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Journal

Alzheimer's & Dementia, 18(7)

ISSN

1552-5260

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Publication Date

2022-07-01

DOI

10.1002/alz.12473

Peer reviewed

HHS Public Access

Author manuscript

Alzheimers Dement. Author manuscript; available in PMC 2023 July 01.

Published in final edited form as:

Alzheimers Dement. 2022 July ; 18(7): 1296–1305. doi:10.1002/alz.12473.

Assessing Bidirectional Associations Between Cognitive Impairment and Late Age-Related Macular Degeneration in the Age-Related Eye Disease Study 2

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AREDS2 Research Group

Abstract

INTRODUCTION: We aimed to investigate bidirectional associations between cognitive impairment and late age-related macular degeneration (AMD).

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METHODS: Participants in the Age-Related Eye Disease Study 2 (AREDS2) received annual eye examinations and cognitive function testing (e.g., Modified Telephone Interview for Cognitive Status (TICS-M)). We examined bidirectional associations between cognitive impairment (e.g., a TICS-M score<30) and late AMD at 5- and 10-years.

RESULTS: 5189 eyes (3157 participants; mean age 72.7 years) were analyzed and followed for a median of 10.4 years. Eyes of participants with cognitive impairment at baseline were more likely to progress to late AMD at 5-years (Hazard Ratio [HR], 1.24; 95% CI, 1.08–1.43) and 10-years (HR, 1.20; 95% CI, 1.05–1.37) than eyes of participants without cognitive impairment. Worse baseline AMD severity was not associated with developing cognitive impairment.

DISCUSSION: Cognitive impairment is associated with late AMD progression in AREDS2. Our finding highlights the importance of eyecare for people with cognitive impairment.

Keywords

Age-related macular degeneration; eyes; cognitive impairment; Alzheimer's; ophthalmology; older adults

1. BACKGROUND

Age-related macular degeneration (AMD), an eye condition involving damage to the central retina (macula), is the most common cause of legal blindness in the United States (US).[1,2] Worldwide in 2020, AMD affects 196 million people; among those, 11 million suffer from advanced forms of AMD (e.g., late AMD, a stage of disease when people also begin to experience symptomatic vision loss).[3,4] The projected burden will increase to 288 million and 19 million people, respectively, by 2040.[3,4] AMD arises from a complex interplay among environmental factors and genetics, and the irreversible loss of vision caused by late AMD can lead to decreased quality of life and loss of independence.[5,6]

Cognitive impairment is another age-related cause of disability for older adults that is often progressive and irreversible.[7] As the number of older people increases, a better understanding of risk factors that lead to impairment of cognitive function and dementia syndromes (including Alzheimer's disease [AD]) is critical. Evidence of various strengths has shown associations between AD and AMD as neurodegenerative conditions of aging but this remains controversial.[8–12] Both may share key environmental risk factors (e.g., diet), histopathological features (e.g., deposition of amyloid-β[13]), and pathophysiological mechanisms (e.g., oxidative stress and inflammation) to some extent.[14] Their genetic risk profile, however, is distinct; the only known shared locus is apolipoprotein E (*APOE*) ε4, which is associated with increased risk of AD but may be protective against progression to late AMD.[15,16]

The National Eye Institute-sponsored Age-Related Eye Disease Study (AREDS) and AREDS2 were multicenter, randomized clinical trials (RCTs) of nutritional supplements for the treatment of AMD and cataract. AREDS and AREDS2 revealed benefits of the combination of daily high-dose antioxidant vitamins, minerals, and nutrients in providing a moderate reduction in risk of progression from intermediate to late AMD.[17,18] In AREDS, investigators have previously documented a potential association between AMD

and cognitive impairment in older people.[19] This analysis was cross-sectional, yet the direction of the association between AMD and cognitive impairment is unclear. In AREDS2, investigators tested cognition at baseline and regularly throughout study visits using a cognitive function battery that does not rely on tests that require visual input. The trial showed no effect of AREDS2 supplementation on cognitive outcomes.[20]

In the current analysis, we investigated bidirectional associations between cognitive impairment and late AMD among older adults with intermediate or late forms of AMD who participated in AREDS2. Notably, AREDS2 (via an ancillary study on cognitive function and a 10-years follow-on[21]) is one of the largest studies of older adults with long-term follow-up (median 10 years) and few loss to follow-up (2%).[17]

