Supplementary Online Content

Tran EM, Stefanick ML, Henderson VW, et al. Association of visual impairment with risk of incident dementia in a Women's Health Initiative population. *JAMA Ophthalmol*. Published online April 16, 2020. doi:10.1001/jamaophthalmol.2020.0959

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Subjective Visual Impairment Classification based on Visual Function Questionnaire Responses

Question	Question text	Responses [a]
A2a	"When you wear eye glasses or contact lenses, normally how good would you say your vision is?"	"poor" or "cannot see at all"
A5	"How much difficulty do you have reading ordinary print in newspapers?"	"moderate difficulty," "extreme difficulty," or "stopped doing this because of eyesight"
A6	"How much difficulty do you have doing work or hobbies that require you to see well up close, such as cooking, sewing, fixing things around the house, or using hand tools?"	"moderate difficulty," "extreme difficulty," or "stopped doing this because of eyesight"
A7	"Because of your eyesight, how much difficulty do you have finding something on a crowded shelf?"	"moderate difficulty" or "extreme difficulty"
A8	"How much difficulty do you have reading street signs or names of stores?"	"moderate difficulty," "extreme difficulty," or "stopped doing this because of eyesight"
A9	"How much difficulty do you have going down steps, stairs or curbs in dim light or at night?"	"moderate difficulty," "extreme difficulty," or "stopped doing this because of eyesight"
A10	"Because of your eyesight, how much difficulty do you have noticing objects off to the side while you are walking along?"	"moderate difficulty," "extreme difficulty," or "stopped doing this because of eyesight"
A11	"Because of your eyesight, how much difficulty do you have seeing how people react to things you say?"	"moderate difficulty," "extreme difficulty," or "stopped doing this because of eyesight"
A12	"Because of your eyesight, how much difficulty do you have picking out and matching your own clothes?"	"moderate difficulty," "extreme difficulty," or "stopped doing this because of eyesight"
A13	"Because of your eyesight, how much difficulty do you have visiting with people in their homes, at parties or in restaurants?"	"moderate difficulty," "extreme difficulty," or "stopped doing this because of eyesight"
A14	"Because of your eyesight, how much difficulty do you have going out to see movies, plays or sports events?"	"moderate difficulty," "extreme difficulty," or "stopped doing this because of eyesight"
A15b	[If gave up driving], "Was that mainly because of your eyesight, mainly for some other reason or because of both your eyesight and other reasons?"	"mainly eyesight " or "both eyesight and other reasons"
A15c	"How much difficulty do you have driving during the daytime in familiar places?"	"moderate difficulty" or "extreme difficulty"
A16a	"How much difficulty do you have driving at night?"	"moderate difficulty" or "extreme difficulty"
A16b	"If you don't drive at night, is this because of problems seeing at night?"	"yes"

[a] Participants were classified with subjective visual impairment if they provided one of the listed responses to one or more questions.

eTable 2. Interaction for Hearing Loss and Visual Impairment				
	Subjective Hearing Loss		No Subjective Hearing Loss	
Probable Dementia	**Hazard Ratio**	**95% Confidence Interval**	**Hazard Ratio**	**95% Confidence Interval**
Objective Visual Impairment (20/40 or worse)	3.95	0.88 - 17.76	**2.71**	1.35 - 5.45
Objective Visual Impairment (20/80 or worse)	**20.74**	4.44 - 96.85	**4.25**	1.30 - 13.89
Objective Visual Impairment (20/100 or worse)	**47.62**	7.91 - 286.54	3.50	0.84 - 14.61
Subjective Visual Impairment	4.13	0.92 - 18.46	1.09	0.45 - 2.63
Mild Cognitive Impairment	**Hazard Ratio**	**95% Confidence Interval**	**Hazard Ratio**	**95% Confidence Interval**
Objective Visual Impairment (20/40 or worse)	2.64	0.79 - 8.82	2.08	0.92 - 4.73
Objective Visual Impairment (20/80 or worse)	**6.02**	1.30 - 27.95	**5.81**	1.75 - 19.34
Objective Visual Impairment (20/100 or worse)	**13.01**	1.59 - 106.48	**4.78**	1.13 - 20.18
Subjective Visual Impairment	2.29	0.73 - 7.23	1.75	0.74 - 4.13
Both Mild Cognitive Impairment and Dementia	**Hazard Ratio**	**95% Confidence Interval**	**Hazard Ratio**	**95% Confidence Interval**
Objective Visual Impairment (20/40 or worse)	2.60	0.89 - 7.64	2.13	1.19 - 3.81
Objective Visual Impairment (20/80 or worse	**7.20**	2.01 - 25.88	**4.79**	1.91 - 12.03
Objective Visual Impairment (20/100 or worse)	**21.96**	4.71 - 102.49	**3.55**	1.11 - 11.36
Subjective Visual Impairment	2.17	0.77 - 6.10	1.49	0.78 - 2.82

