An Association Between Large Optic Nerve Cupping and Cognitive Function

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• PURPOSE: To determine if a larger cup-to-disc ratio is associated with poor cognitive function in postmenopausal women without glaucoma or ocular hypertension.

• METHODS: We used data from the Women's Health Initiative (WHI) hormone trial, originally designed to test effects of hormone therapy (HT) on various health outcomes. Large cup-to-disc ratio was defined as greater than 0.6 in either eye based on stereoscopic optic nerve photographs. Global cognitive function was assessed annually by Modified Mini-Mental State Examination (3MSE) in the WHI Memory Study. Exclusions were no information on optic nerve grading; no 3MSE scores at the time of the eye examination, ocular hypertension (intraocular pressure > 23 mm Hg, Goldmann applanation tonometry), or glaucoma medication use. A generalized linear model for log-transformed 3MSE scores was used for determining the association between large cup-to-disc ratio and 3MSE scores, adjusting for age, race, diabetes, body mass index, cardiovascular disease, smoking, HT randomization, education, and diabetic retinopathy.

• RESULTS: Analyses included 1636 women (mean age ± standard deviation, 69.57 ± 3.64 years; 90.39% white). Of those, 122 women had large cup-to-disc ratio. The mean 3MSE scores in women with vs without large cup-to-disc ratio were 95.4 ± 6 vs 96.6 ± 5. In the adjusted model, women with large cup-to-disc ratio had statistically significantly lower 3MSE scores, compared with those without large cup-to-disc ratio, yielding the predicted mean difference in 3MSE scores of 0.75 with a standard error of 0.05 units ($P = .04$).

• CONCLUSIONS: Postmenopausal women who had large cup-to-disc ratio without glaucoma or ocular hypertension exhibited lower global cognitive function. Further investigation is warranted. NOTE: Publication of this article is sponsored by the American Ophthalmological Society. (Am J Ophthalmol 2019;206:40–47. © 2019 Elsevier Inc. All rights reserved.)

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THE OPTIC NERVE AND THE BRAIN ARE BIOLOGICALLY connected based on shared anatomy and pathophysiology of the neurodegenerative process.[1–3] Composed of approximately 1 million axons of the retinal ganglion cells,[4] the optic nerve fibers terminate in the lateral geniculate nucleus in the central nervous system (CNS). During the normal aging process, the optic nerve loses about 0.2%–0.3% per year of its axons and 0.5%–0.6% per year of the retinal ganglion cells,[5,6] resulting in a discernable increase in the optic nerve cupping, as demonstrated in imaging studies, particularly confocal scanning tomography.[6,7] Likewise, both pathologic neurodegenerative conditions of the optic nerve and the brain could lead to increased optic nerve cupping. Although not pathognomonic, the increased optic nerve cupping could represent a neurodegenerative process of the optic nerve and the brain.

Primary open-angle glaucoma (POAG) and Alzheimer disease (AD) are among the most prevalent neurodegenerative disorders of the CNS in elderly individuals.[3,8,9] POAG, considered accelerated aging of the optic nerve, affects the optic nerve and is a leading cause of blindness.[3,10,11] AD affects the brain and is a leading cause of dementia.[9] It is believed that AD and POAG may share overlapping pathophysiology[3,9,12] owing to similar clinical manifestations and characteristics, particularly an age-dependent nature,[3] a progressive loss of affected neurons,[3,13] and a connection to apoptotic cell death[13,14] and neurotoxicity.[9,14–16] A possible link between POAG and AD has been demonstrated by results of basic science, clinical, and epidemiologic studies.[3,9,17–24] Accordingly, further investigations into the relationship between changes in the optic nerve and the brain will lead to better understanding of possible mechanistic connections between aging and neurodegenerative conditions of the optic nerve and the brain.

Prior studies suggest a link between structure and function in the optic nerve and the CNS.[3,9,17–24] Patients with AD without glaucoma demonstrated a larger optic nerve cupping, or cup-to-disc ratio, compared with age-

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matched cognitively normal individuals.[25] Significant thinning of the optic nerve fibers or the peripapillary retinal nerve fiber layer (RNFL) was also observed in patients with AD,[26–30] mild cognitive impairment (MCI),[29,30] or cognitive decline.[2] Hence, it is plausible that thinning of the RNFL, as manifested by increased optic nerve cupping, could serve as a marker for brain aging and neurodegeneration.

