Published in final edited form as:

Alzheimers Dement. 2019 January ; 15(1): 34–41. doi:10.1016/j.jalz.2018.06.2856.

Associations between recent and established ophthalmic conditions and risk of Alzheimer's disease

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Abstract

Introduction: Identifying ophthalmic diseases associated with increased risk of Alzheimer's disease (AD) may enable better screening and understanding of those at risk of AD.

Methods: Diagnoses of glaucoma, age-related macular degeneration (AMD), and diabetic retinopathy (DR) were based on International Classification of Diseases, 9th revision, codes for 3877 participants from the Adult Changes in Thought study. The adjusted hazard ratio for developing probable or possible AD for recent (within 5 years) and established (>5 years) diagnoses were assessed.

Results: Over 31,142 person-years of follow-up, 792 AD cases occurred. The recent and established hazard ratio were 1.46 ($P = .01$) and 0.87 ($P = .19$) for glaucoma, 1.20 ($P = .12$) and 1.50 ($P < .001$) for AMD, and 1.50 ($P = .045$) and 1.50 ($P = .03$) for DR.

Discussion: Increased AD risk was found for recent glaucoma diagnoses, established AMD diagnoses, and both recent and established DR. People with certain ophthalmic conditions may have increased AD risk.

Keywords

Alzheimer's disease; Adult Changes in Thought (ACT); Ophthalmology; Diabetic retinopathy; Age-related macular degeneration; Glaucoma; Cataract

1. Introduction

Over 46 million older adults are affected by dementia worldwide; 131.5 million cases are expected by 2050 [1]. Alzheimer's disease (AD) is the most common dementia [2].

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Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.jalz.2018.06.2856>.

Research regarding AD risk factors may lead to early detection and preventive measures based on better understanding neurodegenerative processes [3].

Referred to as “the window to the brain,” the eye provides substantial information on brain health [4]. Previous studies suggest that glaucoma, age-related macular degeneration (AMD), and diabetic retinopathy (DR) may be associated with dementia due to shared characteristics such as progressive neurodegeneration, characteristic amyloid β deposits, and chronic microvascular insults [4]. Cataract is similar in being heavily age-related. However, cataract is a disease of the lens, so it does not share pathophysiological mechanisms with AD. We hypothesized that the three aforementioned conditions would be associated with AD. Most earlier studies lacked large, prospective cohorts with precise dementia definitions [5–9]. No study has investigated associations of all four sight-threatening conditions with AD risk using research AD diagnostic criteria.

Adult Changes in Thought (ACT) is an ongoing prospective cohort study begun in 1994 of now >5400 adults aged ≥ 65 who were dementia-free at enrollment and followed until development of dementia, dropout, or death [10]. Using this large, prospective cohort’s data, we sought to determine associations with AD risk of glaucoma, AMD, DR, and cataract.

2. Methods

Relevant Institutional Review Boards approved the study. Participants signed informed consent documents. This report is based on the 06/30/2015 data freeze.

2.1. Cohort description

Detailed study methods are published [10,11]. ACT participants are a population-based sample, aged ≥ 65 years and dementia-free at enrollment, and recruited from Kaiser Permanente Washington membership rolls. Kaiser Permanente Washington is an established Washington state health-care delivery system. Comprehensive ophthalmic care was provided for all members, and care was not related to ACT enrollment or any study findings. At recruitment and biennial visits [11,12], participants received cognitive screening tests, medical history and risk factor evaluations, and apolipoprotein E (*APOE*) genotyping.

2.2. AD and dementia evaluation

Participants were screened biennially with the Cognitive Abilities Screening Instrument [13]. Participants with Cognitive Abilities Screening Instrument scores ≤ 85 underwent a standardized diagnostic evaluation, including physical and neurologic examinations and a neuropsychological test battery (eSupplement) [14]. Procedures to address cognitive assessment of individuals with poor vision have been in place since the inception of the study; these procedures are detailed in the eSupplement. Dementia diagnoses were determined at consensus conferences using Diagnostic and Statistical Manual of Mental Disorders, 4th Version, criteria [15], and probable and possible AD diagnoses were determined using National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) criteria [16]. Our primary outcome was either probable or possible late-onset clinical AD as defined

by NINCDS-ADRDA criteria [16], and we also analyzed all-cause dementia by Diagnostic and Statistical Manual of Mental Disorders, 4th Version, criteria [15].

