*),⁷ which has been implicated in the pathogenesis of OAG, specifically normal-tension glaucoma.⁸ However, conflicting data exists as to whether *APOE* polymorphisms increase the risk of OAG.^{9,10}

While there has been growing interest in a possible relationship between these 2 age-related neurodegenerative diseases, the specific mechanisms of a possible shared pathogenesis remain unknown. Structural studies of optic nerves from AD patients have also exhibited degeneration and loss of retinal ganglion cells, similar to that of OAG.¹¹⁻¹³ On a molecular level, caspase activation and abnormal processing of amyloid precursor protein (APP), key events in the pathogenesis of AD, have been shown to occur in a rat model of chronic ocular hypertension.¹⁴ Additionally, $A\beta$ has been implicated in retinal ganglion cell (RGC) apoptosis in the same model of experimental glaucoma.¹⁵

Although several clinical studies have demonstrated increased prevalence of OAG in patients with AD,¹⁶⁻¹⁸ only 1 population-based epidemiologic study has been published to examine whether glaucoma patients have an increased prevalence of AD. That study, from Denmark, did not find an increased risk of AD in glaucoma patients, but the study cohorts were not matched on demographic characteristics.¹⁹

We examined a nationally representative sample of persons in the U.S. with OAG newly diagnosed prior to 1994 and whether these persons were at increased risk of receiving an AD or other dementia (AD/dementia) diagnosis compared to a well-matched control population without a diagnosis of glaucoma over the next 14 years. While studies have linked OAG to AD, associations between OAG and other dementias (OD) are not well documented. We included other dementias with Alzheimer's disease (ADOD) in a broader definition as an alternative to a measure for Alzheimer's disease (AD) only. Many persons are diagnosed with both AD and other dementias in Medicare claims data,²⁰ which suggests some clinical uncertainty in the dementia diagnosis or the specificity of the coding or both.

Methods

Data

We used the 5% sample of Medicare claims data for information on diagnoses (International Classification of Diseases, 9th Revision, Clinical Modification, ICD-9-CM), procedures (Current Procedural Terminology, CPT-4; Healthcare Common Procedure Coding System, HCPCS), U.S. Centers for Medicare and Medicaid Services (CMS) provider physician specialties, and service dates. These data were merged with Medicare denominator files for information on enrollment dates in fee-for-service Medicare, death, and beneficiary demographic characteristics. Data were linked by a unique identifier, allowing longitudinal, person-specific analysis from 1991-2007.

Study Population

Individuals were classified as having OAG (ICD-9-CM codes: 365.1 open-angle glaucoma; 365.10 open-angle glaucoma, unspecified; 365.11 primary open-angle glaucoma; 365.12 low tension glaucoma; 365.15 residual stage of open angle glaucoma) if they received diagnoses of OAG on at least 2 claims, or received at least 1 diagnosis of OAG and 1 OAG-related procedure (CPT-4 codes: 65855, 66150, 66155, 66160, 66165, 66170, 66172, 66180, 66185, 66250, 66710, 66711, 66720) at any time between January 1, 1991 and December 31, 1993. Diagnosis date was recorded as of January 1, 1994.

To ensure that an individual had no prior diagnosis of AD (ICD-9-CM: 331.0) or other dementia (ICD-9-CM: 290, 290.0-4, 290.8-9, 291.0, 291.2, 292.82, 294.0-1, 294.8, 331.1-2, 331.7, 331.82, 797.xx) on a Medicare claim, we also employed the same 3-year look-back period. Individuals without a full look-back period were excluded from the sample. Persons entering in Medicare risk plans (HMO) or residing outside of the U.S. for >12 months during the look-back period and individuals aged <68 and >95 were also excluded. We also required individuals to remain in the sample for at least 1 year following January 1, 1994 and to have at least 3 visits to a general physician (CMS code: 01 (general practitioner), 08 (family practitioner), 11 (internist)) or a specialist in cognitive function (13 (neurologist), 26 (psychiatrist), 86 (neuropsychiatrist)) during the follow-up period to ensure physicians had a valid opportunity to diagnose patients with Alzheimer's disease or other dementia.

