THE GERONTOLOGICAL SOCIETY OF AMERICA®

Journals of Gerontology: Medical Sciences
cite as: *J Gerontol A Biol Sci Med Sci,* 2019, Vol. 74, No. 11, 1786–1792
doi:10.1093/gerona/glz011
Advance Access publication January 9, 2019

OXFORD

Research Article

Sensorineural Impairments, Cardiovascular Risk Factors, and 10-Year Incidence of Cognitive Impairment and Decline in Midlife: The Beaver Dam Offspring Study

Carla R. Schubert, MS,[1,*] Karen J. Cruickshanks, PhD,[1,2] Mary E. Fischer, PhD,[1] A. Alex Pinto, MS,[1] Yanjun Chen, MD,[1] Guan-Hua Huang, PhD,[3] Barbara E. K. Klein, MD,[1] Ronald Klein, MD,[1] James S. Pankow, PhD,[4] Adam J. Paulsen, MS,[1] Dayna S. Dalton, MS,[1] and Ted S. Tweed, MA[1]

[1]Department of Ophthalmology and Visual Sciences, School of Medicine and Public Health, University of Wisconsin–Madison. [2]Department of Population Health Sciences, School of Medicine and Public Health, University of Wisconsin–Madison. [3]Institute of Statistics, National Chiao Tung University, Hsinchu, Taiwan. [4]Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis.

*Address correspondence to: Carla R. Schubert, MS, Department of Ophthalmology and Visual Sciences, School of Medicine and Public Health, University of Wisconsin–Madison, 610 Walnut Street, Madison, WI 53726. E-mail: schubert@episense.wisc.edu

Received: September 28, 2018; Editorial Decision Date: January 2, 2019

Decision Editor: Anne Newman, MD, MPH

Abstract

Background: Sensorineural impairments and cardiovascular risk factors (CVRF) and disease (CVD) in midlife may be important predictors of future cognitive health, but longitudinal studies that include multiple sensorineural measures in middle-aged adults are lacking.

Methods: Hearing, vision, and olfaction, and CVRF and CVD were measured at the Beaver Dam Offspring Study baseline (2005–2008) examination. The Mini-Mental State Examination and Trail Making Tests A and B were administered at all phases and additional cognitive function measures were obtained at 5 (2010–2013) and 10 years (2015–2017). Cox proportional hazards models were used to evaluate associations between baseline sensorineural impairments, CVRF, CVD, and 10-year cumulative incidence of cognitive impairment and decline.

Results: There were 2,556 participants (22–84 years) without cognitive impairment at baseline and data from at least one follow-up. In a multivariable model including age, sex, education, and head injury, visual impairment (hazard ratio = 2.59, 95% confidence interval = 1.34, 5.02), olfactory impairment (hazard ratio = 3.18, 95% confidence interval = 1.53, 6.59), CVD (hazard ratio = 2.37, 95% confidence interval = 1.24, 4.52), and not consuming alcohol in the past year (hazard ratio = 2.21, 95% confidence interval = 1.16, 4.19) were associated with the 10-year cumulative incidence of cognitive impairment. Current smoking and diabetes were associated with increased risk, and exercise with decreased risk, of 10-year decline in cognitive function.

Conclusions: Visual and olfactory impairments, CVRF, and CVD were associated with the 10-year cumulative incidence of cognitive impairment and decline in middle-aged adults. Identifying modifiable factors associated with cognitive decline and impairment in midlife may provide opportunities for prevention or treatment and improve cognitive health later in life.

Keywords: Hearing loss, Olfactory impairment, Epidemiology, Cognitive aging

Small declines in cognitive function due to aging are thought to begin as early as the third or fourth decade of life (1), and by the mid-40s, cognitive decline on functional tests (2) and physical and pathological changes in the brain (3,4) have been reported. However, aging changes in cognitive function are heterogeneous within populations, and the onset, rate and magnitude of decline may be influenced by genetics, environmental exposures, behavioral factors, and disease processes (ie, vascular, metabolic, neurodegenerative). As cognitive changes may begin in middle age, risk factors at midlife may be important predictors of health at older ages.

Sensorineural impairments in hearing, vision, and olfaction, which begin to increase in midlife, have been associated with the development of cognitive impairment in older adults (5–8). Although sensorineural impairments are more likely than expected to co-occur (9), most previous studies of these impairments and cognition have included only one or two sensorineural impairments. The Epidemiology of Hearing Loss Study (EHLS) found when hearing, visual, and olfactory impairments were modeled together each was independently associated with the development of cognitive impairment over 10 years in older adults (6). Cognitive impairment is rare in middle-aged adults, but sensorineural dysfunction has been previously associated with cognitive test performance (10–12). In cross-sectional analyses, the Beaver Dam Offspring Study (BOSS), a primarily middle-aged cohort, found hearing, visual and olfactory impairments, when modeled together, were independently associated with poorer performance on cognitive function tests (10). Sensorineural dysfunctions may be early indicators of changes that are occurring in the central nervous system due to normal aging or vascular, neurodegenerative, or other disease states.

