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Neuroprotective biomarkers and cognitive function in a long-term prospective population-based study of aging U.S. adults

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Abstract

Background: Relationships between brain-derived neurotrophic factor (BDNF), insulin-like growth factor (IGF1), aldosterone, and cognition in aging were evaluated in the population-based Epidemiology of Hearing Loss Study (1993-present).

Methods: Beginning in 1998–2000, cognitive impairment was assessed by report of physician diagnoses and the Mini-mental State Examination. In 2009–2010 and 2013–2016, information was collected on diagnosis of mild cognitive impairment (MCI)/dementia. Decline in cognitive function was assessed by principal component analysis from additional tests administered during 2009–2010 and 2013–2016. BDNF, IGF1, and aldosterone were measured in serum collected in 1998–2000.

Results: There were 1970 participants (mean age=66.9 years; 59.1% female) without cognitive impairment at baseline. Among women, low BDNF was associated with 16-year incident cognitive impairment (Hazard Ratio (HR)=1.76, 95% Confidence Interval (CI)= 1.04, 2.98). Among men, increasing IGF1 was associated with decreased risk (per SD: Relative Risk (RR)=0.57, CI=0.35, 0.92), while increasing aldosterone levels were associated with increased risk (per SD: RR=1.28, CI=1.01, 1.62) for 5-year incident MCI/dementia. Overall, low BDNF was associated with increased risk (RR=1.52, CI=1.02, 2.26) for 5-year cognitive decline.

Conclusion: Low levels of serum BDNF and IGF1 were associated with poorer cognition during aging. There may be differential biomarker effects by sex.

Keywords

Cognition; Aging; Biomarkers; Epidemiology

Introduction:

Increasing incidence of cognitive impairment in the United States is a major public health concern. In a 2016 report from the Alzheimer's Association, 11 percent of the U.S. population over 45 years of age reported worsening confusion or memory loss, and an estimated 5.4 million people had dementia due to Alzheimer's disease (AD). That number was projected to reach 13.8 million by 2050.^{1,2} The decline in function associated with dementia has a great impact on quality of life in those experiencing declines and on their families and care givers.^{1,3} As a larger proportion of the population reaches older ages the burden this places on society is notable. Estimated direct and indirect costs for care and services for people with dementia in the U.S. in 2016 was \$236 billion.¹ Finding potentially protective factors to explain why some people experience healthier aging could help prevent functional declines in future generations and reduce this burden.

A number of modifiable risk factors for cognitive decline have been identified.⁴ Cardiovascular disease (CVD), hypertension (HTN), inflammation, obesity, smoking, and alcohol abuse have been associated with increased risk of cognitive decline and incidence of dementia, whereas education and exercise have been shown to be protective.⁵⁻⁷ Modifications to related behaviors may improve the outlook for healthy brain aging, however, these factors do not explain all risk observed in previous studies. Further research is necessary to identify additional avenues for prevention.

Brain-derived neurotrophic factor (BDNF) has been identified as a protective protein that could reduce risk of incident cognitive decline. BDNF is involved in neurogenesis, synaptic transmission, and cell survival.⁸ BDNF is important for synaptic plasticity, memory acquisition and storage, and low levels of BDNF have been implicated in the pathogenesis of dementia and AD.⁹⁻¹⁰ In post mortem studies of brain tissue, BDNF levels were reduced in patients with AD and Mild Cognitive Impairment (MCI) compared to healthy controls and higher BDNF gene expression in the brain was associated with slower cognitive decline.¹¹⁻¹² Studies involving blood-based measures of BDNF, have not been consistent. Some studies found the concentration of BDNF was reduced in AD compared to other types of dementia or in healthy controls.¹³⁻¹⁴ In the Framingham Heart Study, those with higher concentrations of serum BDNF were less likely to develop all-cause dementia or dementia due to AD over a prospective 10-year follow-up.¹⁵ Other studies found no association with cognitive decline or performance, or found conflicting results where pathologic changes, like white matter atrophy, were associated with decreased BDNF while measures of cognitive function were not.¹⁶⁻¹⁷ Still other studies found increased levels of BDNF in AD and MCI patients.¹⁸⁻¹⁹ Differential effects of BDNF on cognitive function have been found by sex,

with a protective relationship among women only, further complicating the understanding of potential effects.^{15, 20}