2. METHODS

AREDS2 study designs have been well-described in the literature (ClinicalTrials.gov Identifier: NCT00345176 and NCT03367767).[22,23] In brief, investigators randomized participants to receive placebo, lutein/zeaxanthin, docosahexaenoic acid (DHA) plus eicosapentaenoic acid (EPA), or the combination of lutein/zeaxanthin and DHA plus EPA. AREDS2 also evaluated the effects of eliminating beta-carotene, lowering zinc doses, or both in the original AREDS formulation. Certified study personnel performed comprehensive eye examinations at baseline and annual study visits using standardized protocols. Interviewers collected baseline data (e.g., age, sex/gender, education); data on potential risk factors for AMD (e.g. smoking status and diet, the latter measured using the Alternative Mediterranean Diet Index [aMedi],[24] calculated for each participant from responses on a food frequency questionnaire); and other comorbidities (e.g., diabetes, hypertension, and depressive symptoms measured using the Center for Epidemiological Studies-Depression Scale [CES-D]) at time of randomization. The primary outcomes of the trial (2006–2012) included progression to late AMD as measured by color fundus photography at 5 years. Following the end of the clinical trial, participants were invited to participate in an observational follow-on study that comprised telephone interviews every 6 months for an additional 5 years (2013–2018).

The research was conducted under the Declaration of Helsinki; institutional review boards at each study site approved the research protocols; and all participants provided written consent through a process approved by independent data and safety monitoring committees.

2.1 Study population.

AREDS2 recruited adults age 50–85 years with either large drusen (i.e., large lipid deposits that accumulate under the retina) in both eyes or late AMD in one eye and large drusen in the fellow eye, from 82 retinal specialty clinics in the US.[23] Eligible participants were free of conditions that would have made follow-up or adherence to medication difficult; thus, any adults with dementia at baseline were effectively excluded.

2.2 Testing of cognitive function.

AREDS2 included a prespecified ancillary study on cognitive function, involving a battery (comprising eight component tests) that certified interviewers administered by telephone

within 3 months of randomization. Justification for testing cognition by telephone had already been demonstrated using AREDS data,[25] and specific details of tests included in the battery (i.e., Telephone Interview Cognitive Status-Modified [TICS-M], TICS-M Recall, Animal Category, Letter Fluency, Alternating Fluency, The Wechsler Memory Scale Third Edition (WMS-III) Logical Memory Parts I & II, and Digits Backwards) are available in the Supplemental Material 1 (Supplemental Material 1, Tables 1 and 2).[19,20,24] Participants had the option of taking a shortened version of the battery that included the TICS-M rather than the entire suite of tests. AREDS2 interviewers repeated administration of this battery every 2 years until close-out of the trial at 5 years, and then again at 10 years as part of the follow-on study protocol.

2.3 Measurement of cognitive impairment.

AREDS2 investigators measured cognitive impairment using the TICS-M, which is an adaptation of the Modified Mini-Mental State Examination. We decided *a priori* to use a predefined cut-off point for cognitive impairment of 30.[17,23] In addition, we calculated a composite score that represents an overall score for the whole cognitive battery as the sum of the z-scores for each component test, with higher scores indicating better cognition.[25] For the composite score, we defined *a priori* cognitive impairment as a score in the lowest decile,[24] a methodology that has been used in previous studies.[20,25–27]

2.4 Measurement of AMD

In this study, progression to late AMD was defined as the development of geographic atrophy (GA) or neovascular AMD (choroidal neovascularization). Participants in AREDS2 underwent digital stereoscopic 3-field color fundus photography at baseline and annual visits. Certified graders at the Fundus Photograph Reading Center of the University of Wisconsin graded the photographs, without access to any corresponding clinical information, using a standardized protocol. Eyes that progressed to neovascular AMD were no longer assessed for additional progression to GA. Each eye was also graded for AMD severity on the AREDS AMD severity scale[28] (ranging from 1 [low risk] to 11 [high risk]) that has been shown to have value for estimating the risk of progression to late AMD (Supplemental Material 2, Table 1).[29] We decided *a priori* that a participant assigned ≥ 7 on the AREDS AMD severity scale in the worse eye would be considered as having worse AMD severity.[22,23] A table summarizing AMD measurements is provided in the Supplemental Material 2 (Supplemental Material 2, Table 2).

2.5 Genotype analyses

Single nucleotide polymorphisms (SNPs) for a subset of participants (n = 1481) who consented to genotype analysis were analyzed using a custom Illumina HumanCoreExome array.[15] Further details of genetic analyses in AREDS2 are available elsewhere.[30–33]

2.6 Statistical analyses.

2.6.1 Associations between cognitive impairment at baseline and progression to late AMD—

Cox proportional hazards regression with cognitive impairment at baseline (defined by having a TICS-M score < 30) as the exposure and

progression to late AMD (i.e., development of GA or neovascular AMD) as the primary outcome was performed. We also fitted separate models with cognitive function defined using the composite score for the battery. In all cases, the eye was considered the unit of analysis, while excluding eyes with late AMD at baseline, and adjusting for baseline age, sex/gender, and smoking status.