Based on the biological plausibility of eye and brain connection in light of shared anatomy, and based on a possible link between POAG and AD, this work aimed to test if large cup-to-disc ratio, as a sign of optic nerve neurodegeneration, was associated with poorer cognitive function in elderly women without glaucoma or ocular hypertension. We used data from 2 ancillary studies in the Women's Health Initiative (WHI) Hormone Therapy trials: the WHI-Sight Exam (WHISE), conducted from 2000 to 2002, and the WHI Memory Study (WHIMS), conducted between 1996 and 2007. This dataset provided an eye examination, including high-quality optic nerve photographs for optic nerve grading; assessment of global cognitive function, as measured by Modified Mini-Mental State Examination (3MSE) scores during the same period; and well-characterized systemic and lifestyle covariates, as risk factors for cognitive impairment collected in a randomized controlled trial. Based on the possible optic nerve and brain structure-function connection, we hypothesized that an enlarged cup-to-disc ratio (≥0.6) in at least 1 eye may be associated with lower global cognitive function elderly women without glaucoma or ocular hypertension.

METHODS

THE INSTITUTIONAL REVIEW BOARD AT THE UNIVERSITY OF Illinois at Chicago provided an exemption for this secondary data analysis of a de-identified dataset from the WHI. This project adhered to the Declaration of Helsinki and all federal and state laws.

• **DATA SOURCE:** Initiated in 1991 by the National Institutes of Health, the WHI (the parent study) consists of a set of clinical trials and an observational study, which together involved 161 808 generally healthy postmenopausal women aged 50–79 years.[25,26] The clinical trials were designed to test the effects of hormone therapy (HT), diet modification, and calcium and vitamin D supplementation on the incidence of heart disease, fractures, and breast and colorectal cancer. The HT trial was stratified by hysterectomy status: the estrogen plus progestin study of participants with a uterus and the estrogen-alone study of participants without a uterus (ie, those who had undergone hysterectomy). Participants with a uterus received progestin in combination with estrogen to prevent endometrial cancer. In each stratum, the participants were randomly assigned to either a hormone or a placebo arm. The WHI trial is registered at https://www.clinicaltrials.gov (identifier NCT00000611).

Design of Women's Health Initiative-Sight Exam. The WHISE, an ancillary study to the WHI HT trial, was designed to examine an association between fundus photographic evidence of early or late age-related macular degeneration and prior randomization to the initial WHI HT in participants aged 65 years and older. Enrollment occurred between 2000 and 2002, which was, on average, 5 years after the initial WHI randomization. The WHISE recruited 4347 participants who underwent fundus photography of at least 1 eye at 21 WHI clinics. Overall, the WHISE study reached 96.6% of its enrollment goal of 4500 eligible and consenting participants (15.9% of the WHI HT trial, n = 27 347) before termination of the estrogen plus progestin study arm because of an adverse risk-benefit profile after an average follow-up period of 5.2 years.

Design of Women's Health Initiative Memory Study. The WHIMS, an ancillary to the WHI hormone trial, was designed to examine whether postmenopausal HT reduced the risk of all-cause dementia and, secondarily, MCI and global cognitive functioning in healthy women aged 65–79 years (mean age, 69 years at WHIMS baseline).[31,32] The WHI hormone trial was a randomized placebo-controlled trial from which the WHIMS was selected. The WHI hormone trial consisted of 2 parallel, randomized, double-masked clinical trials of conjugated equine estrogen and medroxyprogesterone acetate or conjugated equine estrogen alone compared with placebo. Enrollment began in May 1996 among 27 347 eligible WHI HT trial participants; 4532 (92.6%) consented to participate in the WHIMS conjugated equine estrogen and medroxyprogesterone acetate trial and 2947 (92.1%) consented to participate in the WHIMS conjugated equine estrogen-alone trial.[31] The WHIMS study design, eligibility criteria, and recruitment procedures have been described elsewhere.[32] In brief, WHIMS participants underwent screenings of global cognitive function, as measured with the 3MSE, at enrollment and annually.