Cardiovascular disease (CVD) and cardiovascular-related risk factors (CVRF) such as subclinical atherosclerosis, smoking, adiposity, hypertension, education, and exercise at midlife have also been associated with cognitive function and decline (13–19). In a large study of participants aged 35–82 years, worse cardiovascular risk profile was associated with worse performance on a cognitive test across all age groups, including those less than 45 years (18). In the Framingham Offspring Study, midlife CVRF were associated with changes in brain structure and decline in executive function (19). CVRF at midlife may be important predictors of later-life cognitive health (13–15).

As with CVRF/CVD, sensorineural impairments in midlife may be important predictors of concurrent and future cognitive health, but longitudinal studies that include multiple sensorineural measures in middle-aged adults are lacking. Because CVRF/CVD have been associated with the development of both sensorineural (20–24) and cognitive dysfunction (13–17,19), it is important to evaluate both sensorineural and CVRF/CVD in studies investigating predictors of cognitive decline or impairment. The purpose of the present study was to evaluate the longitudinal associations of sensorineural impairments and CVRF/CVD with impairment and declines in cognitive function over 10 years in a primarily middle-aged cohort. These results extend the previous report from cross-sectional analyses in the BOSS cohort and build on the longitudinal results in the older EHLS cohort.

Methods

Data were collected as part of the BOSS (2004–present), a longitudinal study of sensory health and aging in the adult offspring of participants in the population-based EHLS (1993–present) (8,21,25). The baseline BOSS data collection phase occurred during 2005–2008 (N = 3,298 [66.3%]) with follow-ups at 5 (2010–2012; N = 2,792 [85%]) and 10 years (2015–2017; N = 2,405 [73%]) (23,24). Participants with a Mini-Mental State Examination (MMSE) score less than 24 or report of Alzheimer's disease (AD) or dementia at baseline (n = 9 [0.3%]), or missing baseline MMSE (n = 239 [7.3%]), or follow-up cognitive test data (n = 494 [15%]) were excluded from the present study resulting in data from 2,556 participants available for the analyses of 10-year cognitive decline and impairment. Five-year cognitive decline was analyzed in 1,733 participants who had baseline data and complete cognitive data at both the 5- and 10-year phases.

Data were collected by trained examiners at all phases using standardized protocols. Written informed consent was obtained from all participants at each phase prior to examination and approval for this research was obtained from the University of Wisconsin Health Sciences Institutional Review Board.

The MMSE and Trail Making Tests A (TMTA) and B (TMTB) were administered at all phases, and a Digit Symbol Substitution Test, phonemic Verbal Fluency Test, and modified Rey Auditory Verbal Learning Test were administered at the 5- and 10-year examinations (26–28) (see Supplementary Methods).

Memory problems were ascertained by two questions at the 10-year follow-up: "Have you, your family or your physician ever expressed concerns about your memory?" and "Do (your) memory loss symptoms interfere with your ability to do your own day-to-day activities?"

Hearing was measured by pure-tone air- and bone-conduction audiometry, and impairment was defined as a pure-tone average of the thresholds at 0.5, 1, 2, and 4 kHz greater than 25 dB hearing level in either ear (10). Olfaction was measured using the San Diego Odor Identification Test, and impairment was defined as identifying less than six of eight odorants correctly (8,25). Contrast sensitivity was measured in each eye separately using Pelli–Robson letter charts, and visual impairment was defined as contrast sensitivity of less than 1.55 log units in the better eye (24,29) (see Supplementary Methods).

Height, weight, waist circumference, blood pressure, carotid artery intima-media thickness (IMT), and femoral and radial pulse wave velocity for arterial stiffness were measured. Diabetes was defined as a hemoglobin A1C greater than or equal to 6.5% or a self-report of physician diagnosis of diabetes. Other CVRF data included years of education, smoking history (current, past, never), exercise (at least once per week long enough to work up a sweat), use of statins, history of head injury, weekly alcohol consumption (average g/wk) in the past year, and history of heavy alcohol use (four or more drinks per day). CVD history was classified as positive based on the self-report of any one of 11 physician-diagnosed conditions or procedures (see Supplementary Methods). Participants self-completed the Centers for Epidemiological Studies Depression Scale, and the presence of depressive symptoms was defined as a score greater than 15 (30).

Analyses were conducted with SAS 9.4 (SAS Institute, Inc., Cary, NC). Four cognitive outcomes were evaluated in these analyses: The 10-year cumulative incidence of cognitive impairment, 10-year decline in TMTA and TMTB, and 5-year decline in cognitive function. Performance on cognitive tests, responses to the memory questions, and report of AD/dementia were used to classify cognitive impairment. The 5-year decline in cognitive function was based on decline on a composite score of TMTA, TMTB, Digit Symbol Substitution Test, Verbal Fluency Test, and Auditory Verbal Learning Test that was created using principal component analysis (PCA); the PCA score mean was zero, and the SD was 1. The cognitive outcome definitions are given in Table 1 and detailed in Supplementary Methods.