We then created a control sample to match our OAG sample. Searching Medicare claims from 1991-2007, we required control persons to have never had a claim with a diagnosis of *any* glaucoma-related diagnosis. The baseline date for these individuals was defined as January 1, 1994. We then performed a 3-year look-back with the same age, HMO, and living abroad restrictions. Individuals with a claim with any prior diagnosis of AD or ADOD were also excluded. To confirm the lack of a glaucoma diagnosis, all control individuals had to have at least 1 ophthalmologist/optometrist visit (CMS codes: 18 and 41) in the look back period prior to 1994 and at least 1 visit in the follow-up period. As with the OAG sample, we required control individuals to have a minimum of 3 general physician/neurology specialist visits during follow-up for the detection of AD or ADOD.

We then matched an OAG sample individual to the nearest control pool individual by propensity score matching (described below). Our final matched sample consisted of 63,235 individuals with OAG and an equal number of control individuals. After matching, we followed individuals for 14 years or until censored. Censoring occurred when an individual left fee-for-service Medicare to join an HMO, resided outside of the U.S., or died. Of those in the matched groups, 74.3 percent of persons with an OAG diagnosis died during the 14-year follow-up period while 71.9 percent in the control group did. 13.3 percent in the OAG groups joined at HMO during follow-up compared to 13.0 percent in the control group. 0.1 percent of persons in both groups left the U.S.

Propensity Score Matching

Propensity score matching permitted developing a non-OAG group with similar characteristics to persons with an OAG diagnosis, conditional on observed covariates. Matching on propensity scores reduces selection bias between individuals receiving a specific diagnosis and those without the diagnosis.^{21,22} The first step in the matching process was to conduct a logit analysis in which the dependent variable was 1 if the person was diagnosed with OAG and 0 if not diagnosed with OAG.

Covariates were binary variables for gender, Black race, Hispanic ethnicity, with White race the omitted reference group, and continuous variables for age and Charlson comorbidity index, a measure of general health.²³ The Charlson index contains 19 comorbidity categories, primarily defined from ICD-9-CM codes and some procedure codes. Each category has a weight based on the adjusted risk of 1-year mortality. The index depicts the increased probability of 1-year mortality. Higher scores on the index reflect more severe comorbidity.²⁴

Using the predicted probability of an individual having an OAG diagnosis from the logit regression, we paired an individual with OAG to his/her nearest match without a glaucoma diagnosis. Matching was accomplished using a SAS Greedy 5 to 1 digit match macro²⁵ in which the program attempted to make the best match first by matching OAG individuals

with controls based on exact matches of 5 digits of their propensity score. Considering all persons without an exact 5 digit match, the macro then attempted to match individuals based on 4 digits of their propensity score, then 3, then 2, and 1. Individuals who could not be matched on 1 digit were excluded. Standardized differences were calculated for the matched sample and revealed no differences >10%, resulting in a well-matched sample.^{26,27} We used SAS 9.1 for all statistical analysis conducted for this study.

Dependent Variables

Given matched OAG and non-OAG samples, the next step was to conduct Cox proportional hazard analysis for time to an AD or alternatively, ADOD diagnosis.

Explanatory Variables

Besides demographic characteristics and Charlson comorbidity index, we also included covariates in certain specifications for prior diagnosis of: OAG; wet age-related macular degeneration (AMD); dry AMD; unspecified AMD; background diabetic retinopathy (BDR); proliferative diabetic retinopathy (PDR); vitreous hemorrhage; cataract; pseudophakia or aphakia; and prior receipt of a cataract extraction procedure. For all of these covariates, except cataract extraction procedure, we required individuals to have received at least 2 claims with diagnoses during the look-back period in order to be classified with an eye diagnosis in the analysis. Further, we created a diagnosis hierarchy, assuming eye disease progression to be an absorbing state, i.e., once an individual progressed to a more severe stage, s/he only received a diagnosis for that more severe stage, for the following eye conditions: AMD, diabetic retinopathy, and cataract. For AMD, Wet AMD was the most severe diagnosis, followed by Dry AMD, and Unspecified AMD. PDR was more severe than BDR. Persons receiving a cataract extraction procedure could not simultaneously be coded as being pseudophakic/ aphakic, and pseudophakic/aphakic individuals could not be diagnosed with a cataract.

Statistical Approach

Time to event analysis was performed on the resulting matched sample using a Cox proportional hazards model. Unadjusted and adjusted time to: AD diagnosis alone and ADOD diagnosis were analyzed. We performed 3 specifications: (1) unadjusted for other covariates except OAG; (2) adjusted for OAG and the same covariates used in the propensity score matching described above; and (3) adjusted as in specification 2 but with the addition of comorbid eye conditions present at baseline.