eTable 3: Multivariable Cox Regression Models for Incidence of Dementia or Mild Cognitive Impairment, based on Visual Impairment Severity Ranges [a]

Probably Dementia	**N**	**Hazard Ratio**	**95% Confidence Interval**	**p-value**
Objective Visual Impairment (20/40 - 20/80)	152	1.25	0.58 - 2.71	0.57
Objective Visual Impairment (20/80 - 20/100)	10	3.88	0.74 - 20.28	0.11
Objective Visual Impairment (20/100 or worse)	21	5.66	1.75 - 18.37	0.004
Mild Cognitive Impairment		**Hazard Ratio**	**95% Confidence Interval**	**p-value**
Objective Visual Impairment (20/40 - 20/80)	152	1.06	0.45 - 2.50	0.89
Objective Visual Impairment (20/80 - 20/100)	10	4.70	0.87 - 25.47	0.07
Objective Visual Impairment (20/100 or worse)	21	6.43	1.66 - 24.85	0.007
Both Mild Cognitive Impairment and Dementia		**Hazard Ratio**	**95% Confidence Interval**	**p-value**
Objective Visual Impairment (20/40 - 20/80)	152	1.12	0.61 - 2.08	0.71
Objective Visual Impairment (20/80 - 20/100)	10	3.00	0.80 - 11.32	0.10
Objective Visual Impairment (20/100 or worse)	21	5.54	2.02 - 15.16	0.0009

[a] Regression models adjusted for age, race/ethnicity, hormone therapy trial arm, self-reported education level, self-reported physical activity, self-reported hearing loss, smoking status, depression, 3MS Score at WHISE baseline, and self-reported systemic comorbidities (cardiovascular disease, chronic heart failure, hypertension, hyperlipidemia, chronic pulmonary disease, peptic ulcer disease, liver disease, leukemia or lymphoma, and diabetes mellitus).

e Table 4: Multivariable Cox Regression Models for Incidence of Dementia or Mild Cognitive Impairment, based on Visual Impairment Thresholds in the Better-Seeing Eye [a]

Probably Dementia	**N**	**Hazard Ratio**	**95% Confidence Interval**	**p-value**
Objective Visual Impairment (20/40 or worse)	74	0.96	0.32 - 2.86	0.95
Objective Visual Impairment (20/80 or worse)	3	-	-	-
Objective Visual Impairment (20/100 or worse)	1	-	-	-
Mild Cognitive Impairment		**Hazard Ratio**	**95% Confidence Interval**	**p-value**
Objective Visual Impairment (20/40 or worse)	74	1.51	0.49 - 4.63	0.48
Objective Visual Impairment (20/80 or worse)	3	-	-	-
Objective Visual Impairment (20/100 or worse)	1	-	-	-
Both Mild Cognitive Impairment and Dementia		**Hazard Ratio**	**95% Confidence Interval**	**p-value**
Objective Visual Impairment (20/40 or worse)	74	1.55	0.72 - 3.34	0.26
Objective Visual Impairment (20/80 or worse)	3	-	-	-
Objective Visual Impairment (20/100 or worse)	1	-	-	-