Sensory impairments and CVRF associated with cognition in previous studies were evaluated here. Cox proportional hazards models (10-year cumulative incidence of cognitive impairment, TMTA decline, TMTB decline) via Proc Phreg (ties = discrete) and Poisson models fit to a binary response (5-year decline in PCA score) via Proc Genmod were used to evaluate the association of baseline covariates with each cognitive outcome. Covariates were first tested individually in models adjusted for age and sex. CVRF that were statistically significant ($p < .05$) were then tested in multivariable models;

Table 1. Cognitive Outcome Definitions

Cognitive Outcome	Test Metric/Definition	Time Period/Examination
10-y incidence of cognitive impairment (n = 89)	MMSE score < 24	At 5 or 10 y
	OR	
	Self-report or surrogate report of AD/dementia	At 5 or 10 y
	OR	
	MCI/dementia: Memory concerns AND impairment in 1 (MCI) or more (dementia) cognitive domains based on test performance (DSST, TMTA, TMTB, AVLT, VFT)	At 10 y
10-y decline in TMTA (n = 415)	Increase in TMTA time to complete >11 s	Between baseline and 5 y or between baseline and 10 y
10-y decline in TMTB (n = 413)	Increase in TMTB time to complete >25 s	Between baseline and 5 y or between baseline and 10 y
5-y decline in cognitive function (n = 173)	10% of participants with most decline in PCA summary score (DSST, TMTA, TMTB, AVLT, VFT)	Between 5 and 10 y

Notes: AVLT = Auditory Verbal Learning Test; DSST = Digit Symbol Substitution Test, VFT = Verbal Fluency Test (VFT); MCI = mild cognitive impairment; TMTA = Trail Making Test A; TMTB = Trail Making Test B.

sensory impairments were included in all models. To minimize the effects of collinearity, factors that were closely related were tested in separate models. Stepwise modeling was used to confirm covariate selection. Multivariable models were constructed for each outcome that included age, sex, education, sensorineural impairments, and the CVRF covariates that remained significant at the $p < .05$ level. To have a common set of covariates for the 10-year cognitive outcomes, any covariate retained in a multivariable model for at least one outcome (cognitive impairment, TMTA decline, TMTB decline) was included in the final model for all outcomes.

As depression has been previously associated with some of the risk factors being evaluated and with cognitive impairment and AD, depressive symptoms were tested in all final models.

Results

The mean age of participants at baseline was 49 years (22–84 years) and 88% were 35–64 years of age (Table 2). The 10-year cumulative incidence of cognitive impairment was 4.4% (95% confidence interval (CI) = 3.6, 5.4). Hearing impairment was the most common sensory impairment (13.5%), followed by visual impairment (7.5%) and olfactory impairment (3.7%). The distribution of cognitive outcomes by age are shown in Supplementary Table 1, and mean TMTA and TMTB scores by age and examination phase are shown in Supplementary Table 2.

Cognitive Impairment

There were 89 participants with incident cognitive impairment (mild cognitive impairment: 62; AD/dementia: 14; MMSE< 24: 13) over 10 years. In age- and sex-adjusted models, hearing impairment (hazard ratio [HR] = 1.88, 95% CI = 1.12, 3.16), olfactory impairment (HR = 3.69, 95% CI = 1.87, 7.28), and visual impairment (HR = 3.31, 95% CI = 1.81, 6.07) were each associated with an increased risk of developing cognitive impairment. Modeled together with age, sex, and education, olfactory impairment (HR = 3.31, 95% CI = 1.64, 6.69) and visual impairment (HR = 2.67, 95% CI = 1.43, 4.98), but not hearing impairment (HR = 1.60, 95% CI = 0.94, 2.72), remained independently associated with an increased risk of cognitive impairment; hearing impairment was not significant once visual impairment was added to the model. CVRF associated with cognitive impairment in age- and sex-adjusted models are shown in Supplementary Table 3. In the final multivariable model, olfactory impairment (HR = 3.18, 95% CI = 1.53, 6.59), visual impairment (HR = 2.59, 95% CI = 1.34, 5.02), being male (HR = 2.04, 95% CI = 1.23, 3.39), not consuming alcohol (HR = 2.21, 95% CI = 1.16, 4.19, vs. 0–14 g/wk), and a history of CVD (HR = 2.37, 95% CI = 1.24, 4.52) or head injury (HR = 1.75 95% CI = 1.10, 2.76) were associated with an increased risk of developing cognitive impairment. More years of education (HR = 0.23, 95% CI = 0.11, 0.48, ≥16 vs. <16 years) was associated with a decreased risk of developing cognitive impairment (Table 3). Depressive symptoms were significantly associated with developing cognitive impairment in the final multivariable model, but inclusion of depressive symptoms in the model did not change the associations (results not shown).