We performed a number of sensitivity analyses. (1) Using the OAG sample and the full control pool without performing a propensity score match, we performed Cox regressions adjusting for the same covariates as in the main analysis. (2) We required individuals in the OAG and control pool to have a minimum of 2 physician visits during the follow up. (3) We required individuals in the OAG and control group to have had a minimum of only 1 visit during the follow-up period. (4) We relaxed the OAG inclusion criteria, allowing individuals with just 1 diagnosis of OAG to be included in our sample. For sensitivity analyses 2-4, we then performed propensity score matching and Cox regressions using the same model as in the main analysis. (5) Using the same OAG cohort as in the main analysis, we excluded from the control pool individuals never diagnosed with OAG, but allowed individuals with other types of glaucoma to be included in the control pool. (6) Individuals never diagnosed with OAG and other glaucoma (but not suspect and narrow angle glaucoma) were excluded from the control pool. We then performed propensity score matching and Cox regressions using the same model as in the main analysis. In this way, we sought to provide robustness of the analyses around issues of coding specificity for OAG and AD or ADOD as well as ascertainment bias issues related to access to the care system.

Results

Prior to propensity score matching, control individuals were younger and less likely to be Black as compared to OAG individuals (Table 1). After propensity score matching, the groups were well-matched (no standardized differences >10% between control and OAG samples).^{26,27}

There were no statistically significant differences in the fractions of persons in each cohort diagnosed with AD or ADOD. Persons in both OAG and non-OAG samples had a 0.17 probability of being diagnosed with AD and a 0.32 probability of being diagnosed with ADOD at follow-up (Table 2).

Without controlling for other covariates, individuals diagnosed with OAG had a 9 percent reduced hazard of receiving an AD diagnosis compared to individuals never diagnosed with glaucoma (Hazard ratio (HR): 0.91; 95% Confidence Interval (CI): 0.89,0.94; Table 3). Adjusting for other covariates did not affect the hazard of receiving an AD diagnosis among persons diagnosed with OAG (HR: 0.91; 95% CI: 0.88,0.93) compared to controls. Blacks, individuals with a higher Charlson comorbidity index, older individuals, individuals diagnosed with background diabetic retinopathy (BDR), cataract, pseudophakia/aphakia, and those undergoing a cataract surgery during the look-back period had an increased probability of receiving an AD diagnosis.

In the combined ADOD analysis, persons diagnosed with OAG had a 6 percent reduced hazard of receiving ADOD diagnosis (HR: 0.94; 95% CI: 0.92,0.96) compared to persons never diagnosed with OAG. Controlling for other covariates reduced the hazard of receiving ADOD diagnosis for individuals diagnosed with OAG slightly (HR: 0.93; 95% CI: 0.91,0.95) relative to persons never diagnosed with OAG. As in the AD only analysis, Blacks, persons with a higher Charlson index, more elderly persons, persons diagnosed with BDR, pseudophakia/aphakia, and individuals who had undergone a cataract surgery were more likely to receive an ADOD diagnosis during follow-up. In addition, males, persons diagnosed with wet age-related macular degeneration (AMD), and persons diagnosed with proliferative diabetic retinopathy (PDR) also had an increased hazard of ADOD diagnosis. Particularly in the ADOD analysis, the increased risk of dementia diagnosis during follow-up was substantial for persons who were diagnosed with BDR (HR:1.42; 95% CI: 1.30, 1.55) or PDR (HR:1.59; 95% CI: 1.38, 1.84) during the look-back period. Although smaller in terms of magnitude effects, having been diagnosed with cataract (HR:1.06; 95% CI: 1.02, 1.09), pseudophakia/aphakia (HR:1.12; 95% CI 1.05,1.19) or receiving cataract surgery (HR:1.07, 95% CI: 1.03, 1.11) during the look-back period predicted higher probabilities of receiving an AD diagnosis during follow-up, especially in persons having all 3.

Our results were robust to changes in the 6 separate sensitivity analyses we conducted. After accounting for a full set of covariates, OAG individuals were at a decreased risk of receiving AD and ADOD diagnosis in all sensitivity analyses (not shown).