2.3. Study variable description

The following were based on enrollment and biennial self-reported medical history: smoking, hypertension, congestive heart failure, diabetes, history of cardiovascular disease (myocardial infarction, angina, coronary artery bypass grafting, or angioplasty), and cerebrovascular disease (stroke, transient ischemic attack, or carotid endarterectomy).

Ophthalmic conditions were based on International Classification of Diseases, 9th revision, codes recorded in participants' electronic medical records: glaucoma (365.1*), AMD (362.50, 362.51, 362.52), DR (362.01, 363.02, 362.03, 362.04, 362.05, 362.06), and cataract (366.*).

2.4. Statistical analysis

The primary outcome was probable or possible AD, analyzed using Cox proportional hazards models, including glaucoma, AMD, and DR in a single model. We performed additional analyses that added cataract. Censoring occurred at the time of non-AD dementia. We limited analyses to participants with *APOE* genotype. In the primary analysis, the ophthalmic conditions were categorized as recent (diagnosed within 0–5 years) and established (>5 years) diagnoses. We chose the 5-year cutoff *a priori*. Model assumptions and fit were tenable.

All models controlled for age at study enrollment, sex, education, self-reported white race, any *APOE* $\epsilon 4$ alleles, and time-dependent smoking status. We assessed interactions between ophthalmic conditions and *APOE* $\epsilon 4$ and $\epsilon 2$ alleles and additional confounding by self-reported history of hypertension, congestive heart failure, cardiovascular disease, or cerebrovascular disease.

Secondary analyses included the following: 1) restricting to probable AD, 2) treating non-AD dementia as a competing risk [17], 3) considering any dementia as the outcome, 4) considering non-AD dementia as the outcome, 5) assessing each ophthalmic condition in its own model, and 6) using alternate cutpoints for our *a priori* choice of 5 years to define recent vs. established conditions.

3. Results

A total of 3877 participants without missing data constituted the analytic study sample, who accumulated 31,142 person-years of follow-up (mean >8 years per person) (Fig. 1). Most missing data were from lack of *APOE* genotype, which was more frequent in nonwhite and male participants. Most missing *APOE* genotype data was due to lack of consent for genetic analyses. We found no other significant differences between those with missing data and the analytic sample ($P > .05$; Fisher's exact or *t* test). Half were aged 70–79 years at enrollment, and 42% were male (Table 1). The majority (90%) self-reported white race and at least a high school education (91%). There were 792 incident AD cases (522 probable and 270 possible AD).

3.1. Ophthalmic conditions prevalence and incidence

Of 3877 participants, 404 (10%) had a glaucoma diagnosis at ACT enrollment, and 290 (7%) developed glaucoma; 347 (9%) had an AMD diagnosis at enrollment, and 689 (18%) developed AMD; 136 (4%) had a DR diagnosis at enrollment, and 112 (3%) developed DR; 1990 (51%) had a cataract diagnosis at enrollment, and 1446 (37%) developed cataract. At the data freeze, 213 participants had recent, and 481 had established glaucoma; 420 recent and 616 established AMD; 93 recent and 155 established DR; 741 recent and 2694 established cataract. Some overlap existed across glaucoma, AMD, and DR, as 331 had two of these and 27 had all three conditions (Supplementary Figure). Most (87%) AMD codes did not specify wet versus dry.

3.2. AD risks

In adjusted Cox models, hazard ratios (HRs) for developing AD were 0.95 (95% confidence interval 0.80, 1.14), $P = .61$ for participants with glaucoma, 1.20 (1.02, 1.40), $P = .03$ for participants with AMD, and 1.44 (1.08, 1.94), $P = .02$ for participants with DR, compared with those without.