Ten-Year Cognitive Decline

Risk factors associated with TMTA decline and TMTB decline over 10 years in age- and sex-adjusted models are shown in Supplementary Table 3. In the final multivariable model, older age (HR = 1.28, 95% CI = 1.20, 1.36 for every 5 years), being male (HR = 1.49, 95% CI = 1.18, 1.88), current smoking (HR = 1.48, 95% CI = 1.12, 1.96, vs. nonsmokers), and diabetes (HR = 1.65, 95% CI = 1.12, 2.43) were significantly associated with TMTA decline. Although thicker IMT was not significant in the multivariable model constructed for TMTA decline and not retained for the final model with common covariates, it was associated with TMTA decline in a reduced multivariable model without smoking that included age, sex, education, visual impairment, and diabetes (IMT > 0.79 mm: HR = 1.34, 95% CI = 1.01, 1.79).

Risk factors significantly associated with an increased risk of TMTB decline in the final multivariable model were older age (HR = 1.38, 95% CI = 1.29, 1.46 for every 5 years), olfactory impairment (HR = 1.62, 95% CI = 1.04, 2.54), visual impairment (HR = 1.47, 95% CI = 1.03, 2.09), and a history of head injury (HR = 1.40, 95% CI = 1.10, 1.76; Table 3). There was a J-shaped association with alcohol consumption where both not consuming alcohol (HR = 1.66, 95% CI = 1.18, 2.33) and consuming moderate (HR = 1.46, 95% CI = 1.09, 1.95 for 15–74 g/wk) or greater amounts of alcohol (HR = 1.61, 95% CI = 1.14, 2.29 for 141 g/wk

Table 2. Baseline Beaver Dam Offspring Study Participant Characteristics

Baseline Characteristics	*N* With Data	% or Mean (*SD*)
Age, y	2,556	48.5 (9.8)
<35		6.3
35–44		31.1
45–54		36.2
55–64		20.5
≥65		5.9
Sex	2,556	
Men		45.2
Women		54.8
Education, y	2,542	
≤12		30.8
13–15		33.3
≥16		35.9
Hearing impairment	2,457	13.5
Olfactory impairment	2,458	3.7
Visual impairment	2,456	7.5
Smoking history	2,550	
Never		54.9
Past		28.5
Current		16.7
Body mass index, kg/m^2	2,438	
<25		21.5
25–29.9		34.1
≥30		44.4
Waist circumference, cm	2,437	99.5 (16.4)
Exercise, at least 1/wk	2,549	62.1
History of heavy alcohol consumption	2,547	18.2
Alcohol past year, g/wk	2,550	
None		10.3
0–14		41.2
>14–74		24.1
>74–140		12.0
>140		12.4
Depressive symptoms	2,434	14.2
Head injury	2,553	28.1
Hypertension	2,463	35.4
Carotid mean IMT > 0.79 mm	2,424	12.2
Carotid plaque	2,421	22.8
Cardiovascular disease	2,536	6.4
Statin use	2,461	15.0
Diabetes	2,542	5.3
Carotid–femoral PWV > 12.0 m/s	1,412	8.9
Carotid–radial PWV > 10.6 m/s	1,582	31.7

Notes: IMT = Intima-Media Thickness; PWV = pulse wave velocity.

or more) were associated with an increased risk of TMTB decline when compared with light drinkers (0–14 g/wk). More years of education (HR = 0.70, 95% CI = 0.54, 0.90 for ≥16 vs. <16 years) and exercising at least once a week (HR = 0.71, 95% CI = 0.57, 0.89) were associated with a reduced risk of TMTB decline. The estimate for hearing impairment, though only slightly attenuated from the age- and sex-adjusted model (HR = 1.30, 95% CI = 0.98, 1.71), was not significant in the final multivariable model.

Five-Year Cognitive Decline

The 10% of participants with the most decline on the standardized PCA score between the 5- and 10-year examinations were considered to have cognitive decline. Risk factors associated with 5-year cognitive decline in age- and sex-adjusted models are shown in Supplementary Table 3. In a multivariable model, older age (relative risk [RR] = 1.22, 95% CI = 1.12, 1.32 for every 5 years), olfactory impairment (RR = 1.76, 95% CI = 1.07, 2.90), carotid plaque (RR = 1.43, 95% CI = 1.05, 1.94), CVD (RR = 1.79, 95% CI = 1.21, 2.65), and a history of heavy alcohol use (RR = 1.73, 95% CI = 1.26, 2.36) were associated with an increased risk of cognitive decline over 5 years. Though included in the final model, sex (RR = 1.06, 95% CI = 0.78, 1.44), education (RR = 0.79, 95% CI = 0.57, 1.09), hearing impairment (RR = 0.93, 95% CI = 0.63, 1.36), and visual impairment (RR = 1.39, 95% CI = 0.91, 2.11) were not significantly associated with 5-year cognitive decline. Thicker IMT, modeled separately from carotid plaque, was slightly attenuated and not statistically significant in the multivariable model (IMT > 0.79 mm: RR = 1.38, 95% CI = 0.98, 1.93).