[a] Regression models adjusted for age, race/ethnicity, hormone therapy trial arm, self-reported education level, self-reported physical activity, self-reported hearing loss, smoking status, depression, 3MS Score at WHISE baseline, and self-reported systemic comorbidities (cardiovascular disease, chronic heart failure, hypertension, hyperlipidemia, chronic pulmonary disease, peptic ulcer disease, liver disease, leukemia or lymphoma, and diabetes mellitus).
[b] Insufficient sample size

eTable 5: Multivariable Cox Regression Models for Incidence of Dementia or Mild Cognitive Impairment, based on Visual Impairment Severity Ranges in the Better-Seeing Eye [a]

Probably Dementia	**N**	**Hazard Ratio**	**95% Confidence Interval**	**p-value**
Objective Visual Impairment (20/40 - 20/80)	71	0.98	0.33 - 2.92	0.97
Objective Visual Impairment (20/80 - 20/100)	2	-	-	-
Objective Visual Impairment (20/100 or worse)	1	-	-	-
Mild Cognitive Impairment		**Hazard Ratio**	**95% Confidence Interval**	**p-value**
Objective Visual Impairment (20/40 - 20/80)	71	1.59	0.52 - 4.92	0.42
Objective Visual Impairment (20/80 - 20/100)	2	-	-	-
Objective Visual Impairment (20/100 or worse)	1	-	-	-
Both Mild Cognitive Impairment and Dementia		**Hazard Ratio**	**95% Confidence Interval**	**p-value**
Objective Visual Impairment (20/40 - 20/80)	71	1.61	0.75 - 3.49	0.22
Objective Visual Impairment (20/80 - 20/100)	2	-	-	-
Objective Visual Impairment (20/100 or worse)	1	-	-	-

[a] Regression models adjusted for age, race/ethnicity, hormone therapy trial arm, self-reported education level, self-reported physical activity, self-reported hearing loss, smoking status, depression, 3MS Score at WHISE baseline, and self-reported systemic comorbidities (cardiovascular disease, chronic heart failure, hypertension, hyperlipidemia, chronic pulmonary disease, peptic ulcer disease, liver disease, leukemia or lymphoma, and diabetes mellitus).

[b] Insufficient sample size

eTable 6: Determination of Baseline Systemic Comorbidity Variables

Variable	Assessment
Systemic Comorbidities	
Depression	Self-reported treatment for depression and/or CES-D depression scale score >0.06
Cardiovascular Disease	Composite variable representing one or more of the following: MI: clinical MI (clinical trial and observational study) and/or definite silent MI (clinical trial only) TIA/stroke: adjudicated stroke or TIA Peripheral vascular disease: adjudicated peripheral arterial disease Angina: self-reported angina
Congestive Heart Failure	Adjudicated congestive heart failure
Hyperlipidemia	Self-reported hyperlipidemia
Hypertension	Self-reported hypertension
Chronic Pulmonary Disease	Self-reported COPD, emphysema, or chronic bronchitis
Peptic Ulcer Disease	Self-reported history of stomach or duodenal ulcer
Liver Disease	Self-reported ever told by a doctor that had liver disease (chronic active hepatitis, cirrhosis, or yellow jaundice)
Diabetes Mellitus	Ever treated for diabetes with pills or shots
Leukemia and/or Lymphoma	Adjudicated first-occurrence of leukemia cancer or non-Hodgkins lymphoma, or death due to either
Hearing Loss	Affirmative response to moderate or severe hearing loss symptoms
Physical activity	Self-reported episodes per week of moderate and strenuous recreational physical activity of ≥ 20 minutes duration (includes walking fairly fast or very fast, moderate physical activity and strenuous physical activity)

CES-D scale: Center for Epidemiologic Studies – Depression scale

MI: Myocardial Infarction

TIA: Transient Ischemic Attack

COPD: Chronic Obstructive Pulmonary Disease

eAppendix. Women's Health Initiative, Women's Health Initiative Sight Exam Study, and Women's Health Initiative Memory Study

Women's Health Initiative

The Women's Health Initiative (WHI) is a national health study sponsored by the National Institutes of Health (NIH), focused on studying the major causes of disease in older women. Started in 1993, original multicenter WHI enrollment included 161,808 women post-menopausal women ranging in age from 50 to 79 years. This project has spanned over 20 years, making it one of the most extensive US studies in post-menopausal women's health.