Discussion

Our analysis revealed that individuals aged 68+ years diagnosed with OAG have a decreased rate of AD and ADOD diagnosis compared to control patients who were not diagnosed with OAG. Although OAG and AD are both age-related neurodegenerative diseases, our findings do not support a positive association. In a population matched on characteristics of persons diagnosed with OAG, there was an increased risk of AD and ADOD diagnoses in patients who had diagnoses of pseudophakia/aphakia or had undergone cataract surgery and an increase in AD among persons who had been diagnosed with cataract. Holding several other

potential influences constant, Blacks had a higher probability of acquiring an AD or ADOD diagnosis.

No previous epidemiologic study of OAG and AD in the U.S. has been based on a national longitudinal database with an observational period as long as 14 years. In contrast to our findings, small case series have demonstrated a possible increased rate of glaucoma among patients with AD.¹⁶⁻¹⁸

To date there has been 1 large-scale study to examine whether OAG is associated with increased risk of developing AD.¹⁹ Kessing and colleagues used a nationwide Danish case register of hospital admission data and subsequent outpatient visits to identify the rates of AD diagnosis in several cohorts: persons with OAG, angle-closure glaucoma, cataract, osteoarthritis, and the general population. No increased risk of developing AD was found in the OAG cohort versus the other cohorts or the general population. However, there are several notable differences between the design of our study and this Danish study. In the latter, each cohort was identified initially by discharge diagnosis after hospital admission.. Before 1995, patients in Denmark were hospitalized for glaucoma surgery. Therefore, there is a selection bias for patients with more advanced OAG disease. Additionally, while comparisons were made among the OAG cohort with cohorts with other eye conditions (angle closure glaucoma, cataract), as well as a cohort with osteoarthritis and the general population, the investigators did not match the cohorts on demographics or a comorbidity index, such as the Charlson index. Furthermore, no measures were taken to ensure that patients in the study did not have prior diagnoses of glaucoma or AD prior to hospital discharge.

We likewise found no positive association between the diagnosis of OAG and the subsequent development of AD or ADOD. Indeed, the data reveal a negative association. As such, it may be an actual negative relationship that may shed new light and directions on our understanding of these and related conditions. At the same time, however, there is no known biological or clinical reason why there should be a negative relationship between OAG and onset of AD or ADOD. It is also possible that more severe cases of OAG or AD/ADOD may be related; in claims data, unfortunately, we do not have severity indicators in these 2 disease areas. The percentages of beneficiaries exiting the sample during follow-up due to death, joining an HMO, or leaving the U.S. are too similar between the OAG and the control group to explain the association between OAG and incident AD or ADOD we report. If this negative relationship is spurious, it may be random chance or related to potential sources of ascertainment bias. First, the relationship may be co-existing or that AD may manifest prior to OAG, such that our study methods of examining if those with OAG who then develop AD or ADOD would not capture those situations. Second, some individuals in the control group in the look-back period may have been experiencing undiagnosed or subclinical cognitive decline and had less interest in the use of eyes for reading, watching television, and other activities requiring good vision. For this reason, they may have been less likely to visit eye care providers during latter phases of the look-back period. Eventually, during follow-up, such persons were diagnosed with AD or ADOD. Data from the Salisbury Eye Evaluation Project demonstrated that 2.2% of community-dwelling elderly had Mini-Mental State Examination (MMSE) scores of less than 18 (with moderately impaired cognitive function at scores between 10 and 20) and up to 15% had mildly impaired or worse cognitive function (<24) as measured by the MMSE.^{30,31} In contrast, patients diagnosed with OAG require frequent physician visits and may therefore be less likely to have underlying undiagnosed Alzheimer's disease that manifests as the cohort is followed over 14 years.

Even so, although we found negative relationships between prior diagnosis of OAG and AD and ADOD, we found positive relationships between prior diagnosis of diabetic retinopathy,

cataract and wet AMD (for ADOD) and subsequent AD and ADOD. It is possible that these eye conditions are better diagnosed than OAG because they are more frequently symptomatic and more easily diagnosed. Further, cataract and AMD have been demonstrated to be associated with aging factors that may share relationships with AD or ADOD. However, the literature on the risk of Alzheimer's disease and dementia in patients with age-related eye diseases is mixed. For example, when the Cardiovascular Health Study population was examined for the relationship between ADOD and early age-related macular degeneration (AMD), no relationship was found.³² But the Rotterdam study demonstrated that the presence of late AMD was associated with an increased risk of AD, although after adjusting for smoking and atherosclerosis, the association between late AMD and AD was attenuated and no longer statistically significant.³³ Furthermore, consistent with the Cardiovascular Health Study population, no relationship was found between early AMD and AD. As noted above, claims data in the case of OAG and AD or ADOD are not able to differentiate levels of severity of the disease for this analysis.