• **SAMPLE SELECTION:** Women were selected for this analysis who concurrently participated in the WHISE and the WHIMS. As expected, participants in the WHISE and WHIMS were significantly older than participants in the WHI HT, as the 2 ancillary studies focused on age-related

conditions, such as age-related macular degeneration and dementia. In this study, participants were excluded if they had any of the following: (1) no information on the optic nerve grading; (2) no cognitive testing during the time of the eye examination (2000 to 2002), (3) ocular hypertension based on the criteria used in the Ocular Hypertension Treatment Study (OHTS)[33] (intraocular pressure [IOP] >23 mm Hg with Goldmann applanation tonometry), or (4) glaucoma medication use.

• **TESTING PROTOCOL:** All participants completed a questionnaire on ocular and medical history, as well as lifestyle factors, at enrollment.

Ophthalmic Assessment and Fundus Photography. Eye examinations were performed at the time of WHISE study recruitment.[34,35] The examination included bilateral standard stereoscopic fundus photography and IOP measurements using Goldmann applanation tonometry. After pupillary dilation to at least 6 mm, 30-degree or 35-degree stereoscopic fundus photographs were obtained by certified ophthalmic photographers. The procedure adhered to a specified protocol adapted for the study by photography consultants at the University of Wisconsin.[34,35] In addition, all participants had 2 fundus (red reflex) photographs taken to allow the Reading Center's graders to assess media opacity when reviewing quality of the photographs. The quality control for the grading system included a preliminary and detailed grading followed by an edit of the photograph and adjudication, if needed. Based on stereoscopic fundus photographs, the optic nerve was classified by trained graders into 2 categories: presence of probable large cupping (cup-to-disc ratio ≥0.6) or absence of large cupping (cup-to-disc ratio <0.6).

Cup-to-Disc Ratio Cutoff

For the present analysis, we used existing predefined large cup-to-disc ratio for each woman as a cup-to-disc ratio of 0.6 or greater in at least 1 eye. We recognized racial differences in normal optic nerve cup-to-disc ratio. Particularly, African Americans on average have larger cup-to-disc ratio, compared to white individuals, owing to a larger disc area. Based on population-based studies in predominantly white populations, the mean cup-to-disc ratio was 0.49 with a standard deviation (SD) of 0.14 in individuals aged 55 years and older.[36,37] Approximately 2.5% of individuals aged 49 years and older had a cup-to-disc ratio of 0.7 or larger. In addition, in the Beaver Dam Eye Study including predominantly white participants, aged 40 years and older (n = 4640), the mean cup-to-disc ratio was 0.36, with SD of 0.13.[38] Comparing to whites, African Americans have larger disc areas (2.94 mm^2 vs 2.63 mm^2) and larger cup-to-disc ratio (0.56 vs 0.49) based on stereoscopic optic nerve photographs shown in a large population-based sample of healthy individuals aged 40 years and older in East Baltimore (n = 4877).[39] The racial difference was later supported by a series using confocal scanning laser tomography (n = 243), showing a trend of larger cup-to-disc ratio (0.33 vs 0.27) in African Americans, compared with whites. Notably, this difference was normalized after adjusting for disc area.[40]

Given a limitation of this existing database without available information on a disc area, we used a predefined cup-to-disc ratio of 0.6 cutoff for both white and African American subjects in the main model. We acknowledged that using cup-to-disc ratio cutoff that is closer to a normal mean for African Americans would likely bias results toward null. In a sensitivity analysis, we also limited our inclusion to white only to minimize the effects of racial differences in disc size on cup-to-disc ratio.

Evaluation of Cognitive Function and Cognitive Impairment Risk Factors. Cognitive function was assessed by 3MSE annually from 1996 to 2007.[32] The 3MSE scores range from 0 to 100, with a higher score denoting better cognitive function. The test measures temporal and spatial orientation, immediate and delayed recall, executive function (mental reversal, 3-stage command), naming, verbal fluency, abstract reasoning (similarities), praxis (obeying command, sentence writing), writing, and visuoconstructional abilities (copying). The 3MSE tests were administered during a WHI screening visit and annually afterward by a technician trained and certified in its administration and masked to randomization assignment and reports of symptoms.