Depressive symptoms were not associated with TMTA or TMTB decline or with 5-year cognitive decline in the final multivariable models.

Discussion

We believe this is one of the first studies to analyze the relationship between three sensorineural impairments, CVRF/CVD, and the 10-year incidence of cognitive impairment in a middle-aged cohort. In this longitudinal study with 10 years of follow-up, sensorineural impairments in vision and olfaction, CVRF/CVD, were associated with the 10-year cumulative incidence of cognitive impairment. With the exception of the null findings for hearing impairment, the results were consistent with those of the EHLS, which found hearing, visual, and olfactory impairments independently associated with the development of cognitive impairment in older adults after adjusting for multiple CVRF (6). There are few longitudinal studies of the association between hearing impairment and cognition that include other sensorineural impairments, and these have been in older adults with inconsistent results (6,12,31). In the present study, the hearing impairment estimate for incident cognitive impairment was no longer statistically significant when visual impairment was included in the model. These results are similar to those of Lin and colleagues where, in a large study of older women, hearing impairment was not significantly associated with cognitive decline in a multivariable model that included vision impairment (31).

In general, the present study found that impairments in sensorineural functions predicted decline in cognitive function over 5 and 10 years, though results varied by outcome. Visual and olfactory impairments were associated with 10-year decline in TMTB, but none of the sensorineural impairments were significant in the multivariable model for TMTA decline. Sensorineural functions may load more heavily on cognitive domains assessed by the TMTB (executive function) versus the TMTA (speed). The current results therefore differed slightly from the previous cross-sectional analyses in this cohort where hearing, visual, and olfactory impairments were all independently associated with poorer performance on the TMTA and TMTB (10). In the analyses of 5-year cognitive decline measured by PCA summary score, only olfactory impairment was associated with an increased risk of cognitive decline over 5 years.

As sensorineural and cognitive functions both rely on good brain function, and functional tests of either one cannot be performed without the other (ie, cognitive tests require hearing or vision; sensorineural tests require attention, executive function, memory), sensorineural dysfunctions may be early markers for brain changes that

Table 3. Multivariable Models for 10-Y Cumulative Incidence of Cognitive Impairment and Decline in the Beaver Dam Offspring Study

	10-Y Incidence of Cognitive Impairment	10-Y Decline in TMTA	10-Y Decline in TMTB
Baseline Factors	HR (95% CI)	HR (95% CI)	HR (95% CI)
N	2,413	2,342	2,331
Age, per 5 y	1.03 (0.91, 1.17)	1.28 (1.20, 1.36)	1.38 (1.29, 1.46)
Sex, male	2.04 (1.23, 3.39)	1.49 (1.18, 1.88)	1.13 (0.89, 1.44)
Education, ≥16 y	0.23 (0.11, 0.48)	0.94 (0.74, 1.19)	0.70 (0.54, 0.90)
Hearing impairment	1.40 (0.81, 2.44)	0.88 (0.66, 1.19)	1.30 (0.98, 1.71)
Olfactory impairment	3.18 (1.53, 6.59)	1.25 (0.78, 1.99)	1.62 (1.04, 2.54)
Visual impairment	2.59 (1.34, 5.02)	1.41 (0.99, 2.03)	1.47 (1.03, 2.09)
Smoking, current (vs. nonsmokers)	1.19 (0.68, 2.08)	1.48 (1.12, 1.96)	1.24 (0.93, 1.66)
Exercise, at least 1/wk	0.66 (0.42, 1.04)	0.96 (0.77, 1.20)	0.71 (0.57, 0.89)
Alcohol past year, g/wk (vs. 0–14 g/wk)			
None	2.21 (1.16, 4.19)	1.09 (0.77, 1.54)	1.66 (1.18, 2.33)
15–74	0.92 (0.47, 1.81)	1.04 (0.78, 1.38)	1.46 (1.09, 1.95)
75–140	1.62 (0.78, 3.35)	1.15 (0.80, 1.64)	1.39 (0.96, 2.02)
≥141	1.31 (0.64, 2.65)	1.11 (0.79, 1.57)	1.61 (1.14, 2.29)
History of head injury	1.75 (1.10, 2.76)	1.16 (0.92, 1.47)	1.40 (1.10, 1.76)
Cardiovascular disease	2.37 (1.24, 4.52)	1.30 (0.90, 1.88)	0.86 (0.57, 1.30)
Diabetes	0.85 (0.37, 1.98)	1.65 (1.12, 2.43)	1.10 (0.73, 1.68)