Insulin-like growth factor (IGF1) is a protein important for brain development and continued regulation of structure and function throughout adulthood.²¹ Like BDNF, IGF1 is involved in neurogenesis and cell survival.²² Studies have reported higher levels of IGF1 being associated with AD, low levels associated with better cognitive performance, or no effect.^{23–25} Two cross-sectional studies found lower serum IGF1 levels were associated with cognitive impairment, though one of these studies was limited to those 80 years of age or older.^{26–27} The Mayo Clinic Study of Aging found a cross-sectional association between higher levels of IGF1 and better cognitive performance among women only.²⁸ Similar findings were reported in longitudinal studies, with one indicating those with low IGF levels had greater decline of information processing speed, and the other displaying less cognitive decline among those with higher levels.^{29–30}

Aldosterone is a mineralocorticoid involved in regulation of ions and ion transport including sodium and potassium.³¹ Aldosterone improves survival of nerve cells in the cochlea, and blocks apoptotic pathways.³² These neuroprotective mechanisms could extend to other parts of the nervous system and protect cognitive function during aging. Limited research has investigated the aldosterone-cognition relationship. In one study, higher plasma aldosterone concentration was associated with worse performance on the Mini-mental State Examination.³³ The reported potential mechanism for this association was aldosterone increasing risk of HTN and in turn cognitive impairment. However, in another study, those with the highest level of aldosterone at baseline demonstrated the greatest improvement in executive function after 12 months of blood pressure treatment, indicating a potential positive effect of aldosterone could be masked by negative effects of high blood pressure.³⁴ Little is known about the effect of circulating aldosterone on cognition in the general population.

As the number of older adults in the U.S. increases, the need to find factors that decrease risk of decline in cognitive function becomes more important. The present study aims to investigate the potentially neuroprotective effects of BDNF, IGF1, and aldosterone on incident cognitive impairment and decline.

Methods:

Study population

Details of the recruitment and demographics of the EHLS have been previously reported.^{35–36} Briefly, the EHLS is a population-based study of aging in residents of Beaver Dam, Wisconsin (aged 43–84 years in 1987–1988). The baseline EHLS was in 1993–1995 with follow-up examinations occurring approximately every five years (1998–2000, 2003–2005, 2009–2010, and 2013–2016). The second phase (1998–2000) is used as baseline in the current investigation because biomarker assays used samples from this time point. The EHLS was approved by the Health Sciences Institutional Review Board of the University of Wisconsin. All participants provided written informed consent prior to each examination.

Cognitive assessment

The Mini-mental state examination (MMSE) was completed by participants at all phases. Possible scores range from 0 to 30. At the fourth and fifth examination phases, additional tests of cognition were performed, including the Trail Making Test, parts A (TMTA) and B (TMTB), a modified Rey auditory verbal learning test (AVLT), digit-symbol substitution test (DSST), and verbal fluency test (VFT).³⁷ The TMTA and TMTB measure visual attention and executive function, recording the length of time needed to complete the tasks. Lower times are considered better function, with a maximum of 300 seconds. Participants unable to complete the task in the allotted time were assigned a score of 301. The AVLT measures memory using a 15 verbally presented word list. The AVLT score is the number of words recalled in the final trial, following 3 initial trials and 1 distractor list. The DSST is a timed test measuring attention, speed, and executive function. Participants use a key to replace numbers with symbols, with 90 seconds to complete as much of the task sheet as possible. The score is the number of correctly drawn symbols. Finally, the VFT measures language and verbal ability. Participants have one minute to produce as many words as they can which begin with a given letter. Scores are determined by the number of distinct words produced for each letter (F,A,S). Information on physician diagnoses was collected during an examiner administered interview. Participants reported if a physician had ever told them they had AD, dementia, or MCI. Concerns about memory and cognitive function complaints were also collected.

Serum neuroprotective biomarker measures

Serum samples stored at -80°C were used to measure BDNF, IGF1, and aldosterone by the Advanced Research and Diagnostic Laboratory at the University of Minnesota in 2017. BDNF and IGF1 levels were measured by quantitative sandwich enzyme immunoassay technique using the Human BDNF Quantikine ELISA kit (R&D Systems, Minneapolis, MN; coefficient of variation (CV)=6.6%) and the IGF1 Quantikine ELISA kit (R&D Systems, Minneapolis, MN; CV=6.8%), respectively. Aldosterone was measured by chemiluminescent immunoassay (DiaSorin, Stillwater, MN) using Liaison (DiaSorin, Stillwater, MN; CV=5.2%).