The baseline demographic (age and race), lifestyle (education and smoking), and clinical factors (body mass index [BMI], hypertension, diabetes, cardiovascular disease, and HT assignment) were collected through self-report from the interviews and examinations at the WHI randomization visit. Diabetes at WHI baseline was defined by self-report of a physician's diagnosis or current drug therapy. Hypertension was defined as a self-report of a physician's diagnosis, current drug therapy, or a measurement of systolic blood pressure of at least 140 mm Hg or diastolic blood pressure of 90 mm Hg or higher.

• **STATISTICAL ANALYSIS:** As a secondary data analysis of a clinical trial, we determined if demographic and clinical characteristics, including risk factors for cognitive impairment, were statistically significantly different by optic nerve cupping status in the subcohort of the women who met our inclusion criteria. χ^2 tests were used for categorical variables, and Wilcoxon rank sum tests or t tests were used for continuous variables. The covariates included age at WHI enrollment, race, diabetes, BMI, cardiovascular disease, smoking, HT randomization, education level, and presence of diabetic retinopathy in either eye.

In the main model (all women) and alternative model (white only), a generalized linear model was used for

TABLE. Risk Factors for Cognitive Impairment by Optic Nerve Cupping Status

Risk Factor for Cognitive Impairment	Large Cup-to-Disc Ratio		*P* Value
	Without (N = 1514)	With (N = 122)	
Age at WHI enrollment, y (mean ± SD)	69.54 ± 3.62	69.96 ± 3.78	.24
Race, n (%)			
White	1371 (90.73)	105 (86.07)	.03*
AfricanAmerican	89 (5.89)	12 (9.84)	
Hispanic/Latino	27 (1.79)	(0.00)	
Other	24 (1.79)	5 (4.10)	
Education, n (%)			
No high school	88 (5.83)	7 (5.74)	.58
High school	361 (23.91)	23 (18.85)	
Post high school	585 (38.73)	48 (39.34)	
College graduate	476 (31.52)	44 (36.07)	
Cigarette smoking,[a] n (%)			
Never smoked	858 (57.12)	71 (61.74)	.58
Past smoker	556 (37.02)	39 (33.91)	
Current smoker	88 (5.89)	5 (4.35)	
BMI, kg/m^2, n (%)			
Underweight (<18.5)	13 (0.86)	1 (0.82)	.97
Normal (18.5 to <25)	423 (28.13)	38 (31.15)	
Overweight (25.0 to <30)	520 (34.57)	43 (35.25)	
Obesity class 1 (30 to <35)	361 (24.00)	27 (22.13)	
Obesity class 2 (35 to <40)	134 (8.91)	9 (7.38)	
Extreme obesity (≥40)	53 (3.52)	4 (3.28)	
Diabetes,[b] n (%)			
Yes	154 (10.17)	10 (8.20)	.48
No	1360 (89.83)	112 (91.80)	
Prior cardiovascular disease,[c] n (%)			
Yes	241 (16.23)	14 (11.76)	.20
No	1244 (83.77)	105 (88.24)	
Diabetic retinopathy, n (%)			
Yes	193 (12.76)	19 (15.57)	.37
No	1319 (87.24)	103 (84.43)	
Hormone therapy assignment, n (%)			
E-alone intervention	266 (17.57)	29 (23.77)	.34
E-alone control	304 (20.08)	23 (18.85)	
E+P intervention	474 (31.31)	38 (31.15)	
E+P control	470 (31.94)	32 (26.23)	

BMI = body mass index; E = estrogen; E+P = estrogen plus progestin; WHI = Women's Health Initiative.
Asterisk (*) indicates statistical significance.
[a]Smoking status determined from the WHI categorization.
[b]Diabetes is self-reported from the WHI, WHI Memory Study, and/or the WHI Sight Exam questionnaires or by those receiving current therapy.
[c]Prior cardiovascular disease is defined as myocardial infarction, angina, percutaneous transluminal coronary angioplasty, coronary bypass grafting, or stroke.

determining the association between large optic nerve cupping in at least 1 eye and 3MSE scores, adjusting for age, race, diabetes, BMI, cardiovascular disease, smoking, HT randomization, education, and presence of diabetic retinopathy in either eye at the baseline eye examination. As 3MSE scores were nonnormally distributed, a log transformation, log(102 - 3MSE score), was used. Statistical tests using SAS software version 9.4 (SAS Institute Inc, Cary, North Carolina, USA) were considered significant at $P = .05$.