Notes: CI = confidence interval; HR = hazard ratio; TMTB = Trail Making Test B.

are occurring due to physiologic aging or pathology. Alternatively, it has been hypothesized that some sensory impairments may cause cognitive changes due to social isolation, sensory deprivation, or increased cognitive load, but robust evidence for these pathways is lacking (5). Of the three sensorineural impairments, olfactory impairment had the most consistent associations across cognitive outcomes. Aging and disease-related pathology have been shown to begin early in areas of the brain associated with olfactory processing, and the amount and type of pathology in these areas has been correlated with performance on odor identification tests proximal to death (32,33). As olfactory impairment is uncommon in middle-aged adults (23,25), early dysfunction in olfaction may be an indicator of accelerated cognitive aging. AD-related pathology has also been found in the peripheral and central visual system and central auditory system, but the temporality and effects of these findings are less clear (5).

Vascular health is a determining factor for brain health; CVRF, subclinical atherosclerosis, and CVD are associated with aging and physical and pathological changes in the brain (19,34,35). Carotid atherosclerosis in midlife has been associated with worse cognitive function, the presence of white-matter hyperintensities, ischemia, and lower neuronal viability in the brain (17,35,36). In the present study, a history of CVD, an indicator of clinical vascular disease, was associated with the 10-year cumulative incidence of cognitive impairment and decline, and carotid artery plaque, a marker of subclinical atherosclerosis, was associated with 5-year decline in cognitive function. Diabetes, which increases the risk for atherosclerosis and CVD, was also associated with 10-year decline in TMTA.

Other demographic and behavioral CVRF associated with the incidence of cognitive impairment and decline included older age, being male, current smoking, alcohol consumption, education, and exercise. In the present study, smoking was only a significant predictor of 10-year TMTA decline. Previous studies of smoking and cognition have been inconsistent (14–16,37). In one study, midlife smoking was not associated with cognitive decline over 6 years of follow-up (16), and in another study, it was associated with concurrent function in some, but not all cognitive domains and not associated with decline (37). Consistent with previous studies, nondrinkers had an increased risk of cognitive decline but in contrast to some previous studies, those who reported moderate alcohol consumption also had an increased risk of cognitive decline (38). Our findings may have differed from others, as we chose to use light drinkers versus nondrinkers as the reference as nondrinkers may have health problems or a previous history of alcohol abuse. Although several previous studies have reported midlife hypertension to be associated with higher risk of dementia later in life, there was no association in the present study with cognitive impairment or decline (14–16,39). Associations with hypertension have been strongest for later-life dementia or AD and less consistent with cognitive decline or mild cognitive impairment (39,40). Dementia was too rare in this younger cohort to analyze independently, and with only 10 years of follow-up when compared with 20 or more years in some previous studies, follow-up may not have been long enough to detect an association (14,15).

The cohort was predominantly non-Hispanic white, well educated, and healthy. In this primarily middle-aged cohort, the prevalence of sensorineural impairments and CVD were low as was the incidence of cognitive impairment, which could have limited our ability to detect some associations. Cognitive test measures of memory and language were not administered until the second phase of the study, which limited the measures of 10-year decline to the domains of attention, speed, and executive function. Finally, dementia was rare, and the definition of cognitive impairment included those who met the criteria for mild cognitive impairment, which may have prevented us from identifying factors associated with more severe cognitive dysfunction. The strengths of the study include the large, well-characterized cohort, and prospective design with 10 years of follow-up. Objective measures of sensorineural function, CVRF, and cognitive function were obtained using standard protocols and covered a spectrum of cognitive decline. The consistency of the findings for cognitive impairment and TMTB, the two outcomes with a 10-year follow-up that measure executive or higher-order modalities, is a strength.

In conclusion, visual and olfactory impairments, CVRF, and CVD were associated with the 10-year cumulative incidence of cognitive impairment and 5- and 10-year cognitive decline in middle-aged adults. Visual and olfactory impairments were associated with cognitive function independently of CVD and CVRF and may be markers of changes occurring in the shared environment of the brain due to normal physiologic aging or pathology. As vascular disease is an important contributor of pathology in the brain, behavioral modification or treatments targeted toward preventing, reducing, or delaying vascular disease in midlife in the general population may provide opportunities to delay or reduce the effects of physiologic aging or disease on cognitive function later in life.

Supplementary Material

Supplementary data is available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

Funding

This work was supported by the National Institute on Aging; National Eye Institute; and National Institute on Deafness and Other Communication Disorders (R01AG021917 to K.J.C.) and an unrestricted grant from Research to Prevent Blindness. The content is solely the responsibility of the authors and does not necessarily reflect the official views of the National Institute on Aging or the National Institutes of Health.

Conflict of Interest

None reported.