Other covariates

Baseline covariates were considered in this investigation. Height, weight, waist circumference, and blood pressure (BP) were measured following standard protocols. Body Mass Index (BMI) was calculated (kg/m^2) and classified as normal (<25), overweight (25–29), or obese (30+). Hypertension was defined as a systolic BP ≥ 140 mmHg, a diastolic BP ≥ 90 mmHg, or reported physician diagnosis of HTN with current BP medication use. Carotid artery ultrasound was used to measure intima-media thickness (IMT; mean of up to 12 wall thicknesses).⁵ C-reactive protein (CRP) was measured using a latex-particle enhanced immunoturbidimetric assay kit (Roche Diagnostics, Indianapolis, IN) and read on the Roche Modular P Chemistry analyzer, CV=4.5%. Interleukin-6 (IL6) and tumor necrosis factor-alpha (TNF- α) were measured by quantitative sandwich enzyme immunoassay using the IL-6 QuantiKine High Sensitivity kit (R&D Systems, Minneapolis, MN), CV=11.7%, and the Human TNF- α QuantiGlo immunoassay (R&D Systems, Minneapolis, MN),

CV=13.0%, respectively. *APOE-4* carrier status was genotyped using the Illumina IBC array to investigate its relationship to cognitive outcomes. Age, sex, education, smoking status (never, past, or current), exercise (at least once a week), alcohol consumption (past year), history of head injury, and detailed health history including CVD were assessed by in-person interview or self-administered questionnaire.

Statistical analyses

Cognitive Outcomes

16-year Cumulative Incidence of Cognitive Impairment: Incident cognitive impairment was defined as a MMSE score < 24 or self- or surrogate-report of physician diagnosis of AD or dementia at any examination during 16 years of follow-up among those without impairment at baseline.³⁸

5-year Incidence of MCI/Dementia

Incident MCI/dementia was defined using the cognitive tests and responses to questions regarding concerns about memory problems at the 2009–2010 and 2013–2016 examinations. Details on these definitions have been previously reported.⁶ In short, MCI was defined by impairment, based on published normative data, in 1 of the 3 tested cognitive domains (executive function, memory, verbal fluency), and reported participant memory concerns. Dementia was defined by a measured impairment in at least 2 of 3 tested cognitive domains and reported interference in ability to do day-to-day activities due to memory problems. Participants who did not meet these criteria at the 2009–2010 phase were an incident case if they met this definition in the 5-year follow-up period.

5-year Incidence of Cognitive Decline

Cognitive decline between the 2009–2010 and 2013–2016 examinations was defined using a principal component analysis (PCA) to construct a composite measure, with a mean of zero and a standard deviation (SD) of 1, of the cognitive test data (MMSE, TMTA, TMTB, AVLT, DSST, and VFT). One eigenvalue was greater than 1 and the first component was retained. A PCA score was calculated as a linear combination of the standardized observed variables, using factor loadings from the 2009–2010 data as weights. A decline of less than or equal to –0.5 on this score between phases was used to define 5-year cognitive decline.

Biomarker Levels

Quintiles were formed for each biomarker in the overall population and sex-specifically. The lowest quintile (Q1) was compared to the highest quintile (Q5) in analyses to investigate potential effects of low circulating levels on development of cognitive impairment, MCI/dementia, and decline in cognitive function. Additional analyses to assess the dose-response relationship between these markers and cognitive outcomes were conducted by modeling biomarkers per SD and by doubling of biomarker levels, using base two logarithms.

Statistical Modeling

Age-, sex-, and education-adjusted models were used to examine the relationship between biomarker levels and cognitive outcomes, and to identify potential confounders. Variables

suggestive of a relationship with outcomes (p -value < 0.2) were considered for final multivariable models. Multivariable models were constructed for each outcome using a backwards elimination approach for selection of covariates. The associations between biomarkers and cumulative incidence of cognitive impairment were tested using a discrete-time hazard model with a complimentary log-log link to estimate hazard ratios (HRs) and 95% confidence intervals (CI).^{39–40} A modified Poisson regression model with robust error variances was used to estimate relative risk (RR) and 95% CIs for the 5-year incidence of MCI/dementia and cognitive decline. In order to address potential sex-specific effects by biomarker, all models were repeated including interaction terms and sex-stratified analyses were conducted.

All analyses were completed with SAS software, version 9.4 (SAS Institute, Inc.).

Results:

Baseline characteristics of the study sample are presented in Table 1. There were 1970 participants free of cognitive impairment at the 1998–2000 examination with measured biomarkers (mean age=66.9 years (SD=8.6), N=1165 (59.1%) female). There were 970 participants at risk of incident MCI/dementia at the 2009–2010 examination and 809 had the necessary data at the 2013–2016 phase for analysis of cognitive decline. Incidence of cognitive outcomes by biomarker levels, overall and sex-specifically, can be seen in Figure 1. Risk estimates of potential confounders of relationships between biomarkers of interest and cognitive outcomes are displayed in Table 2.