2.6.2 Associations between worse AMD severity at baseline and the development of cognitive impairment—Cox proportional hazards regression was conducted with having worse AMD severity (versus not having worse AMD severity) at baseline as the exposure and development of cognitive impairment (i.e., TICS-M score < 30) as the primary outcome. We also fitted separate models with cognitive function defined using the composite score for the battery. In all cases, individual participant was considered the unit of analysis, while excluding participants who had cognitive impairment at baseline, and adjusting for baseline age, sex, and known predictors of cognitive impairment determined based on the literature,[19,23] such as smoking status, risk of depression (i.e., CES-D score ≥ 16), history of diabetes and hypertension, and baseline cognitive test scores.

2.6.3 Additional details—The two timepoints considered in our primary analyses were 5 years (close-out of the trial) and 10 years (end of the follow-on study). Participants were censored (i.e., no longer contribute person-time to our analysis) at the time of the event (e.g., actual time to event such progression to late AMD or development of cognitive impairment). Participants were censored at time of their last study visit/interview if they were lost to follow-up or died.

As additional analyses, we (1) further adjusted all models for education, diet (aMedi tertiles), and AREDS2 treatment group; (2) examined associations with cognitive function defined by each of component tests, treating scores as continuous (with higher scores representing better function) or dichotomous (with a score in the lowest decile representing impairment) variables, and (3) included either an interaction term between baseline cognitive function status and genotype (i.e., *APOE* haplotypes [which we defined by rs429358 and rs7412][34], *CFH* [rs1061170] and *ARMS2* [rs10490924], which are two loci with highest attributable risk of late AMD; and the AMD genetic risk score [15] of 52 SNPs) for models examining associations with progression to late AMD as the outcome, or an interaction term between worse AMD severity at baseline and *APOE* haplotypes for models examining associations with development of cognitive impairment as the outcome.

Additionally, for models examining associations between baseline cognitive impairment and AMD, we repeated analyses to 5 years with AMD outcomes defined by subtype (i.e., either GA or neovascular AMD; data by AMD subtype were not available for all participants in the 10-year follow-on study. For each model, participants (or eyes) were excluded if they had missing covariates or data for a relevant cognitive test. We tested the proportional hazards assumption for all models and, where applicable, adjusted for correlation between eyes using the robust sandwich estimator for the covariance matrix in the Wald tests.[35] A 2-sided p-value < 0.05 was considered statistically significant, and all analyses were conducted with SAS version 9.4 (SAS Institute Inc).

3. RESULTS

AREDS2 enrolled 4,203 participants, and most (3501/4203; 83%) consented to participating in the ancillary study of cognitive function Among them 3,157/3501 (90%) participants, representing 5,189 eyes with fundus data also available, were included in the present analysis examining the outcome progression of late AMD; and 2684/3501 (77%) were included for the outcome of development of cognitive impairment. Table 1 describes baseline demographic and clinical characteristics. The plurality of participants was female (57%), older adults (mean age 72.7 years; standard deviation 7.8 years) who were never (43%) or former smokers (50%), and who achieved a highest level of education that includes at least some college (48%) or higher (22%). Median follow-up time in the AREDS2 study for participants in our analyses was 10.4 years (range: 0.8 – 12.2 years). Characteristics of participants we included in the analysis examining associations between AMD severity at baseline and the development of cognitive impairment are similar (Supplemental Material 3, Tables 1 and 2).

3.1 Associations between cognitive impairment at baseline and progression to late AMD

Figure 1 shows the cumulative incidence of eyes progressing to late AMD by baseline cognitive impairment status for our analysis. Over the 10 years of follow-up, 2522/5189 (49%) eyes progressed to late AMD, and we observed that the cumulative incidence of progressing to late AMD was higher among eyes of participants with cognitive impairment at baseline than among those without, i.e., 56% vs. 47% or 60% vs. 48%, defining cognitive impairment as having a TICS-M score < 30 (n = 5,189 eyes of 3,157 participants) or composite score (n = 4,207 eyes of 2,543 participants) in the lowest decile (i.e., score ≤ −6.93), respectively.

Eyes of participants who were cognitively impaired (as defined by TICS-M score < 30) at baseline were more likely to develop late AMD at 5 years (Hazard Ratio [HR], 1.24; 95% Confidence Interval [95% CI], 1.08 to 1.43) and at 10 years (HR, 1.20; 95% CI, 1.05 to 1.37), compared with eyes of participants who were not cognitively impaired (Figure 2). Magnitude of associations at 5 years (HR, 1.20; 95% CI, 1.05 to 1.37) and 10 years (HR, 1.23; 95% CI, 1.04, 1.46) were similar when we defined cognitive impairment as having a composite score in the lowest decile. Examining by subtypes of late AMD, baseline cognitive impairment was associated with increased risk of both GA (HR, 1.26; 95% CI, 1.03 to 1.54) and neovascular AMD (HR, 1.26; 95% CI, 1.05 to 1.51).