The study was initially comprised of two major arms – a Clinical Trial (CT) and an Observation Study (OS). The randomized controlled Clinical Trial arm enrolled 68,132 women, who could choose to take part in one to three components: a Hormone Therapy trial (estrogen/estrogen plus progestin vs. placebo), a Dietary modification trial (usual eating pattern vs. low-fat diet), and Calcium/vitamin D (calcium/vitamin D supplementation vs. placebo). The Observation Study recruited 93,676 women, following their health habits and medical events in order to evaluate associations between lifestyle risk factors and disease outcome.

Women in the double-blinded Hormone Therapy clinical trial arm were randomized to estrogen supplementation (with or without progesterone, depending on hysterectomy status). Women who had not had a prior hysterectomy were randomized to either 0.625 mg/day of conjugated equine estrogen with 2.5mg/day of progestin (CEE/MPA; Prempro®, Wyeth Ayerst, St. David's, Pennsylvania, USA) or placebo. Women who were post-hysterectomy were randomized to either 0.625 mg/day of conjugated equine estrogen alone (CEE; Premarin®, Wyeth Ayerst, St. David's, Pennsylvania, USA) or placebo. Women were excluded from the WHI Hormone Trial if they had any medical condition with a predicted survival of <5 years, had prior breast or other cancer except nonmelanoma skin cancer <10 years, had an acute myocardial infarction or stroke in the past six months, and/or had severe hypertension (systolic blood pressure >299 mm Hg or diastolic blood pressure >105 mm Hg).

In addition to the main WHI study, ancillary investigations have and continue to enroll WHI participants for further studies involving abstraction of records, biospecimen assays, or collection of new clinical data. To date, the WHI had approved and funded over 250 Ancillary Studies (AS), two of which are the Women's Health Initiative Sight Exam Study (WHISE) and the Women's Health Initiative Memory Study (WHIMS).

Women's Health Initiative Sight Exam Study

WHISE was an ancillary study to the WHI hormone therapy trial. WHISE initially recruited participants between April 2000 and March 31, 2002, such that their initial WHISE study visit occurred an average of 5.1 years after randomization to hormone replacement therapy regimens versus placebo. Women were eligible to participate if they were aged 65 and older at the time of WHISE enrollment, had pupils that could be pharmacologically dilated, would sign a consent form, and agreed to have fundus photography. Participants received an eye exam, including documentation of visual acuity, intraocular pressure and fundus photography, and had blood drawn. At 1, 2, and 3 years following their baseline eye exam, participants completed a telephone or mail survey regarding new eye diseases, treatments, or visual problems. In total, 4383 subjects completed a visual function questionnaire, and 4347 subjects completed WHISE enrollment by having objective measurement of visual acuity and at least one fundus photograph.

Visual acuity assessments at the initial WHISE baseline eye examination was performed at distance with participant's current corrective lenses (glasses or contact lenses). Different logMAR visual acuity charts were used for participants' right eye and left eye, respectively. Measurements were first performed at with the participant at 4 meters distance from the charts. If a participant was unable to read at least three out of five letters on the 20/40 visual acuity line, they were given a pinhole occluder to hold in front of their glasses or over their contact lenses and instructed to continue reading down the chart, to see if any additional letters could be read with the pinhole. If a participant was unable to correctly read any letters at the 4 meter distance, the logMAR chart was moved to 2 meters from the participant and the same procedure followed again. If the participant could not read any letters at 2 meters distance, the chart was moved to 1 meter distance. If the participant could not read more than 2 letters on the chart at 1 meter, it is recorded as "Cannot Measure". The examiner would then test to see if the participant could count fingers, see hand movements, or perceive light (tested with a penlight) at a distance of 1 foot. If no light is perceived or the eye is enucleated, "No Light" (perception) was recorded.