Incidence of Cognitive Impairment

Cognitive impairment cumulative incidence was 11.8% in the 16-year follow-up period. Risk increased with age (per 5 years: sex-adjusted HR=1.86, 95%CI=1.72, 2.01), men were more likely to develop impairment than women (age-adjusted HR=1.41, 95%CI=1.09, 1.83), and risk was reduced among those with at least a college degree (age- and sex-adjusted HR=0.48, 95% CI=0.31, 0.72).

In overall models adjusting for age, sex, and education there was no significant association between baseline level of serum biomarkers (BDNF, IGF-1, Aldosterone) and incident cognitive impairment (see Table 3). However, in sex-stratified analysis, there was a significant association of BDNF level among women, with those in Q1 having an increased risk (HR=1.76, 95%CI= 1.04, 2.98) compared to Q5. In models adjusting for additional confounders, results were similar though no longer statistically significant (HR=1.84, 95%CI= 0.98, 3.47) (see Table 4). A potential dose-response relationship can be observed among women. In both the continuous and doubling models, increasing levels of BDNF were protective, although not statistically significant (HR=0.90, 95%CI=0.72, 1.11; HR=0.71, 95%CI=0.45, 1.12, respectively).

Incidence of MCI/Dementia

Among the 970 participants at risk of MCI/dementia in 2009–2010, 76 (7.8%) developed MCI/dementia in the follow-up period. Risk increased with age, controlling for sex (per 5 years: RR=1.64, 95% CI=1.45, 1.86), while there was no significant difference by sex or

education (male sex RR=1.19, 95% CI=0.78, 1.82; college education or greater RR=0.83, 95% CI=0.50, 1.40).

In models adjusted for age, sex, and education, low biomarker levels were not associated with increased risk of incidence of MCI/dementia overall (see Table 3), though among men increasing IGF1 levels were protective (per SD RR=0.59, 95%CI=0.38, 0.92; doubling RR=0.39, 95%CI=0.19, 0.81). This sex-specific association remained in models controlling for additional covariates (per SD RR=0.57, 95%CI=0.35, 0.92; doubling RR=0.36, 95%CI=0.17, 0.77), and was also seen in the overall doubling model (RR=0.60, 95%CI=0.37, 0.97) (Table 4). Increasing levels of aldosterone were associated with higher risk of MCI/dementia in expanded models only among men (RR=1.28, 95%CI=1.01, 1.62).

Incidence of Cognitive Decline

Of the 803 participants at risk of cognitive decline in 2009–2010, 197 participants (24.5%) experienced a decline in score in 5 years of follow-up. Risk increased with age, controlling for sex (per 5 years: RR=1.35, 95% CI=1.25, 1.46). There was no significant difference by sex or education (male sex RR=1.04, 95% CI=0.82, 1.31; college education or greater RR=0.88, 95% CI=0.66, 1.16).

In overall models adjusted for age, sex, and education, those in Q1 of BDNF at baseline were more likely to experience cognitive decline (RR=1.55, 95% CI=1.05, 2.28) compared to Q5, though no association was seen for IGF-1 or aldosterone. Sex-stratified analysis showed this association was stronger among women (RR=1.62, 95% CI=1.03, 2.55) than men (RR=1.31, 95% CI=0.72, 2.36) (see Table 3). In models adjusting for additional confounders, results were similar though only risk of cognitive decline in the overall analysis remained statistically significant (RR=1.52, 95%CI=1.02, 2.26) (see Table 4). The association of BDNF was also observed in dose-response models adjusted for age, sex and education, with increasing levels associated with decreased risk of cognitive decline (per SD RR=0.88, 95%CI=0.78, 0.99; doubling RR=0.77, 95% CI=0.60, 0.98). These results were similar in the models adjusted for additional confounders, though no longer statistically significant. No significant associations were found for a sex by biomarker level interaction term with any of the cognitive outcomes.

Discussion:

In this study, low levels of BDNF and IGF, were associated with poorer cognitive outcomes in the EHLS cohort, suggesting a potential protective effect of the neurotrophins. Although we cannot directly discern the pathway by which this protection may occur, several potential mechanisms have been identified. BDNF and IGF1 are involved in neurogenesis, synaptic transmission, and survival of neurons, so people with higher circulating levels may have a direct benefit and be protected from the declines in function seen in people with low levels.^{8, 22} People with higher levels of BDNF or IGF1 may be able to adapt and maintain neuronal function. This could occur through new connections or by greater resiliency and may protect them from deficits due to cell death experienced by those with lower levels.