3.2 Associations between worse AMD severity at baseline and the development of cognitive impairment

In this analysis, over the course of the 10-year follow-up, 670/2684 (25%) participants developed cognitive impairment (Supplemental Material 4, Figure) and we observed that the cumulative incidence of developing cognitive impairment is higher among AREDS2 participants with worse AMD severity at baseline than among those without, i.e., 18% vs. 13% or 11% vs. 6%, defining baseline cognitive impairment as having a TICS-M score < 30 (n = 2,684 participants) or composite score (n = 1,904 participants) in the lowest decile, respectively. When we modeled data using proportional hazards regression, however, there

was no statistically significant association between worse AMD severity at baseline and development of cognitive impairment as defined by TICS-M score at either 5 years (HR, 1.13; 95% CI, 0.89 to 1.44) or 10 years (HR, 1.10; 95% CI, 0.92 to 1.32) (Figure 3). Results did not change significantly when we examined associations at 5 years (HR, 1.09; 95% CI, 0.92 to 1.32) or 10 years (HR, 1.23; 95% CI, 0.81, 1.88) with the outcome instead defined as having a composite score in the lowest decile.

3.3 Additional analyses

Results for primary analyses were similar when we adjusted for diet, education, or AREDS2 treatment group (Supplemental Material 4, Tables 1–4) or examined cognitive function by each of the individual component tests (Supplemental Material 5, Figures 1–4) as continuous measures. We noted that memory test scores (HR, 0.9956; 95% CI 0.9909 to 1.0002) seem less strongly associated with progression to late AMD at 10 years, compared to category test scores (e.g., animal category: HR, 0.9853; 95% CI, 0.9753 to 0.9955) or fluency test scores (e.g., alternating fluency: HR, 0.9741; 95% CI, 0.9507 to 0.9981). Overall, however, tests trended in the same direction as composite results: a one unit increase in test score was associated with a lower risk of progression to late AMD. Examining associations between having worse AMD severity at baseline and cognitive impairment measured by each of the component tests in the battery at follow-up, the consistently null results across each individual test support our main findings. We found no interactions influencing progression to late AMD between cognitive impairment status at baseline and genotype (i.e., *APOE* haplotypes, *CFH*, *ARMS2*, and genetic risk score for progression to late AMD in this study). Similarly, no interactions were observed between baseline AMD severity status and *APOE* haplotypes in analyses examining development of cognitive impairment as an outcome (Supplemental Material 6).

4. DISCUSSION

We evaluated the association between cognitive impairment and progression to late AMD among older adults participating in AREDS2. We found that cognitive impairment, measured using TICS-M or a composite score of a cognitive function battery, was associated with 1.2 times higher risk of progression to late AMD. The associations did not change after further adjustment for factors such as education and diet or a term for interactions with genotype. We observed that worse AMD severity (e.g., having an AREDS AMD scale score ≥ 7 in the worse eye) at baseline was not associated with developing cognitive impairment in our population at 10 years. These observations complement an earlier cross-sectional analysis using data from AREDS alone.[19]

Our findings highlight a need to raise the awareness of physicians, particularly of geriatricians and eyecare providers who examine older adults, to the relationship between cognitive and visual impairments. People with cognitive impairment or dementia should have regular eyecare to optimize detection and treatment for diseases such as AMD. Cognitive impairment may potentially impede an individual's ability to identify or express changes happening in their vision; or the individual might not have adequate access to eyecare services because of other more obvious issues linked to cognitive impairment.

Certain forms of late AMD (e.g., neovascular AMD) are eminently treatable, but require rapid detection for optimal visual outcomes.[29,36,37] This should not be underrated, as having combined cognitive and visual deficits places older adults at higher risk of negative consequences including loss of independence.[5,6]

Our findings also contribute to the spectrum of emerging literature that aims to quantify associations between cognitive and visual impairments. Most previous, large investigations have examined AMD as a risk factor for AD. For example, the Rotterdam Study[38], Atherosclerosis Risk in Communities Study[39], Cardiovascular Health Study[40], and Blue Mountain Eye Study[41] are longitudinal population-based cohorts that observed a potentially higher risk of incident AD or lower cognitive test scores in people with late AMD. These associations, however, are based on small case numbers and attenuated after adjustment for risk factors such as smoking status.[19,38,39] We have also identified analyses of larger electronic health records that have produced mixed results. Keenan et al. found that risk of subsequent AD or dementia diagnosis after AMD in the English National Health Service was not raised among 65,894 patients with an admission or day case care with AMD.[14] Tsai et al., however, observed that, among the 28,958 patients in the Taiwan National Health Insurance Research Database, those with AMD had a 1.44-fold greater risk of subsequent AD or dementia than matched controls.[42]