Overall, 24% of participants with glaucoma developed AD, versus 20% of those without. Participants with recent glaucoma had a HR of 1.46 (1.08, 1.91), $P = .01$, but the HR was not elevated for those with established glaucoma (Table 2, Fig. 2). For those with recent AMD, there was a no significantly increased risk, whereas we found 50% increased risk for established AMD (Table 2, Fig. 2). Those with both recent and established DR had increased risk (Table 2, Fig. 2). There was no evidence of interactions on AD risk between *APOE* $\epsilon 4$ or *APOE* $\epsilon 2$ genotype or dose-increase AD risk or interaction between three ophthalmic conditions when added to the primary model. Additional analyses controlling for hypertension, congestive heart failure, cardiovascular disease, or cerebrovascular disease had little effect on model estimates.

Cataract diagnosis was not an AD risk factor when it was added to primary models. HRs were 0.99 (0.73, 1.32) $P = .92$ for recent and 1.21 (0.93, 1.57) $P = .15$ for established cataract.

3.3. Secondary analyses

Restricting to probable AD ($n = 522$) resulted in similar estimates for recent (HR 1.46 [1.03, 2.08], $P = .03$) and established glaucoma (0.91 [0.70, 1.18], $P = .046$), for recent (1.29 [0.98, 1.70], $P = .07$) and established AMD (1.40 [1.10, 1.71], $P = .01$), and for recent (1.46 [0.78, 2.74], $P = .24$) and established DR (1.40 [0.85, 2.11], $P = .20$). Including non-AD dementia as a competing risk produced similar estimates for recent (1.48 [1.10, 1.98], $P = .01$) and established glaucoma (0.86 [0.69, 1.07], $P = .18$); recent (1.18 [0.93, 1.50], $P = .18$) and established AMD (1.65 [1.37, 1.99], $P < .001$) were slightly stronger than the primary model, and estimates were somewhat attenuated for recent (1.41 [0.83, 2.39], $P = .21$) and established DR (1.27 [0.87, 1.85], $P = .21$).

For all-cause dementia, glaucoma risks were attenuated though still non-null for recent diagnosis. Recent and established AMD and DR were associated with all-cause dementia,

and risks for DR were much larger (Supplementary Table 1). Models with non-AD dementia that treated AD as a competing risk [17] confirmed the expected strong relationship between DR and non-AD dementia (Supplementary Table 1).

Risk estimates assessing each disease on its own model were similar to those in primary models (Supplementary Table 2). Restricting the “recent” diagnosis window to 2 years resulted in a higher HR for recent glaucoma (1.93 [1.13, 3.28], $P = .02$) and AMD (2.35 [1.72, 3.22], $P < .001$) but had little effect on risk associated with recent DR (1.68 [0.63, 4.49], $P = .30$). Broadening the “recent” diagnosis window to 10 years had little effect on HRs for AMD or DR, but both estimates for glaucoma were attenuated (Supplementary Table 3). Use of alpha agonists did not confound associations between glaucoma and AD (Supplementary Table 4).

4. Discussion

We found glaucoma, AMD, and DR are associated with increased risk of AD controlling for age, sex, education, *APOE* genotype, and smoking in a cohort of 3877 participants followed over 31,142 person-years. There was no association between cataract and AD. Without a temporal window, 20% higher AD risk was found in participants with AMD and 44% higher AD risk in those with DR compared with those without. When we separated recent vs. established ophthalmic conditions, we found a 46% higher AD risk in participants with recent glaucoma compared with those without, but no increased risk for those with established glaucoma. In comparison with those without AMD, AD risk in participants with recent and established AMD were 20% and 50% higher; only the latter was statistically different from the null. Participants with recent and established DR were at a higher AD risk by 67% and 50% compared with those without.