RESULTS

FINAL ANALYSIS INCLUDED 1636 WOMEN WITH A BASELINE cup-to-disc ratio, health data, and 3MSE scores at the time of the eye examination. The mean age (± SD) was 69.57 ± 3.64 years; 90.39% were white. Of those, 122 women (7.56%) had a large cup-to-disc ratio, and 1514 women did not. The Table shows the baseline characteristics of women in the final analysis by optic nerve cupping status. Women with a large cup-to-disc ratio were

significantly more likely to be African American than those without. Other baseline characteristics were similar, including age, education, cigarette smoking, BMI, diabetes, prior cardiovascular disease, presence of diabetic retinopathy, and HT assignment by optic nerve status.

In the main model (all women), the mean 3MSE scores in women with vs without large cup-to-disc ratio were 95.4 ± 6 vs 96.6 ± 5. In the adjusted model, women with the large cup-to-disc ratios had statistically significantly lower 3MSE scores (worse cognitive function), compared to those without large cup-to-disc ratio, yielding the predicted mean difference in 3MSE scores of 0.75 with a standard error of 0.05 units ($P = .04$).

In the alternative model (white only), there were 1476 white women, including 105 white women with large cup-to-disc ratio (7.11%). In the adjusted model, white women with large cup-to-disc ratio had statistically significantly lower 3MSE scores, compared to white women without large cup-to-disc ratio, yielding a predicted mean difference in 3MSE scores of 0.61 with a standard error of 0.06 units ($P = .03$).

DISCUSSION

IN THE PRESENT STUDY, WE FOUND AN ASSOCIATION between large optic nerve cupping and minor cognitive differences in cognitively intact women aged 65 years and older without glaucoma or ocular hypertension. The observed association between large cup-to-disc ratio and poorer cognitive function in this cohort may represent the association between aging of the optic nerve and the CNS, or may reflect the link between neurodegeneration of the optic nerve and AD. Our analysis yielded the predicted mean difference in 3MSE of 0.75 units between women with vs without large cup-to-disc ratio. According to Espeland and associates,[41] a mean difference of 0.21 3MSE units was associated with a 76% increased hazard for dementia. These findings may therefore have clinical implications when one is monitoring patients with optic nerve and CNS neurodegeneration.

The biologic plausibility of the structure-function connection between the optic nerve and the brain is based on shared anatomy of the eye and the brain, as well as shared pathophysiology of the common neurodegenerative conditions such as POAG and AD.[1–3] During embryologic development, the optic nerve extends from the CNS, resulting in similar microvascular and neuronal anatomy, function, immunologic responses, and degenerative process.[1] Many common neurodegenerative diseases of the CNS such as AD, Parkinson disease, and multiple sclerosis (MS) manifest in the eye. Specifically, patients with AD, Parkinson disease, and MS may have thinner RNFL, resulting in an increased cup-to-disc ratio.[1] In addition, in patients with AD, POAG may progress rapidly at a normal IOP.[19–22] Similarly, 75% of patients with MS experience optic neuritis, an inflammatory optic neuropathy associated with demyelination of the retinal ganglion cells.[1] Based on these connections, optic nerve imaging may serve as a noninvasive tool to detect and monitor aging changes, as well as neurodegenerative diseases of the brain.