Our finding, that BDNF may be protective against incident cognitive outcomes, is consistent with some previous studies that found BDNF reduced in AD and increased concentrations of BDNF associated with lower incidence of all-cause dementia.^{13–15} Though our findings differed from studies that showed increased levels of BDNF in AD and MCI patients, one of these had exclusion criteria for the AD group, including CVD, which may have affected results, while the other focused on analysis of post-mortem brain tissue.^{18–19} Our population-based cohort study may not be easily compared to the results of these studies. The association of BDNF with cognition was stronger among women and the association of IGF1 was stronger among men. Women with low BDNF showed a 76% increase in risk for incident cognitive impairment, controlling for age, sex, and education, while no association was observed among men. Although this association was no longer statistically significant when controlling for additional factors, this may have been due to a decrease in power. In analyses of men and women, those in Q1 had a 52% increased risk of 5-year cognitive decline, compared to Q5, controlling for multiple covariates. This association, however, was largely driven by the relationship observed among women, as they had a 62% increased risk compared to the 22% increase among men. This result is consistent with earlier studies.^{15, 20}

Men with increasing levels of IGF1 had lower risk at follow-up in multivariable models, indicating a potentially protective effect of IGF1, though this association was not significant among women. A previous study reported the contrary with protective effects being observed among women, though their population was older at baseline, 70–89 years.²⁸ The observed differences by sex may be related to sample size or potential differences in survival among men and women in each of these studies. Our finding of a protective association is in agreement with a number of studies, and contrary to two, though one of these was in a small clinical population and the other in those with exceptional longevity in Ashkenazi Jews.^{26–30, 23–24} The differences seen may be due to the selection of these groups, compared to the current study. The reported increased risk of decline in cognitive function shows there may be preclinical effects of low BDNF. The measure of decline used in this study allowed for the investigation of changes in cognitive function prior to a diagnosis of cognitive impairment. So even including individuals who have not yet met the threshold for a diagnosis, BDNF levels at baseline were predictive of decline in cognitive function in 5 years. This may indicate BDNF levels may be useful as a screening tool for risk of future decline, and help identify those in need of routine monitoring or potentially preventative interventions. Similarly, the reported association between IGF1 and decreased incidence of MCI/dementia may indicate a potential avenue for reducing future cases.

It should be noted that while BDNF and IGF1 were not significantly associated with outcomes in both sexes, the direction was predominantly consistent. This may imply the sex-specific associations noted in this study are more closely related to power than to the mechanism by which they affect the outcomes, and would explain why no significant interactions between sex and biomarker level were observed. In contrast, the associations observed for aldosterone were in opposite directions by sex. Among men, increasing levels of aldosterone were associated with increased risk of MCI/dementia, and among women the association was in the opposite direction, though not statistically significant. A previous study reported a negative effect of aldosterone among hypertensives and hypothesized aldosterone may have a negative impact on vascular health and in turn effect cognition,

though could also just be a marker for vascular health or damage.³³ The association between aldosterone and cognition was observed only among men in the continuous model so this finding may be significant by chance alone.

Strengths of this study include a large well-characterized cohort with long standing follow-up examinations and standardized measurements. However, biomarker levels were measured at only 1 time point, and long term exposure cannot be characterized. Future studies investigating long-term levels of potentially protective biomarkers are needed to understand how chronic low levels may affect cognitive outcomes. Additionally, cognitive outcomes were assessed according to standard research protocols but no clinical assessment was conducted. Finally, the relatively low number of cases, especially with regards to MCI/dementia, may have limited the power to detect associations.

In conclusion, BDNF and IGF1 were associated with cognitive outcomes in a longitudinal study of older adults, though results differed by sex. These results suggest BDNF and IGF1 may play a role in neuroprotection which contributes to maintenance of cognitive capacity in aging adults. Future study should address the role of these biomarkers by sex and investigate long-term levels of the biomarkers and their effects on cognition.

Conflicts of Interest and Source of Funding:

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Figure 1: Overall and sex-specific unadjusted incidence (% of participants) meeting case status of cognitive outcomes by biomarker levels

BDNF= Brain-derived neurotrophic factor, IGF-1= Insulin-like growth factor,

PCA=principal components analysis, MCI=mild cognitive impairment, Q=quintile

Table 1:

Baseline characteristics of the Epidemiology of Hearing Loss Study sample

Characteristic	N (%) or Mean (SD)
Overall	1970
Mean age (years)	66.9 (8.6)
Female sex	1165 (59.1)
Less than college education	1596 (81.1)
Alcohol consumption (g/week)	
0	381 (19.6)
1–14	847 (43.5)
15–74	319 (16.4)
75–140	203 (10.4)
>=141	196 (10.1)
Smoking status	
Never	920 (47.2)
Past	827 (42.4)
Current	202 (10.4)
Mean waist circumference (cm)	97.8 (16.2)
Mean BMI (kg/m ²)	30.2 (5.8)
Exercise at least 1/week	863 (44.3)
Diabetes	221 (11.3)
History of head injury	522 (26.5)
History of CVD	251 (12.9)
Mean carotid IMT (mm)	0.86 (0.21)
Mean CRP (mg/L)	4.1 (6.9)
Mean IL6 (pg/mL)	2.4 (3.6)
Mean TNF- α (pg/mL)	1.4 (1.1)
APOE-4 Carrier	254 (14.4)
Mean BDNF (ng/mL)	21.1 (6.3)
Mean IGF1 (ng/mL)	74.9 (26.6)
Mean Aldosterone (ng/dL)	9.5 (6.2)

SD=Standard Deviation, BMI=Body Mass Index, CVD= cardiovascular disease, IMT=intima-media thickness, CRP=C-Reactive Protein, IL6=Interleukin-6 TNF- α =Tumor Necrosis Factor- α , BDNF=Brain-derived neurotrophic factor, IGF=Insulin-like growth factor

Age-, sex-, and education-adjusted hazard ratios (HR) and 95% confidence intervals (CI) for potential confounders of the relationship between biomarkers and cognitive outcomes

Table 2:

	Incident cog imp		Incident MCI/Dementia	Cognitive decline	
	HR (95% CI)	p-value	HR (95% CI)	p-value	
Age (per 5 years)	1.86 (1.72, 2.01)	<0.0001	1.64 (1.45, 1.86)	<0.0001	
Male Sex	1.41 (1.09, 1.83)	0.01	1.19 (0.78, 1.82)	0.42	0.77
College education or greater	0.48 (0.31, 0.72)	0.001	0.83 (0.50, 1.40)	0.49	0.36
Alcohol consumption (g/week)					
0	Reference		Reference		
1–14	0.73 (0.52, 1.01)	0.06	0.81 (0.42, 1.54)	0.52	0.42
15–74	0.87 (0.58, 1.32)	0.52	1.27 (0.63, 2.56)	0.51	0.46
75–140	0.58 (0.33, 1.03)	0.06	0.79 (0.31, 2.02)	0.63	0.32
>=141	1.16 (0.74, 1.83)	0.51	1.79 (0.85, 3.78)	0.12	0.14
Smoking status					
Never	Reference		Reference		
Past	0.93 (0.70, 1.24)	0.63	1.22 (0.80, 1.85)	0.36	0.25
Current	1.68 (1.04, 2.70)	0.03	1.02 (0.41, 2.54)	0.97	0.20
Waist Circumference (per 5 cm)	1.01 (0.96, 1.05)	0.77	1.06 (0.99, 1.13)	0.11	0.03
BMI (kg/m ²)					
<25.0	Reference		Reference		
25 - <30.0	1.02 (0.70, 1.47)	0.93	1.86 (0.85, 4.08)	0.12	0.05
>=30.0	1.01 (0.70, 1.46)	0.95	1.66 (0.77, 3.61)	0.20	0.08
Exercise at least 1/week	0.97 (0.74, 1.26)	0.82	1.19 (0.77, 1.81)	0.43	0.04
Diabetes	1.19 (0.83, 1.73)	0.35	1.24 (0.59, 2.58)	0.57	0.25
History of head injury	1.06 (0.78, 1.43)	0.71	1.12 (0.68, 1.84)	0.65	0.90
History of CVD	1.01 (0.71, 1.42)	0.97	0.96 (0.47, 1.98)	0.92	0.02
Mean carotid IMT (per 0.1mm)	1.08 (1.01, 1.15)	0.03	0.96 (0.84, 1.09)	0.51	0.13
CRP (mg/L)					
<1.0	Reference		Reference		