Prior studies lacked well-characterized cohorts with baseline and follow-up cognitive data, use of AD research diagnostic criteria, and extensive follow-up. The association between glaucoma and AD has been inconsistent. A population linkage study using English National Health Service data showed no increased AD risk in 87,658 participants with primary open angle glaucoma (rate ratio 1.01, [0.96, 1.06]) compared to 2,535,472 controls [18]. Glaucoma and AD were based on hospital admission and specialist care data, thus capturing only advanced glaucoma or AD. Our finding of no relationship between established glaucoma and AD risk is consistent with their findings. Similarly, a retrospective study using 5% of Medicare claims data revealed no increased AD risk in people with glaucoma ($n = 63,235$) compared with propensity score-matched people without glaucoma during 14 years of follow-up (HR 0.91, [0.88, 0.93]) [19]. In contrast, a smaller population-based cohort of 812 in three French cities showed substantially increased dementia risk (odds ratio 3.9, [1.5, 10.4]) in participants with glaucoma during 3 years, but only analyzed 2436 person-years, roughly 1/6 of our follow-up [20].

The Rotterdam Study followed 1438 dementia-free participants aged 75 years for an average of 25 months and found increased AD risk in those with advanced AMD (HR 2.1, [1.1, 4.3]), but this became insignificant with smoking and atherosclerosis included in the model [21]. Our primary model adjusted for smoking, we had a much longer followup, and

including cerebrovascular disease did not change the strength of association between AMD and AD risk. A study of the Taiwan National Health Insurance Research Database showed a HR of 1.44 (1.26, 1.65) for participants with AMD for developing AD or dementia in a case-control study of 4993 with AMD and 24,965 without [6], similar to our all-cause dementia findings (Supplementary Table 1). Two additional studies suggested increased risk of cognitive dysfunction or dementia in people with AMD, but neither utilized research diagnostic criteria [22,23].

Microvascular retinopathy was associated with cognitive decline (odds ratios 1.17 to 5.57) in a systematic review of six studies [24]. In a review of 29,961 participants aged 60 years, increased AD incidence was noted in participants with type 2 diabetes after controlling for sociodemographic and vascular factors (HR 1.32, [1.17, 1.49]) [7]. This study only included participants with severe DR, which may explain the higher HR found in our cohort. Furthermore, an earlier ACT study found that elevated glucose levels were associated with increased AD risk for people with and without diabetes, suggesting glucose control may play a role in DR and AD [25]. It is possible that the association we found between DR and AD reflects the association between diabetes and AD [7,8,26,27]. However, when we tested AD risks in participants with treated DM with DR and without DR, only participants with DR had significantly elevated AD risks (HR 1.46, 95% confidence interval 1.09, 1.97 vs. participants without DR, HR 1.01, 95% confidence interval 0.78, 1.31). Future investigations that assess associations between AD and DR severity will be important.

Several hypotheses may explain our findings. First, it may seem tempting to dismiss these findings as age-related phenomena. Several factors suggest the effects we found are specific to these ophthalmic conditions and not merely age-related phenomena. We controlled finely for age by using age as our time axis, as has been recommended [28]. We further controlled for age by including terms for age at entry. Our specific findings also mitigate the possibility that they merely reflect age-related phenomena. We included separate terms for recent vs. established condition, and the pattern of findings was not consistent across conditions. We did not find increased risk associated with cataract, which is highly age-related. Taken together, these factors suggest quite strongly that our results are not exclusively due to age effects.

A second possibility is that these ophthalmic conditions may result from AD neurodegenerative pathways whose activities precede AD diagnosis. Extremely long preclinical stages have been suggested for AD, and we cannot test this possibility in our study. A third possibility is that all three conditions have multimechanistic pathophysiology, and their associated neurodegenerative pathways could play roles in causing or exacerbating AD in susceptible individuals [29–31]. Thus, some people who develop these ophthalmic conditions may be prone to developing AD since neurodegenerative insults have already occurred. Finally, some or all of the ophthalmic conditions may be in the same AD neurodegenerative pathway(s) and may be precursors [32]. This assumes that ophthalmic conditions precede development or early stage AD unlike the second possibility, which has the opposite relationship. We performed analyses that were helpful in identifying similarities across retinal conditions and differences with a lens condition. These findings, together with the lack of findings for cataract, suggest that a simplistic model of eye disease leading to

poor vision leading to AD risk is not sufficiently supply to explain the overall pattern of findings. These results suggest the likely benefit of further study to elucidate mechanisms underlying our findings.