We are aware of two recent systematic reviews that investigated cognition in people with AMD.[8,36,43] Zhou et al., which included seven studies in their synthesis, found that people with AMD had lower scores than those without AMD on the mini-mental state examination (standardized mean difference, −0.32; 95% CI, −0.51 to −0.13).[43] Rong et al., which included 21 studies,[19] noted that dementia conferred greater risk for late AMD (odds ratio, 1.37; 95% CI, 1.17 to 1.60). Notably, the studies included in these systematic reviews were clinically heterogeneous, typically cross-sectional, and relied, for the most part, on vision-dependent testing of cognitive function.[8]

Collectively, these results including findings of the current study advance discussion on the relationship between two age-related neurodegenerative diseases and on the directionality of their associations. AMD and AD share some common pathophysiological and aging processes that could be further explored. For example, amyloid-β peptide, a major proinflammatory constituent of neuritic plaques in AD, has been identified in drusen of eyes with AMD.[9,10,44] There is also evidence of co-accumulation of amyloid-β with vascular endothelial growth factor in the brains of patients with AD.[45] Oxidative stress, inflammation, and complement activation are thought to be implicated in both diseases.[14] Further research could assess whether accumulation may somehow accelerate AMD progression; or whether people with cognitive impairment may be more likely to adopt a worsened diet and other risk factors that may alter biology and risk of progression to late AMD. Additionally, although we did not observe an interaction with genotype, we recognize that further research using a Mendelian randomization approach, which leverages genetic variability in AMD risk, may contribute towards unraveling causal relations between cognitive impairment and AMD.

Our study has limitations. First, our study is constrained by limitations of the parent study design (i.e., a randomized clinical trial of nutritional supplements in people with intermediate to late AMD), which necessitates careful interpretation of the target population. We recognize that participants in our analyses were rather healthy, well-nourished, and highly educated (Supplemental Material 3),[46] and the AREDS2 eligibility criteria excluded people with early stages of AMD. This may explain why we did not observe a statistically significant association between baseline AMD severity and development of cognitive impairment. Second, it is possible that our study is relatively underpowered in one direction but not in the other; for example, in the primary comparison looking at development of cognitive impairment, the unit of analysis is participants (n = 2684) rather than eyes (n = 5189). Third, there is possibility of residual or unmeasured confounding; however, we note that our findings are consistent with those reported in the literature, including prior analyses undertaken in AREDS. Future studies with more diverse, historically underserved populations may overcome some limitations. Further, researchers may also design longitudinal studies to examine more specific forms of cognitive impairment (e.g. subtypes of dementia such as vascular dementia) or other stages and subtypes of AMD (e.g., polypoidal choroidal vasculopathy).

Our study has several strengths. First, AREDS2 relied on standardized assessment of AMD by a central reading center using established grading criteria. Second, consistency in the results, in addition to long participant follow-up periods, bolster validity of our findings. The multi-site design of the parent study also allowed us to increase geographic representation through 82 recruiting sites and we were able to conduct sensitivity analyses by AMD subtypes. Third, AREDS2 achieved high rates of repeated cognitive function testing (83%) in a controlled setting, with a large, well-characterized study population with more advanced forms of AMD over 10 years. Administration of the battery by interviewers was appropriate for a population with visual impairments and necessarily short to minimize burden.[47] AREDS2 also eliminated reliance on tests that require visual input, and we certified interviewers to attain better control over administration procedures across study sites.

5. CONCLUSION

In conclusion, using 10-year longitudinal data from a large, multi-center randomized trial, we provide evidence that cognitive impairment is prospectively and positively associated with progression to late AMD. We did not, however, observe an association between AMD severity at baseline and development of cognitive impairment. Understanding the relationship between cognitive and visual impairments is critical, given increased prevalence of both in older people.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial support

This AREDS2 study was supported by intramural program funds and contracts (contract HHS-N-260–2005-00007-C; ADB contract N01-EY-5–0007) from the National Eye Institute/National Institutes of Health (NEI/NIH), Department of Health and Human Services, Bethesda, MD. Funds were generously contributed to these contracts by the following NIH institutes: Office of Dietary Supplements; National Center for Complementary and Alternative Medicine; National Institute on Aging; National Heart, Lung, and Blood Institute; and National Institute of Neurological Disorders and Stroke.

Role of Sponsor

The NIH sponsored this study. In that capacity, the sponsoring organization was involved in each of the following: design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The views and opinions expressed in this article are those of the authors and do not necessarily reflect those of the National Institutes of Health, the Department of Health and Human Services, or the United States government.