	Incident cog imp		Incident MCI/Dementia		Cognitive decline	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
1.0-3.0	0.72 (0.52, 1.01)	0.05	1.31 (0.71, 2.43)	0.38	1.62 (1.10, 2.37)	0.02
>3.0	0.81 (0.58, 1.13)	0.21	1.02 (0.54, 1.94)	0.94	1.73 (1.17, 2.56)	0.006
IL6 (pg/mL)						
T1 (<1.2)	Reference		Reference		Reference	
T2 (1.2-<2.4)	1.17 (0.86, 1.59)	0.32	1.54 (0.95, 2.49)	0.08	1.12 (0.84, 1.49)	0.46
T3 (2.4)	1.16 (0.82, 1.63)	0.40	1.33 (0.75, 2.36)	0.33	1.44 (1.08, 1.93)	0.01
TNF- α (pg/mL)						
T1 (<1.0)	Reference		Reference		Reference	
T2 (1.0-<1.5)	0.69 (0.50, 0.96)	0.03	0.75 (0.42, 1.33)	0.32	0.82 (0.61, 1.10)	0.18
T3 (1.5)	0.84 (0.61, 1.15)	0.27	1.38 (0.84, 2.26)	0.20	0.94 (0.70, 1.25)	0.66
APOE-4 Carrier	0.79 (0.51, 1.23)	0.30	0.59 (0.28, 1.26)	0.17	1.07 (0.79, 1.47)	0.65
BDNF (ng/mL)						
Q1 (<15.8)	1.27 (0.84, 1.91)	0.26	1.23 (0.65, 2.33)	0.53	1.55 (1.05, 2.28)	0.03
Q2 (15.8-<19.3)	0.94 (0.60, 1.48)	0.80	0.60 (0.28, 1.30)	0.20	1.27 (0.85, 1.89)	0.24
Q3 (19.3-<22.4)	1.37 (0.91, 2.06)	0.14	1.19 (0.65, 2.20)	0.58	1.26 (0.84, 1.89)	0.26
Q4 (22.4-<26.0)	1.36 (0.90, 2.07)	0.14	0.78 (0.40, 1.55)	0.48	1.37 (0.92, 2.03)	0.12
Q5 (26.0)	Reference		Reference		Reference	
IGF1 (ng/mL)						
Q1 (<54.1)	0.96 (0.65, 1.42)	0.84	1.71 (0.79, 3.74)	0.18	1.31 (0.89, 1.92)	0.17
Q2 (54.1-<66.3)	0.84 (0.56, 1.26)	0.41	1.22 (0.56, 2.69)	0.62	1.13 (0.76, 1.69)	0.54
Q3 (66.3-<77.8)	0.84 (0.56, 1.28)	0.42	1.09 (0.49, 2.43)	0.83	0.94 (0.62, 1.42)	0.76
Q4 (77.8-<93.6)	0.78 (0.51, 1.19)	0.25	0.98 (0.45, 2.13)	0.96	1.08 (0.73, 1.59)	0.70
Q5 (93.6)	Reference		Reference		Reference	
Aldosterone (ng/dL)						
Q1 (<5.0)	1.21 (0.78, 1.86)	0.40	1.31 (0.63, 2.75)	0.47	1.11 (0.77, 1.60)	0.58
Q2 (5.0-<7.0)	1.20 (0.78, 1.85)	0.41	1.22 (0.58, 2.56)	0.61	0.99 (0.68, 1.44)	0.97
Q3 (7.0-<9.3)	1.06 (0.69, 1.62)	0.79	1.52 (0.74, 3.11)	0.25	1.07 (0.73, 1.56)	0.74
Q4 (9.3-<12.4)	1.85 (1.27, 2.71)	0.002	1.68 (0.81, 3.45)	0.16	1.00 (0.67, 1.49)	0.99

	Incident cog imp		Incident MCI/Dementia		Cognitive decline	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Q5 (12.4)	Reference		Reference		Reference	

BMI=Body mass index, CVD=cardiovascular disease, IMT=intima-media thickness, CRP=C-Reactive Protein, IL6=Interleukin-6, TNF- α =Tumor Necrosis Factor- α , BDNF=Brain-derived neurotrophic factor, IGF=Insulin-like growth factor, T=tertile, Q=quintile

Table 3:

Risk of cognitive outcomes by baseline neuroprotective factors: Hazard Ratios (HRs), Relative Risk (RR), and 95% Confidence Intervals (CIs)^a