The association between cup-to-disc ratio and cognitive function in cognitively intact individuals has not been investigated. A previous cross-sectional investigation by Tsai and associates,[25] however, demonstrated a statistically significantly higher cup-to-disc ratio in 26 patients with AD, compared with 36 age-matched patients without AD. All patients were white, were aged 55 years and older, had visual acuity better than 20/25, and had no ocular hypertension. Patients with clinically defined AD had a higher cup-to-disc ratio, compared with controls (mean ± SD, 0.5 ± 0.1 vs 0.4 ± 0.1; $P < .001$). Furthermore, patients with AD had a higher cup volume, lower disc rim area, and higher proportion of detectable RNFL defects by red-free photography, compared with controls. Notably, in patients with AD, the degree of the optic nerve pallor and other optic nerve parameters including the cup-to-disc ratio, cup volume, and disc area were significantly correlated with Alzheimer's Disease Assessment Scale scores and longer duration of disease. In comparison, we analyzed data from a large cohort of older women with normal cognition. Similarly, we found that an increased cup-to-disc ratio was associated with lower cognitive function. These findings suggest a potential role for optic nerve head analysis in monitoring cognitive function.

Complementary to conventional photography, optical coherence tomography (OCT) offers quantitative assessment of the optic nerve head and its fibers (the peripapillary RNFL). In healthy populations, several studies have demonstrated an association between RNFL thickness and cognitive function.[42–44] Notably, in the European Prospective Investigation of Cancer (EPIC)-Norfolk cohort study, a significantly higher RNFL thickness was associated with better cognitive test performance assessing global function, recognition, learning, episodic memory, and premorbid intelligence in 5563 participants, with a mean age of 67 years.[45] Likewise, UK Biobank including 32 038 participants demonstrated that a thinner RNFL was associated with worse cognitive function in individuals with normal cognition and greater likelihood of future cognitive decline.[44] In addition, OCT has recently emerged as a noninvasive structural test for CNS disorders. Results of several studies demonstrated that OCT not only detects statistically significant RNFL thinning in patients with AD[26–30] and MCI[29,30] but also predicts cognitive decline in patients with normal cognition.[2] Overall thinning of the RNFL was observed in both patients with AD and patients with MCI.[2,26–29,46] In addition, although the magnitude of OCT parameters was not consistently related to the degree of cognitive impairment, OCT

provided an insight into the pattern of RNFL loss in patients with cognitive impairment.[2] Specifically, findings of several studies suggested a selective loss of RNFL in inferior[30,47] and/or superior[48] optic disc sectors in patients with AD,[30,48] MCI,[30] and normal cognition with cognitive decline.[2,47] This observation is particularly intriguing, because the selective RNFL loss in the inferior sector in patients with cognitive decline and cognitive impairment is consistent with the preferential RNFL loss demonstrated in normal aging and glaucoma.[6] Notably, while they share a similar pattern of neuroretinal rim loss, the rate of loss is 3.7 times faster in glaucomatous progression[6,7] compared to expected age-related loss.[7] These pattern similarities further support the shared pathophysiology of the neurodegeneration of normal aging, POAG, and AD.

In addition to the optic nerve structural changes, vascular contributions have also been explored. The presence of retinal microvascular abnormalities such as retinopathy was associated with poorer cognitive function. In the Atherosclerosis Risk in Communities study, the presence of retinopathy on retinal photographs predicted cognitive decline in middle-aged individuals (n = 8734).[49] Similarly, Haan and associates[34] demonstrated a cognitive decline in postmenopausal women in the WHISE and WHIMS (n = 511). As noted by Tsai and associates,[25] the extent of the optic nerve pallor was associated with cognitive test scores and duration of AD. Consistently, a decreased retinal blood flow measured by retinal laser Doppler imaging was also observed in patients with AD and MCI, compared with controls.[50] These findings highlight the potential complementary benefits of OCT and fundus photography as a noninvasive aid in the detection and monitoring of cognitive decline.

• **STRENGTHS AND LIMITATIONS:** Conducted in the setting of a randomized clinical trial, this secondary analysis of the WHISE and WHIMS offered a rich dataset on factors that might influence optic nerve cupping and cognitive function. Particularly, the WHISE offered high-quality stereoscopic optic nerve photography, IOP measurements, and a history of glaucoma outcomes such as glaucoma medication use. Furthermore, the WHIMS offered comprehensive data on risk factors for cognitive impairment.