A possible explanation for the positive relationship between cataract and AD is that both cataract and AD are age-related disorders in which misfolded proteins aggregate into deposits associated with late disease onset; hence, it has been hypothesized that the two diseases may share a common biochemical pathway.³⁴ Indeed, β -amyloid has been identified in cataractous lenses and the lens protein α -crystallin has been found in brains of AD patients.^{35,36}

We also found an association between Black race and AD and AD/OD. Although there has been debate as to whether Black race increases the risk of AD diagnosis, there is a growing body of evidence that such an association exists.³⁷⁻⁴¹ We may have identified this relationship because we created a sample matched on glaucoma in which Blacks are overrepresented and more frequently interacting with physicians, therefore increasing the likelihood of receiving an AD or ADOD diagnosis as compared to Blacks without glaucoma.⁴² Other possible confounders, including education, apolipoprotein E genotype, history of stroke, hypertension, and diabetes mellitus, were not examined separately and may play a role in the relationship between race and ADOD.⁴³

Strengths of our study include use of a large, longitudinal, nationally representative sample of elderly individuals in the U.S. with a 14-year follow-up period. The matched cohorts of individuals with and without an OAG diagnosis allowed us to adjust for comorbid conditions and relevant demographics, thus eliminating the possibility of confounding risk factors that may affect ADOD diagnosis. Furthermore, we required all control individuals to have had at least one ophthalmologist/optometrist visit at baseline and during the follow-up period in order to confirm the lack of a glaucoma diagnosis.

We acknowledge several limitations. Identification of OAG and ADOD required a coded diagnosis in Medicare claims data by an eye care provider. Claims data, which are designed for administrative use, are often insensitive and subject to misclassification, failing to identify all persons with the diagnosis of interest. This may be particularly problematic for a diagnosis such as AD given the overlap with other broader diagnoses such as senile dementia, which is why we conducted a separate analysis to examine the relationship between OAG and the risk of receiving an AD or other dementia diagnosis. While under ascertainment may affect identification of AD cases, Taylor *et al.* found that 3 years of Medicare claims data are needed to adequately identify 80% of individuals with AD or other dementia. Our study used a 14-year follow-up period, ensuring a high level of sensitivity.⁴⁴ Our sensitivity analyses were designed to be able to address these issues to the extent possible within the constraints of administrative datasets.

In sum, this nationally longitudinal study documented that patients with open-angle glaucoma do not have increased rates of AD diagnosis. However, OAG patients with cataract or who have undergone cataract surgery may have increased rates of AD diagnosis, an area that deserves further exploration. Although glaucoma and Alzheimer's disease are both age-related neurodegenerative diseases, these findings do not support an increased risk of AD or dementia in glaucoma patients, although the two entities may share common pathophysiologic mechanisms.