The temporal relationship in ophthalmic conditions with AD risk is intriguing. AD risk appears to be higher with recent glaucoma diagnosis, perhaps suggesting a common pathway. The risk found in recent glaucoma may be an artifact because the association becomes null when we include all glaucoma diagnoses without the temporal window. However, when we performed sensitivity analyses by varying the recency window, glaucoma had a duration-dependent risk for AD such that glaucoma diagnoses close to the index data had higher HR for AD than glaucoma diagnoses further from the index date (Supplementary Table 3). Additional confounders must be considered with glaucoma and AD risk. Alpha agonists used for treatment of glaucoma such as brimonidine have been associated with CNS depression and may impact cognitive function [33,34]. However, we did not find confounding from alpha agonists in our cohort. In theory, retinal nerve fiber layer (RNFL) thinning associated with AD can be potentially confused with glaucoma, although additional criteria are usually met before a clinical glaucoma diagnosis. Glaucoma diagnoses were made by ophthalmologists who were not dementia researchers and who would not have been aware that participants were part of ACT. The prevalence of glaucoma in our cohort was higher than that reported for the US population [35]. Using an alternate criterion for glaucoma diagnosis such as the use of glaucoma medications in addition to International Classification of Diseases, 9th revision, codes may have produced different findings. The AMD effect appears to be both recent and long-term, given highest risk with recent diagnosis and increasing trend with longer duration of AMD. Unlike the case for glaucoma, we found that AMD diagnosed proximal to (0–2 years) and further from (0–10 years) the index date had significantly elevated risks for AD (P-values < .001 to .005, Supplementary Table 3). Structural brain changes are thought to precede cognitive changes in AD by years or decades [36]. Thus, the trend we found for AMD could suggest an initial insult propagating degenerative pathways in the eye and brain, in addition to chronic degenerative/inflammatory pathways. In contrast, similar risk for AD in participants who have DR regardless of its duration suggest that microvascular insults or ischemia found in DR may occur concurrently with the changes in brain associated with diabetes.

Our study has several strengths. First, we enrolled a large cohort of dementia-free participants and followed them over an extended period of time, accumulating >30,000 person-years and >750 incident AD cases. Second, AD diagnoses were made systematically with a panel of experts. Third, we evaluated both recent and established conditions, providing intriguing clues regarding temporal sequence. Finally, our cataract findings act as something of a negative control, arguing against the possibility that our findings may reflect age-related confounding. Cataract is as strongly age-related as the other conditions we studied, and we found no association between cataract and AD risk.

Limitations of our study include a geographically confined cohort. The study population's ethnic and socioeconomic characteristics are similar to the surrounding county, but whether these associations would hold in nonwhite ethnic groups is unknown. AD incidence in our cohort is comparable with that in other studies [10], so our findings may be generalizable.