References

1. Salthouse TA. When does age-related cognitive decline begin? *Neurobiol Aging*. 2009;30:507–514. doi:10.1016/j.neurobiolaging.2008.09.023
2. Singh-Manoux A, Kivimaki M, Glymour MM, et al. Timing of onset of cognitive decline: results from Whitehall II prospective cohort study. *BMJ*. 2012;344:d7622. doi:10.1136/bmj.d7622
3. Fotenos AF, Snyder AZ, Girton LE, Morris JC, Buckner RL. Normative estimates of cross-sectional and longitudinal brain volume decline in aging and AD. *Neurology*. 2005;64:1032–1039. doi:10.1212/01.WNL.0000154530.72969
4. Braak H, Braak E. Frequency of stages of Alzheimer-related lesions in different age categories. *Neurobiol Aging*. 1997;18:351–357.
5. Albers MW, Gilmore GC, Kaye J, et al. At the interface of sensory and motor dysfunctions and Alzheimer's disease. *Alzheimers Dement*. 2015;11:70–98. doi:10.1016/j.jalz.2014.04.514
6. Fischer ME, Cruickshanks KJ, Schubert CR, et al. Age-related sensory impairments and risk of cognitive impairment. *J Am Geriatr Soc*. 2016;64:1981–1987. doi:10.1111/jgs.14308
7. Gallacher J, Ilubaera V, Ben-Shlomo Y, et al. Auditory threshold, phonologic demand, and incident dementia. *Neurology*. 2012;79:1583–1590. doi:10.1212/WNL.0b013e31826e263d
8. Schubert CR, Carmichael LL, Murphy C, Klein BE, Klein R, Cruickshanks KJ. Olfaction and the 5-year incidence of cognitive impairment in an epidemiological study of older adults. *J Am Geriatr Soc*. 2008;56:1517–1521. doi:10.1111/j.1532-5415.2008.01826.x
9. Fischer ME, Cruickshanks KJ, Klein BE, Klein R, Schubert CR, Wiley TL. Multiple sensory impairment and quality of life. *Ophthalmic Epidemiol*. 2009;16:346–353. doi:10.3109/09286580903312236
10. Schubert CR, Cruickshanks KJ, Fischer ME, et al. Sensory impairments and cognitive function in middle-aged adults. *J Gerontol A Biol Sci Med Sci*. 2017;72:1087–1090. doi:10.1093/gerona/glx067
11. Humes LE. Age-related changes in cognitive and sensory processing: focus on middle-aged adults. *Am J Audiol*. 2015;24:94–97. doi:10.1044/2015_AJA-14-0063
12. Valentijn SA, van Boxtel MP, van Hooren SA, et al. Change in sensory functioning predicts change in cognitive functioning: results from a 6-year follow-up in the Maastricht Aging Study. *J Am Geriatr Soc*. 2005;53:374–380. doi:10.1111/j.1532-5415.2005.53152.x
13. Bendlin BB, Carlsson CM, Gleason CE, et al. Midlife predictors of Alzheimer's disease. *Maturitas*. 2010;65:131–137. doi:10.1016/j.maturitas.2009.12.014
14. Gottesman RF, Albert MS, Alonso A, et al. Associations between midlife vascular risk factors and 25-year incident dementia in the Atherosclerosis Risk in Communities Study. *JAMA Neurol*. 2017;74:1246–1254. doi:10.1001/jamaneurol.2017.1658
15. Whitmer RA, Sidney S, Selby J, Johnston SC, Yaffe K. Midlife cardiovascular risk factors and risk of dementia in late life. *Neurology*. 2005;64:277–281. doi:10.1212/01.WNL.0000149519.47454.F2
16. Knopman D, Boland LL, Mosley T, et al.; Atherosclerosis Risk in Communities (ARIC) Study Investigators. Cardiovascular risk factors and cognitive decline in middle-aged adults. *Neurology*. 2001;56:42–48.
17. Zhong W, Cruickshanks KJ, Huang GH, et al. Carotid atherosclerosis and cognitive function in midlife: the Beaver Dam Offspring Study. *Atherosclerosis*. 2011;219:330–333. doi:10.1016/j.atherosclerosis.2011.07.013
18. Joosten H, van Eersel ME, Gansevoort RT, Bilo HJ, Slaets JP, Izaks GJ. Cardiovascular risk profile and cognitive function in young, middle-aged, and elderly subjects. *Stroke*. 2013;44:1543–1549. doi:10.1161/STROKEAHA.111.000496
19. Debette S, Seshadri S, Beiser A, et al. Midlife vascular risk factor exposure accelerates structural brain aging and cognitive decline. *Neurology*. 2011;77:461–468. doi:10.1212/WNL.0b013e318227b227
20. Fischer ME, Schubert CR, Nondahl DM, et al. Subclinical atherosclerosis and increased risk of hearing impairment. *Atherosclerosis*. 2015;238:344–349. doi:10.1016/j.atherosclerosis.2014.12.031
21. Cruickshanks KJ, Nondahl DM, Dalton DS, et al. Smoking, central adiposity, and poor glycemic control increase risk of hearing impairment. *J Am Geriatr Soc*. 2015;63:918–924. doi:10.1111/jgs.13401
22. Schubert CR, Cruickshanks KJ, Nondahl DM, Klein BE, Klein R, Fischer ME. Association of exercise with lower long-term risk of olfactory impairment in older adults. *JAMA Otolaryngol Head Neck Surg*. 2013;139:1061–1066. doi:10.1001/jamaoto.2013.4759
23. Schubert CR, Cruickshanks KJ, Fischer ME, et al. Carotid intima media thickness, atherosclerosis, and 5-year decline in odor identification: the beaver dam offspring study. *J Gerontol A Biol Sci Med Sci*. 2015;70:879–884. doi:10.1093/gerona/glu158
24. Paulsen AJ, Schubert CR, Johnson LJ, et al. Association of cadmium and lead exposure with the incidence of contrast sensitivity impairment among middle-aged adults. *JAMA Ophthalmol*. 2018;136(12):1342–1350. doi:10.1001/jamaophthalmol.2018.3931
25. Schubert CR, Cruickshanks KJ, Fischer ME, et al. Olfactory impairment in an adult population: the Beaver Dam Offspring Study. *Chem Senses*. 2012;37:325–334. doi:10.1093/chemse/bjr102
26. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12:189–198.
27. Reitan RM. *Trail Making Test Manual for Administration and Scoring*. Tucson, AZ: Reitan Neuropsychology Laboratory; 1992.
28. Strauss E, Sherman EMS, Spreen O. *A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary*. 3rd ed. New York, NY: Oxford University Press; 2006.
29. Pelli DG, Robson JG, Wilkins AJ. The design of a new letter chart for measuring contrast sensitivity. *Clin Vis Sci*. 1988;2:187–199.
30. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. *Appl Psychol Meas*. 1977;1:385–401.
31. Lin MY, Gutierrez PR, Stone KL, et al.; for the Study of Osteoporotic Fractures Research Group. Vision impairment and combined vision and hearing impairment predict cognitive and functional decline in older women. *J Am Geriatr Soc*. 2004;52:1996–2002. doi:10.1111/j.1532-5415.2004.52554.x