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References

1. Kwon YH, Fingert JH, Kuehn MH, Alward WL. Primary open-angle glaucoma. *N Engl J Med*. Mar 12; 2009 360(11):1113–1124. [PubMed: 19279343]
2. Whitcup SM. Clinical trials in neuroprotection. *Prog Brain Res*. 2008; 173:323–335. [PubMed: 18929119]
3. Sloane PD, Zimmerman S, Suchindran C, et al. The public health impact of Alzheimer's disease, 2000-2050: potential implication of treatment advances. *Annu Rev Public Health*. 2002; 23:213–231. [PubMed: 11910061]
4. Blennow K, de Leon MJ, Zetterberg H. Alzheimer's disease. *Lancet*. Jul 29; 2006 368(9533):387–403. [PubMed: 16876668]
5. Masters CL, Simms G, Weinman NA, Multhaup G, McDonald BL, Beyreuther K. Amyloid plaque core protein in Alzheimer disease and Down syndrome. *Proc Natl Acad Sci U S A*. Jun; 1985 82(12):4245–4249. [PubMed: 3159021]
6. Grundke-Iqbal I, Iqbal K, Tung YC, Quinlan M, Wisniewski HM, Binder LI. Abnormal phosphorylation of the microtubule-associated protein tau (tau) in Alzheimer cytoskeletal pathology. *Proc Natl Acad Sci U S A*. Jul; 1986 83(13):4913–4917. [PubMed: 3088567]
7. Bu G. Apolipoprotein E and its receptors in Alzheimer's disease: pathways, pathogenesis and therapy. *Nat Rev Neurosci*. May; 2009 10(5):333–344. [PubMed: 19339974]
8. Vickers JC, Craig JE, Stankovich J, et al. The apolipoprotein epsilon4 gene is associated with elevated risk of normal tension glaucoma. *Mol Vis*. Oct 14; 2002 8:389–393. [PubMed: 12379839]
9. Zetterberg M, Tasa G, Palmer MS, et al. Apolipoprotein E polymorphisms in patients with primary open-angle glaucoma. *Am J Ophthalmol*. Jun; 2007 143(6):1059–1060. [PubMed: 17524782]
10. Copin B, Brezin AP, Valtot F, Dascotte JC, Bechettille A, Garchon HJ. Apolipoprotein E-promoter single-nucleotide polymorphisms affect the phenotype of primary open-angle glaucoma and demonstrate interaction with the myocilin gene. *Am J Hum Genet*. Jun; 2002 70(6):1575–1581. [PubMed: 11992263]
11. Hinton DR, Sadun AA, Blanks JC, Miller CA. Optic-nerve degeneration in Alzheimer's disease. *N Engl J Med*. Aug 21; 1986 315(8):485–487. [PubMed: 3736630]
12. Sadun AA, Bassi CJ. Optic nerve damage in Alzheimer's disease. *Ophthalmology*. Jan; 1990 97(1):9–17. [PubMed: 2314849]
13. Tsai CS, Ritch R, Schwartz B, et al. Optic nerve head and nerve fiber layer in Alzheimer's disease. *Arch Ophthalmol*. Feb; 1991 109(2):199–204. [PubMed: 1993028]
14. McKinnon SJ, Lehman DM, Kerrigan-Baumrind LA, et al. Caspase activation and amyloid precursor protein cleavage in rat ocular hypertension. *Invest Ophthalmol Vis Sci*. Apr; 2002 43(4):1077–1087. [PubMed: 11923249]
15. Guo L, Salt TE, Luong V, et al. Targeting amyloid-beta in glaucoma treatment. *Proc Natl Acad Sci U S A*. Aug 14; 2007 104(33):13444–13449. [PubMed: 17684098]
16. Bayer AU, Ferrari F, Erb C. High occurrence rate of glaucoma among patients with Alzheimer's disease. *Eur Neurol*. 2002; 47(3):165–168. [PubMed: 11914555]