Declarations of interest

Dr. Le, Chew, Keenan, and Agron are federal employees of the National Eye Institute, National Institutes of Health. In addition, authors have disclosed the following: Dr. Keenan is co-inventor on a patent application on “Methods and systems for predicting rates of progression of age-related macular degeneration” and is an unpaid voting member on the data and safety monitoring board for the APL2–103 interventional study (Apellis Pharmaceuticals). Dr. Clemons has received a National Eye Institute contract to the Emmes Corporation LLC. Dr. Brenowtiz has received grants from the National Institute on Aging (K01AG062722) and the Alzheimer’s Association (AARF-18–565846), paid to institution. Dr. Yaffe has received grants/contracts from the National Institutes of Health and the Department of Defense; support for attending meetings/travel (Beeson, Alzheimer’s Association International Conference); has participated on a Data Safety Monitoring Board or Advisory Board for the National Institutes of Health and Eli Lilly; and is on the Board of Directors for Alector Inc. Dr. Chew has participated on a Data Safety Monitoring Board or Advisory Board for NGM Biopharmaceuticals and Bionic Sight LLC.

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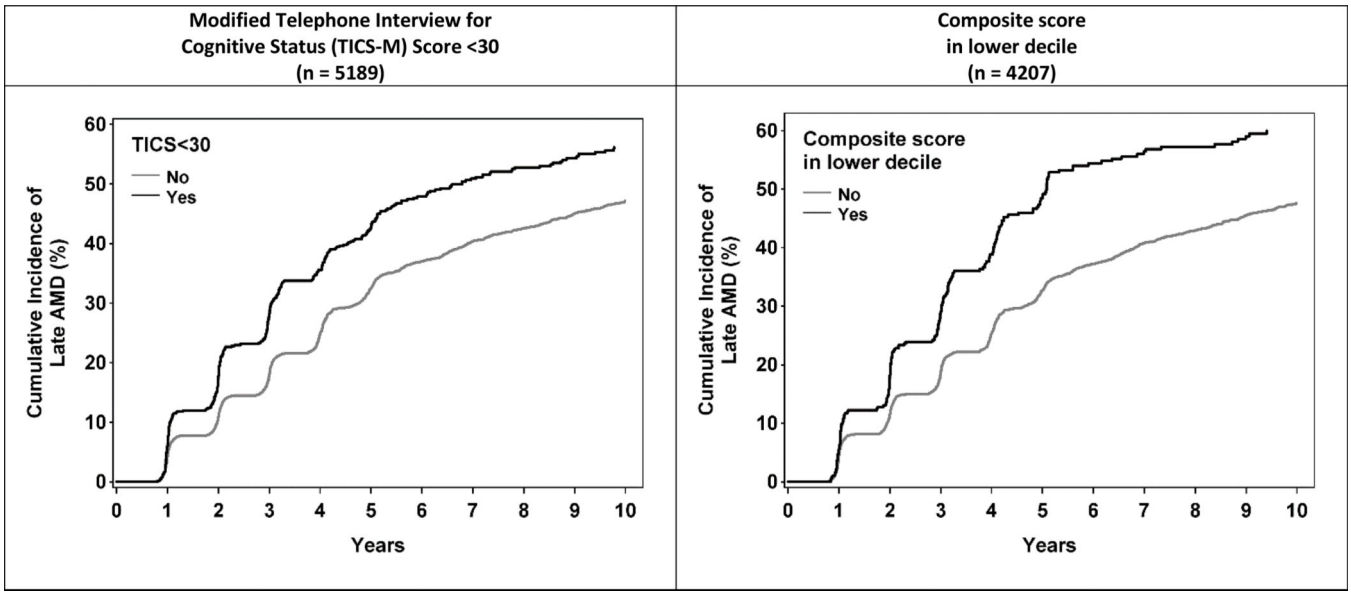
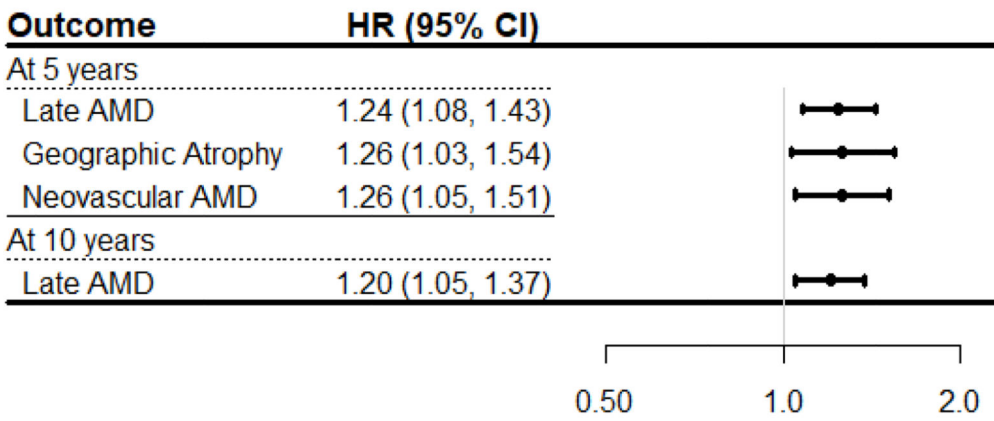


Figure 1.