Women's Health Initiative Memory Study

WHIMS was designed to formally assess cognitive function over time among WHI participants aged 65 and older. The WHIMS ancillary studies, also based on a subset of participants in the WHI hormone therapy trial, were completed in several phases: during the hormone therapy trial (WHIMS, 1995 through 2002 or 2004, depending on hormone therapy arm), during the post-trial extension period (WHIMS Extension, through 2007), and during the subsequent period (WHIMS-Epidemiology of Cognitive Health Outcomes, or WHIMS-ECHO, 2008-2021). These ancillary studies enrolled progressively narrowing subsets of participants: 7427 in WHIMS, 5385 in WHIMS Extension, and 2900 in WHIMS-ECHO.

For participants in WHIMS and WHIMS Extension, cognitive scores were determined by annually administered Modified Mini Mental State Exam (3MSE). Participants received further cognitive testing and clinical assessment if they scored below a cutoff point on the 3MSE: 80 for women with 8 or fewer years of formal education and 88 for those with 9 or more years of formal education. Additional testing consisted of administration of a comprehensive cognitive battery assessing memory, language, executive function, and visuoconstruction; clinical evaluation; and optional laboratory/imaging studies. Clinical evaluation assessed several factors, including mental status, capacity to complete activities of daily living, onset and progression of symptoms, history of head injury, psychiatric disorders, and medications, among many others. Laboratory and imaging studies include head CT (computed tomography), CBC (complete blood count), and various serologies, among several others. For those subsequently followed in WHIMS ECHO, beginning in 2008, researchers used a validated telephone-based cognitive battery that included cognitive tests of memory, language, executive function and working memory. Friends or family members (names provided at the beginning of the trial) were also interviewed regarding participant's cognitive status and functional abilities. A central adjudication committee then reviewed all data to classify participants into one of three categories: no cognitive impairment, mild cognitive impairment (MCI), or probable dementia using standardized DSM-IV diagnostic criteria. Two experts in diagnoses of cognitive impairment independently reviewed all the data and made classifications. Disagreements were discussed on regularly schedule conference calls until consensus was reached.

Acknowledgments

We also thank and acknowledge the investigators and staff who have led WHI investigations:

Program Office: (National Heart, Lung, and Blood Institute, Bethesda, Maryland)
Jacques Rossouw, Shari Ludlam, Joan McGowan, Leslie Ford, and Nancy Geller
Clinical Coordinating Center: (Fred Hutchinson Cancer Research Center, Seattle, WA)
Garnet Anderson, Ross Prentice, Andrea LaCroix, and Charles Kooperberg

Investigators and Academic Centers: (Brigham and Women's Hospital, Harvard Medical School, Boston, MA) JoAnn E. Manson; (MedStar Health Research Institute/Howard University, Washington, DC) Barbara V. Howard; (Stanford Prevention Research Center, Stanford, CA) Marcia L. Stefanick; (The Ohio State University, Columbus, OH) Rebecca Jackson; (University of Arizona, Tucson/Phoenix, AZ) Cynthia A. Thomson; (University at Buffalo, Buffalo, NY) Jean Wactawski-Wende; (University of Florida, Gainesville/Jacksonville, FL) Marian Limacher; (University of Iowa, Iowa City/Davenport, IA) Jennifer Robinson; (University of Pittsburgh, Pittsburgh, PA) Lewis Kuller; (Wake Forest University School of Medicine, Winston-Salem, NC) Sally Shumaker; (University of Nevada, Reno, NV) Robert Brunner

Women's Health Initiative Memory Study: (Wake Forest University School of Medicine, Winston-Salem, NC) Sally Shumaker, Mark Espeland, Steve Rapp

For a list of all the investigators who have contributed to WHI science, please visit:
https://www.whi.org/researchers/Documents%20%20Write%20a%20Paper/WHI%20Investigator%20Long%20List.pdf