17. Bayer AU, Keller ON, Ferrari F, Maag KP. Association of glaucoma with neurodegenerative diseases with apoptotic cell death: Alzheimer's disease and Parkinson's disease. *Am J Ophthalmol.* Jan; 2002 133(1):135–137. [PubMed: 11755850]
18. Tamura H, Kawakami H, Kanamoto T, et al. High frequency of open-angle glaucoma in Japanese patients with Alzheimer's disease. *J Neurol Sci.* Jul 15; 2006 246(1-2):79–83. [PubMed: 16564058]
19. Kessing LV, Lopez AG, Andersen PK, Kessing SV. No increased risk of developing Alzheimer disease in patients with glaucoma. *J Glaucoma.* Jan; 2007 16(1):47–51. [PubMed: 17224749]
20. Ukraintseva S, Sloan F, Arbeev K, Yashin A. Increasing rates of dementia at time of declining mortality from stroke. *Stroke.* May; 2006 37(5):1155–1159. [PubMed: 16601210]
21. D'Agostino RB. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Statistics in Medicine.* Oct; 1998 17(19):2265–2281. [PubMed: 9802183]
22. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika.* 1983; 70(1):41–55.
23. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A New Method of Classifying Prognostic Comorbidity in Longitudinal Studies: Development and Validation. *Journal of Chronic Diseases.* 1987; 40(5):373–383. [PubMed: 3558716]
24. Manitoba Centre for Health Policy. [Accessed 5/27/2011] Concept: Charlson Index. 2009. <http://mchp-appserv.cpe.umanitoba.ca/viewConcept.php?conceptID=1098>
25. Parsons, LS. Reducing Bias in Propensity Score Matched-Pair Sample Using Greedy Matching Techniques. Seattle, WA:
26. Austin PC. Propensity-score matching in the cardiovascular surgery literature from 2004 to 2006: A systematic review and suggestions for improvement. *Journal of Thoracic Cardiovascular Surgery.* 2007; 134:1128–1135. 1135.e1121–1135.e1123.
27. Normand SL, Landrum MB, Guadagnoli E, et al. Validating recommendations for coronary angiography following acute myocardial infarction in the elderly: A matched analysis using propensity scores. *J Clin Epidemiol.* 2001; 54:387–398. [PubMed: 11297888]
28. Chandra V, Bharucha NE, Schoenberg BS. Conditions associated with Alzheimer's disease at death: case-control study. *Neurology.* Feb; 1986 36(2):209–211. [PubMed: 3945392]
29. Schwartzbaum J, Ahlbom A, Feychting M. Berkson's Bias reviewed. *European Journal of Epidemiology.* Dec; 2003 18(12):1109–1112. [PubMed: 14758866]
30. Rubin GS, West SK, Munoz B, et al. A comprehensive assessment of visual impairment in a population of older Americans. The SEE Study. Salisbury Eye Evaluation Project. *Invest Ophthalmol Vis Sci.* Mar; 1997 38(3):557–568. [PubMed: 9071208]
31. Munoz B, West S, Rubin GS, Schein OD, Fried LP, Bandeen-Roche K. Who participates in population based studies of visual impairment? The Salisbury Eye Evaluation project experience. *Ann Epidemiol.* Jan; 1999 9(1):53–59. [PubMed: 9915609]
32. Baker ML, Wang JJ, Rogers S, et al. Early age-related macular degeneration, cognitive function, and dementia: the Cardiovascular Health Study. *Arch Ophthalmol.* May; 2009 127(5):667–673. [PubMed: 19433718]
33. Klaver CCW, Ott A, Hofman A, Assink JJM, Breteler MMB, de Jong P. Is age-related maculopathy associated with Alzheimer's disease? The Rotterdam Study. *Am. J. Epidemiol.* Nov; 1999 150(9):963–968. [PubMed: 10547142]
34. Harding JJ. Cataract, Alzheimer's disease, and other conformational diseases. *Curr Opin Ophthalmol.* Feb; 1998 9(1):10–13. [PubMed: 10178625]
35. Goldstein LE, Muffat JA, Cherny RA, et al. Cytosolic beta-amyloid deposition and supranuclear cataracts in lenses from people with Alzheimer's disease. *Lancet.* Apr 12; 2003 361(9365):1258–1265. [PubMed: 12699953]
36. Bjorkdahl C, Sjogren MJ, Zhou X, et al. Small heat shock proteins Hsp27 or alphaB-crystallin and the protein components of neurofibrillary tangles: tau and neurofilaments. *J Neurosci Res.* May 1; 2008 86(6):1343–1352. [PubMed: 18061943]

37. Demirovic J, Prineas R, Loewenstein D, et al. Prevalence of dementia in three ethnic groups: The south Florida program on aging and health. *Annals of Epidemiology*. Jul; 2003 13(6):472–478. [PubMed: 12875807]
38. Fillenbaum GG, Heyman A, Huber MS, et al. The prevalence and 3-year incidence of dementia in older Black and White community residents. *Journal of Clinical Epidemiology*. Jul; 1998 51(7): 587–595. [PubMed: 9674666]
39. Hebert LE, Scherr PA, Bienias JL, Bennett DA, Evans DA. Alzheimer disease in the US population - Prevalence estimates using the 2000 census. *Archives of Neurology*. Aug; 2003 60(8):1119–1122. [PubMed: 12925369]
40. Husaini BA, Sherkat DE, Moonis M, Levine R, Holzer C, Cain VA. Racial differences in the diagnosis of dementia and in its effects on the use and costs of health care services. *Psychiatric Services*. Jan; 2003 54(1):92–96. [PubMed: 12509673]
41. Tang MX, Cross P, Andrews H, et al. Incidence of AD in African-Americans, Caribbean Hispanics, and Caucasians in northern Manhattan. *Neurology*. Jan; 2001 56(1):49–56. [PubMed: 11148235]
42. Clark PC, Kutner NG, Goldstein FC, et al. Impediments to timely diagnosis of Alzheimer's disease in African Americans. *Journal of the American Geriatrics Society*. Nov; 2005 53(11):2012–2017. [PubMed: 16274388]
43. Shadlen MF, Siscovick D, Fitzpatrick AL, Dulberg C, Kuller LH, Jackson S. Education, cognitive test scores, and black-white differences in dementia risk. *Journal of the American Geriatrics Society*. Jun; 2006 54(6):898–905. [PubMed: 16776783]
44. Taylor DH Jr, Fillenbaum GG, Ezell ME. The accuracy of medicare claims data in identifying Alzheimer's disease. *J Clin Epidemiol*. Sep; 2002 55(9):929–937. [PubMed: 12393082]