Cumulative incidence of eyes progressing to late AMD by cognitive impairment status at baseline

Notes and abbreviations: a composite score ≤ −6.93 is considered to be in the lowest decile. AMD = age-related macular degeneration; TICS = Modified Telephone Interview for Cognitive Status

A) Adjusted hazard ratios and 95% confidence interval (95% CI) for progression to late AMD or subtypes, comparing participants vs. without baseline cognitive impairment (reference) defined as having a TICS-M score < 30, at 5 and 10 years (N = 5189 eyes)



B) Adjusted hazard ratios and 95% confidence interval (95% CI) for progression to late AMD or subtypes, comparing participants with vs. without baseline cognitive impairment (reference) defined as having a composite score in the lowest decile, at 5 and 10 years (N = 4207 eyes)

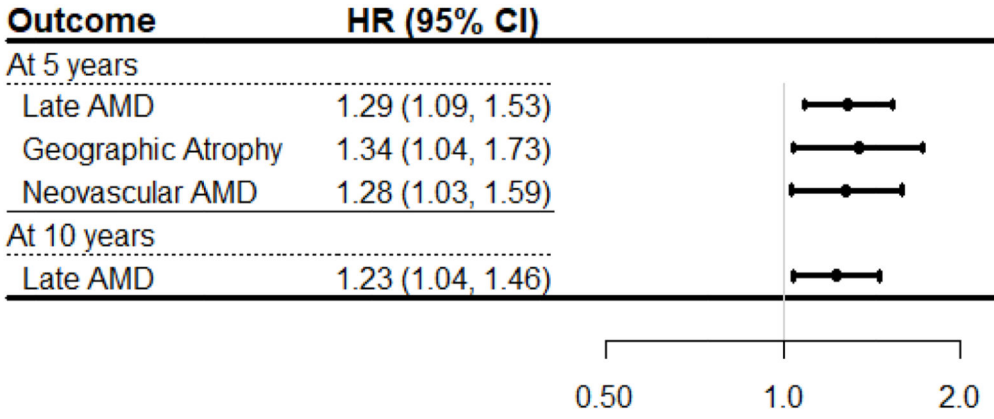


Figure 2.

Adjusted hazard ratios and 95% confidence interval (95% CI) for progression to late AMD or subtypes, comparing participants vs. without baseline cognitive impairment (reference) defined as (A) having (A) TICS-M score < 30 or (B) composite score in the lowest decile, at 5 and 10 years

Notes and abbreviations: Models have been adjusted for age, sex, and smoking status, all at baseline. A composite score ≤ −6.93 is considered to be in the lowest decile. AMD = age-related macular degeneration; HR (95% CI) = Hazard Ratio and 95% Confidence Interval; TICS-M= Modified Telephone Interview for Cognitive Status