32. Braak H, Braak E. Diagnostic criteria for neuropathologic assessment of Alzheimer's disease. *Neurobiol Aging*. 1997;18(4 suppl):S85–S88.
33. Wilson RS, Arnold SE, Schneider JA, Tang Y, Bennett DA. The relationship between cerebral Alzheimer's disease pathology and odour identification in old age. *J Neurol Neurosurg Psychiatry*. 2007;78:30–35. doi:10.1136/jnnp.2006.099721
34. Gorelick PB, Scuteri A, Black SE, et al.; American Heart Association Stroke Council, Council on Epidemiology and Prevention, Council on Cardiovascular Nursing, Council on Cardiovascular Radiology and Intervention, and Council on Cardiovascular Surgery and Anesthesia. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2011;42:2672–2713. doi:10.1161/STR.0b013e3182299496
35. Haley AP, Tarumi T, Gonzales MM, Sugawara J, Tanaka H. Subclinical atherosclerosis is related to lower neuronal viability in middle-aged adults: a 1H MRS study. *Brain Res*. 2010;1344:54–61. doi:10.1016/j.brainres.2010.05.006
36. Romero JR, Beiser A, Seshadri S, et al. Carotid artery atherosclerosis, MRI indices of brain ischemia, aging and cognitive impairment. The Framingham Study. *Stroke*. 2009;40:1590–1596. doi:10.1161/STROKEAHA.108.535245
37. Sabia S, Marmot M, Dufouil C, Singh-Manoux A. Smoking history and cognitive function in middle age from the Whitehall II Study. *Arch Intern Med*. 2008;168:1165–1173. doi:10.1001/archinte.168.11.1165
38. Anstey KJ, Mack HA, Cherbuin N. Alcohol consumption as a risk factor for dementia and cognitive decline: meta-analysis of prospective studies. *Am J Geriatr Psychiatry*. 2009;17:542–555. doi:10.1097/JGP.0b013e3181a2fd07
39. Kivipelto M, Helkala EL, Hänninen T, et al. Midlife vascular risk factors and late-life mild cognitive impairment: a population-based study. *Neurology*. 2001;56:1683–1689.
40. Plassman BL, Williams JW Jr, Burke JR, Holsinger T, Benjamin S. Systematic review: factors associated with risk for and possible prevention of cognitive decline in later life. *Ann Intern Med*. 2010;153:182–193. doi:10.7326/0003-4819-153-3-201008030-00258