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Table 1

Descriptive statistics of the unmatched and matched samples

Covariates used in matching	Unmatched		Matched		Std. Diff.
	OAG (n=63,325)	Control (n=421,217)	OAG (n=63,325)	Control (n=63,325)	
Male	0.36	0.37	0.36	0.34	-4.74
Black	0.11	0.041	0.11	0.11	0.025
Other race	0.02	0.017	0.02	0.021	-0.055
Charlson index [†]	1.28	1.21	1.28	1.34	3.34
Age (years)	78.5	77.0	78.5	78.5	-0.027

Notes: OAG: Open angle glaucoma; Std Diff – Standardized differences are calculated by subtracting the mean of the control group from the mean of the OAG group. We then divide the difference by the square root of the sum of the squared standard deviations of the control and OAG group divided by 2.

Std Diff = $100 * (x_i - x_{nti}) / (((s^2_i + s^2_{nti}) / 2) ^ {0.5})$

Data is presented as proportions unless otherwise noted.

[†]The Charlson index contains 19 comorbidity categories, which are weight based on the adjusted risk of 1-year mortality. The index depicts the increased probability of 1-year mortality with higher scores reflecting more severe comorbidity. Male, Black, and Other race are expressed as proportions, they too are mean values.

Table 2

Descriptive statistics: Outcomes and additional covariates

	OAG (n=63,325)	Control (n=63,325)
Outcomes		
Alzheimer's	0.17	0.17
Alzheimer's or other dementia	0.32	0.32
Additional covariates		
Age related macular degeneration (AMD), dry	0.031	0.027 †
AMD, wet	0.017	0.011 †
AMD, unspecified	0.055	0.050 †
Background diabetic retinopathy	0.015	0.013 †
Proliferative diabetic retinopathy	0.006	0.004 †
Vitreous hemorrhage	0.008	0.003 †
Cataract	0.29	0.28 †
Pseudophakia or aphakia	0.062	0.031 †
Cataract surgery	0.21	0.17 †
Narrow angle glaucoma	0.063	0.00 †
Other glaucoma	0.18	0.00 †
Suspect glaucoma	0.14	0.00 †

Notes: Data is presented as proportions. OAG –

† Open angle glaucoma; p<0.001.

Table 3

Hazard of Receiving Alzheimer's disease and Alzheimer's or other dementia Diagnosis: Hazard ratios and 95% confidence intervals in parentheses.*

	Alzheimer's disease (n=126,650)		Alzheimer's/other dementia (n=126,650)	
Open-angle glaucoma	0.91 (0.89,0.94)	0.91 (0.88,0.93)	0.94 (0.92,0.96)	0.93 (0.91,0.95)
Male		0.98 (0.95,1.01)		0.97 (0.95,0.99)
Black race		1.21 (1.16,1.26)		1.23 (1.20,1.27)
Other race		0.984 (0.892,1.084)		1.026 (0.96,1.10)
Charlson comorbidity index		1.033 (1.024,1.041)		1.07 (1.07,1.08)
Baseline age (in years)		1.083 (1.08,1.09)		1.10 (1.10,1.10)
Age-related macular degeneration (AMD), dry		1.04 (0.96,1.12)		1.05 (0.99,1.11)
AMD, wet		1.09 (0.98,1.22)		1.11 (1.03,1.20)
AMD, unspecified		1.03 (0.97,1.09)		1.03 (0.99,1.07)
Background diabetic retinopathy		1.20 (1.05,1.37)		1.42 (1.30,1.55)
Proliferative diabetic retinopathy		1.17 (0.92,1.48)		1.59 (1.38,1.84)
Vitreous hemorrhage		1.15 (0.95,1.39)		1.03 (0.90,1.18)
Cataract		1.06 (1.02,1.09)		1.02 (1.00,1.05)
Pseudophakia/aphakia		1.12 (1.05,1.19)		1.13 (1.08,1.18)
Cataract surgery		1.07 (1.03,1.11)		1.05 (1.03,1.08)

* The hazard ratio for open-angle glaucoma is unadjusted in the first and third specifications and adjusted in the second and fourth specifications.