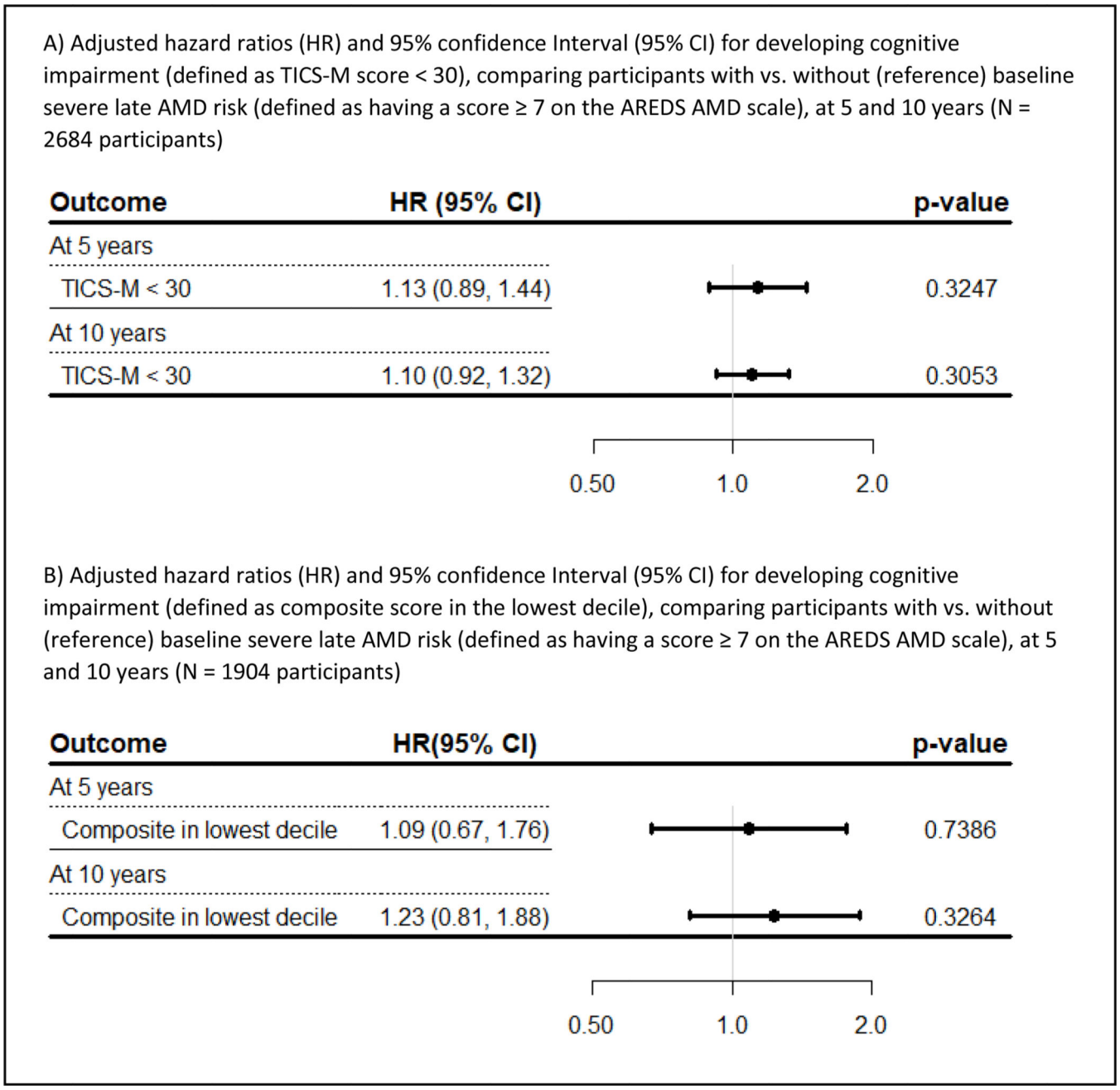


Figure 3.

Adjusted hazard ratios (HR) and 95% confidence Interval (95% CI) for developing cognitive impairment (defined as having (A) TICS-M score < 30 or (B) composite score in the lowest decile), comparing participants with vs. without (reference) baseline severe late AMD risk (defined as having a score ≥ 7 on the AREDS AMD scale), at 5 and 10 years

Notes and abbreviations: Models have been adjusted for for age, sex, smoking status, history of diabetes, history of hypertension, at risk of depression (CES-D ≥ 16), and cognitive score, all at baseline. A composite score ≤ −6.93 is considered to be in the lowest decile. AMD

= age-related macular degeneration; AREDS = Age-Related Eye Disease Study; TICS-M = Modified Telephone Interview for Cognitive Status

Table 1.

Baseline characteristics of participants in the Age-Related Eye Disease Study 2 included in analysis of outcome of late AMD (N = 3157)

	n	%
Sex		
Female	1796	56.9
Male	1361	43.1
Age		
Mean (SD)	72.7	(7.8)
Smoking status		
Never smoked	1362	43.1
Former smoker	1577	50.0
Current smoker	218	6.9
Highest level of education		
Unknown	55	1.7
High school or less	906	28.7
At least some college	1502	47.6
Post-graduate	694	22.0
History of diabetes		
No	2752	87.2
Yes	405	12.8
History of hypertension		
Unknown	4	0.1
No	1345	42.6
Yes	1808	57.3
Depression score Center for Epidemiologic Studies Depression (CES-D) Scale > 16		
Unknown	22	0.7
No	1820	57.6
Yes	1315	41.7
Modified alternative Mediterranean diet index (aMedi) tertiles		
Unknown/not available	99	3.1
1st tertile	1000	31.7
2nd tertile	927	29.4
3rd tertile	1131	35.8
Telephone Interview Cognitive Status-Modified score (TICS-M) < 30		
No	2708	85.8
Yes	449	14.2
Mean (SD)	32.9	3.5
Composite score in the lowest decile (i.e., score ≤ −6.93)		
Unknown	614	19.4
No	2293	72.6
Yes	250	7.9

	n	%
Mean (SD)	0.3	5.3
AMD severity scale score ≥ 7 (in the worse eye)		
No	751	23.8
Yes	2406	76.2
Follow-up time		
Median (range)	10.4	(0.8 – 12.2)