Participants may have been underdiagnosed for ophthalmic conditions or have incorrect recent versus established durations of the disease if they had no eye care provider. However, our most recent data showed that 98.6% of entire ACT study cohort was seen at least once by eye care providers in our system for an average of 26.7 times. Ophthalmic diagnoses relied on International Classification of Diseases, 9th revision, codes rather than formal evaluation by a single team of ophthalmologists, so significant variation may have existed, especially in borderline cases. However, the extensive longitudinal follow-up in the majority of our cohort makes this possibility less likely because most participants would have been seen by multiple providers over the course of long-term ophthalmic care. Another limitation is diagnosis data starting in 1993; everyone had 2 years of follow-up before enrollment, and only 5.5% lacked >5 years of exposure data. Therefore, ophthalmic diagnoses in earlier participants may have been missed or identified as “recent,” resulting in a conservative bias and mildly affecting findings related to recent versus established conditions. ACT enrolls people aged 65 years and free of dementia; we have no cases of early-onset AD and cannot comment on associations with early-onset AD. Possibility of confounding in ophthalmic conditions exists due to overlap between diseases, and future studies incorporating longitudinal clinical data will be beneficial. Finally, there is tremendous heterogeneity in the underlying causes of all-cause dementia defined by Diagnostic and Statistical Manual of Mental Disorders, 4th Version, criteria. Many analyses thus use clinical AD diagnoses using standard research criteria, such as the NINCDS-ADRDA criteria employed here. These diagnoses are more specific than all-cause dementia diagnoses. Nevertheless, there is still an imperfect relationship between NINCDS-ADRDA clinical diagnoses of AD and neuropathological Alzheimer’s findings of neuritic plaques and neurofibrillary tangles [37,38]. Many studies do not have access to autopsy data; the vast majority of papers on AD risk factors are published with only clinical AD diagnoses. It is common to evaluate risk factors in the larger group of people with clinical diagnoses and attempt to confirm those risk factors with more specific neuropathology data in the smaller subset of individuals who have died and come to autopsy. Even though our primary outcome was clinical AD diagnosis, we found similar relationships with all-cause dementia with all three ophthalmic conditions (Supplementary Table 1).

The 5-year cutoff to delineate recent versus established condition could be viewed as a limitation. However, we selected 5-year *a priori*. Sensitivity analyses suggest that different choices would have minimal impact on our conclusions. Using any diagnosis to date, the HRs of both AMD and DR were significantly elevated for AD risk. We found similar relationships with all-cause dementia (Supplementary Table 1) but chose to emphasize AD findings because clinical AD is a more homogeneous group compared with all-cause dementia. Whether the relationship between DR and AD is driven simply by diabetes severity or glucose control versus ophthalmic processes remains uncertain. Finally, our study only evaluated the temporal sequence that starts with ophthalmic conditions followed by AD and not vice-versa thus we are unable to assess whether increased risk for ophthalmic conditions may exist in individuals with AD.

In summary, glaucoma, AMD, and DR are associated with increased AD risk, whereas cataract is not. Subsequent studies of ophthalmic diseases in relation to AD and dementia

may provide important insights into shared pathological pathways, thus enabling better techniques to prevent and treat.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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RESEARCH IN CONTEXT

1. Systematic review: Using PubMed, we identified and reviewed publications on reporting the associations between cognitive decline or AD with the following ophthalmic diseases: DR, AMD, glaucoma, or cataract. Most of the clinical research were cross-sectional, case control, or claim-based studies with a limited sample size and/or ill-defined diagnostic criteria for AD. Some studies found AD to be associated with DR, AMD, and glaucoma and some studies did not.
2. Interpretation: Our results from a very large population with extensive longitudinal follow-up (>31,000 person-years of observation and nearly 800 cases of incident AD) show that recent (within 5 years) diagnosis of glaucoma (HR 1.46, $P = .01$), established diagnosis of AMD (HR 1.50, $P < .001$), and recent/established diagnosis of DR (HR 1.50, $P = .045$; 1.50, $P = .03$, respectively) were independently associated with the risks of developing AD after controlling for age at baseline, sex, education, self-reported white race, any apolipoprotein E (APOE) $\epsilon 4$ alleles, and time-dependent smoking status. However, cataract diagnosis was not associated with AD.
3. Future directions: Caregivers and health-care workers should facilitate adequate ophthalmic care for older individuals at risk of dementia. Eye care providers should be aware of increased AD risk in certain ophthalmic conditions. Subsequent studies of ophthalmic diseases in relation to AD may provide important insights in their shared pathological pathways, thus enabling better techniques to prevent and treat.

Fig. 1. Flow diagram of participants included in the study. ACT, Adult Changes in Thought. Abbreviation: *APOE*, apolipoprotein E.