Despite the many strengths, this study has limitations. First, as a secondary data analysis, only existing data could be used. Our study used a photographic cup-to-disc ratio measurement, which may not be as sensitive as new imaging technologies. However, cup-to-disc ratio is still widely used in large-scale studies, and remains an important measurement in clinical practice. Similarly, 3MSE is widely used as a measure of global cognitive function and has very good inter-rater reliability (0.98), internal consistency (0.91), and test-retest reliability (0.78) when used with older adults.[51] Furthermore, it is proven to be an excellent clinical measure, with the area under the curve for detecting dementia of 0.93.[52] Hence, we believe that both cup-to-disc ratio and 3MSE scores are valid measures and good indicators for aging and/or neurodegenerative process of the CNS and cognition. In addition, the optic nerve grading was dichotomous, not continuous, which might have decreased the power. Specifically, while detailed grading of the optic nerve is preferable, this information is not available in this existing database as part of an original study for age-related macular degeneration. Neither optic disc size nor the pattern of optic nerve changes was available. Hence, further investigations including detailed grading of the optic nerves are warranted. Second, we used predefined cup-to-disc ratio of 0.6 for both whites and African Americans. In the main model, we acknowledged that using a cup-to-disc ratio cutoff that was closer to a normal mean for African Americans would likely bias results toward null. Specifically, for P value of .04, we accepted a 4% chance that this association might be found by chance. Given a plausible hypothesis, consistent findings in the main and alternative models, and anticipated direction of the association, we believe that this represents a true significant finding. Third, ocular hypertension and glaucoma was based on a single IOP measurement and the history of glaucoma medication use. Fourth, without longitudinal data demonstrating changes in cup-to-disc ratio over time in relationship to changes in cognitive function, it is not known if monitoring the optic nerve will practically be useful. In this analysis, we hypothesized that increased cup-to-disc ratio beyond expected mean in elderly women could represent aging or neurodegenerative process. This assumption is supported by imaging studies that demonstrated an increase in cup-to-disc ratio with increasing age, or with a neurodegenerative process, such as glaucoma.[6,7] Likewise, several cross-sectional analyses using stereoscopic disc photography suggested that cup-to-disc ratio was larger in older, compared to younger, populations. However, this age-related change over time was only demonstrated in imaging studies using confocal laser scanning tomography, but not in studies using stereoscopic disc photography.[38,39,53] As the present study used stereoscopic disc photographs to determine cup-to-disc ratio and information of the past appearance of the optic nerve was not available, we did not know if there was a change in cup-to-disc ratio over time. Given an inability of standard photographs to detect normal aging, a discernable increase in cup-to-disc ratio on photographs may reflect a neurodegenerative process beyond averaged age-related changes. In our longitudinal analysis (data not shown), we further examined an association between baseline cup-to-disc ratio and 3MSE scores over time. An adjusted mixed linear model suggested that women with cup-to-disc ratio of 0.6 or larger at baseline demonstrated a lower 3MSE scores, compared with women without large cup-to-disc ratio during a 4-year follow up ($P = .02$). Notably, given significant missing data in this longitudinal analysis, a future study

needs to confirm this significant finding. Lastly, although we corrected for the potential risk factors of cognitive impairment, the analysis was not adjusted for visual acuity, which might have affected visual-related 3MSE scores. Lastly, as this cohort selectively included elderly postmenopausal woman aged 65 years and older, our findings may not be applicable to American women in general.

In conclusion, the present study represents the first analysis suggesting an association between optic nerve cupping status and cognitive performance in women without glaucoma and/or ocular hypertension. Results of the final analysis suggest that postmenopausal women who had a large cup-to-disc ratio without glaucoma or ocular hypertension exhibited poorer cognitive function. These findings further support the link between structure-function of the eye and the CNS and the possible role of ocular imaging as a noninvasive aid for detecting and monitoring CNS disorders. Ophthalmologists and neurologists should therefore consider this important relationship that might reflect the CNS aging when monitoring POAG and AD. Further investigation using detailed optic nerve grading and recent imaging technology in a larger sample size with a long-term follow-up is warranted.

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