Fig. 2. Survival curves for glaucoma, AMD, and DR, from the primary model for probable or possible Alzheimer's disease. Abbreviations: AMD, age-related macular degeneration; DR, diabetic retinopathy.

Table 1Demographic and baseline clinical factors by ophthalmic condition status at the end of follow-up^{*}

Baseline factors	People who ultimately developed glaucoma (n = 694)	People who ultimately developed AMD (n = 1036)	People who ultimately developed DR (n = 248)	People who did not develop glaucoma, AMD, or DR by the end of the study period (n = 2284)	All participants (n = 3877)
Age					
65–69	126 (18%)	158 (15%)	65 (26%)	779 (34%)	1070 (28%)
70–79	366 (53%)	512 (49%)	144 (58%)	1131 (50%)	1957 (50%)
80–101	202 (29%)	366 (35%)	39 (16%)	374 (16%)	850 (22%)
Male	261 (38%)	355 (34%)	109 (44%)	1011 (44%)	1615 (42%)
Caucasian	622 (90%)	981 (95%)	203 (82%)	2041 (89%)	3502 (90%)
HS education	622 (90%)	936 (90%)	221 (89%)	2085 (91%)	3522 (91%)
<i>APOE</i> genotype					
ε3/ε4 or ε4/ε4	159 (23%)	185 (18%)	56 (23%)	579 (26%)	910 (24%)
ε2/ε2 or ε2/ε3	99 (15%)	144 (14%)	38 (16%)	296 (13%)	511 (13%)
ε2/ε4	15 (2%)	19 (2%)	3 (1%)	44 (2%)	76 (2%)
ε3/ε3	408 (60%)	670 (66%)	147 (60%)	1308 (59%)	2293 (61%)
Hypertension	454 (66%)	666 (64%)	187 (75%)	1298 (56%)	2334 (60%)
Diabetes	130 (20%)	163 (17%)	230 (93%)	253 (12%)	621 (17%)
Cardiovascular disease	206 (27%)	344 (33%)	109 (44%)	575 (25%)	1090 (28%)
Cerebrovascular disease	168 (24%)	274 (26%)	76 (31%)	419 (18%)	829 (21%)
Smoking					
Current	14 (2%)	21 (2%)	5 (2%)	74 (3%)	108 (3%)
Past	332 (48%)	502 (48%)	128 (52%)	1125 (49%)	1903 (49%)
Never	348 (50%)	513 (50%)	115 (46%)	1085 (48%)	1866 (48%)

Abbreviations: AMD, age-related macular degeneration; *APOE*, apolipoprotein E; DR, diabetic retinopathy; HS, high school.

NOTE. Cardiovascular disease defined as any history of myocardial infarction, angina, coronary artery bypass grafting, or angioplasty; cerebrovascular disease defined as any history of stroke, transient ischemic attack, or carotid endarterectomy.

^{*} People could develop more than one ophthalmic condition so the first three columns are not mutually exclusive groups.

Table 2

HR of developing Alzheimer's disease in the primary (combined) model

Risk factor	HR (95% CI)	P value
Glaucoma		
0–5 years	1.46 (1.08, 1.91)	.013
More than 5 years	0.87 (0.71, 1.07)	.19
Age-related macular degeneration		
0–5 years	1.20 (0.95, 1.50)	.12
More than 5 years	1.50 (1.25, 1.81)	<.001
Diabetic retinopathy		
0–5 years	1.67 (1.01, 2.74)	.045
More than 5 years	1.50 (1.05, 2.15)	.027
Age	1.11 (1.10, 1.13)	<.001
Male	0.93 (0.78, 1.08)	.32
Education	0.95 (0.93, 0.97)	<.001
Caucasian	0.88 (0.69, 1.12)	.29
Any APOE-ε4	1.57 (1.17, 2.11)	<.001
Smoking		
Current	0.89 (0.52, 1.53)	.68
Past	1.00 (0.87, 1.16)	.99

Abbreviations: *APOE*, apolipoprotein E; HR, hazard ratio.