	16-year Incident Cognitive Impairment	5-year Incident MCI/Dementia	5-year Incident Cognitive Decline
BDNF	HR (95% CI)	RR (95% CI)	RR (95% CI)
Overall			
Q1 (vs. Q5)	1.27 (0.84, 1.91)	1.23 (0.65, 2.33)	1.55 (1.05, 2.28)
Continuous (per SD)	0.96 (0.85, 1.10)	0.93 (0.75, 1.15)	0.88 (0.78, 0.99)
Doubling	0.92 (0.70, 1.20)	0.84 (0.53, 1.33)	0.77 (0.60, 0.98)
Women			
Q1 (vs. Q5)	1.76 (1.04, 2.98)	1.37 (0.62, 3.02)	1.62 (1.03, 2.55)
Continuous (per SD)	0.88 (0.74, 1.05)	0.90 (0.67, 1.20)	0.86 (0.74, 0.99)
Doubling	0.72 (0.51, 1.03)	0.73 (0.39, 1.39)	0.75 (0.55, 1.02)
Men			
Q1 (vs. Q5)	0.75 (0.38, 1.45)	0.67 (0.20, 2.23)	1.31 (0.72, 2.36)
Continuous (per SD)	1.09 (0.90, 1.32)	1.00 (0.73, 1.37)	0.92 (0.74, 1.14)
Doubling	1.24 (0.82, 1.90)	1.07 (0.55, 2.07)	0.80 (0.53, 1.22)
IGF1			
Overall			
Q1 (vs. Q5)	0.96 (0.65, 1.42)	1.71 (0.79, 3.74)	1.31 (0.89, 1.92)
Continuous (per SD)	1.02 (0.90, 1.16)	0.81 (0.60, 1.09)	0.95 (0.82, 1.10)
Doubling	0.98 (0.76, 1.25)	0.70 (0.44, 1.12)	0.87 (0.68, 1.11)
Women			
Q1 (vs. Q5)	1.04 (0.63, 1.73)	1.35 (0.59, 3.12)	1.26 (0.81, 1.96)
Continuous (per SD)	1.00 (0.85, 1.19)	0.98 (0.68, 1.40)	0.94 (0.78, 1.13)
Doubling	0.96 (0.71, 1.30)	0.93 (0.53, 1.62)	0.85 (0.64, 1.13)
Men			
Q1 (vs. Q5)	0.89 (0.48, 1.65)	4.43 (0.92, 21.4)	1.18 (0.60, 2.32)
Continuous (per SD)	1.05 (0.86, 1.28)	0.59 (0.38, 0.92)	0.96 (0.77, 1.20)
Doubling	1.01 (0.66, 1.56)	0.39 (0.19, 0.81)	0.89 (0.57, 1.41)
Aldosterone			
Overall			
Q1 (vs. Q5)	1.21 (0.78, 1.86)	1.31 (0.63, 2.75)	1.11 (0.77, 1.60)
Continuous (per SD)	0.97 (0.86, 1.09)	1.01 (0.81, 1.25)	0.98 (0.86, 1.12)
Doubling	0.99 (0.84, 1.15)	0.98 (0.75, 1.29)	0.97 (0.83, 1.12)
Women			
Q1 (vs. Q5)	1.32 (0.74, 2.34)	1.95 (0.69, 5.54)	1.30 (0.78, 2.16)
Continuous (per SD)	0.94 (0.81, 1.10)	0.89 (0.62, 1.28)	0.95 (0.79, 1.14)
Doubling	0.95 (0.77, 1.16)	0.82 (0.58, 1.17)	0.91 (0.74, 1.11)

	16-year Incident Cognitive Impairment	5-year Incident MCI/Dementia	5-year Incident Cognitive Decline
BDNF	HR (95% CI)	RR (95% CI)	RR (95% CI)
Men			
Q1 (vs. Q5)	0.83 (0.41, 1.64)	0.93 (0.30, 2.89)	0.89 (0.53, 1.50)
Continuous (per SD)	1.01 (0.84, 1.21)	1.15 (0.91, 1.44)	1.05 (0.88, 1.25)
Doubling	1.05 (0.82, 1.35)	1.24 (0.79, 1.94)	1.05 (0.82, 1.35)

^aOverall models adjusted for age, sex, and education. Sex specific models adjusted for age and education.

MCI= Mild Cognitive Impairment , BDNF= Brain-derived neurotrophic factor, IGF1= Insulin-like growth factor, Q=Quintile, SD=Standard Deviation

Table 4:

Multivariable adjusted risk of cognitive outcomes by baseline neuroprotective factors: Hazard Ratios (HRs), Relative Risk (RR), and 95% Confidence Intervals (CIs)

	16-year Incident Cognitive Impairment ^a	5-year Incident MCI/Dementia ^b	5-year Incident Cognitive Decline ^c
BDNF	HR (95% CI)*	RR (95% CI)*	RR (95% CI)*
Overall			
Q1 (vs. Q5)	1.39 (0.85, 2.25)	1.08 (0.57, 2.03)	1.52 (1.02, 2.26)
Continuous (Per SD)	0.95 (0.82, 1.11)	0.95 (0.76, 1.18)	0.89 (0.78, 1.00)
Doubling	0.88 (0.63, 1.21)	0.86 (0.53, 1.41)	0.79 (0.61, 1.01)
Women			
Q1 (vs. Q5)	1.84 (0.98, 3.47)	1.29 (0.60, 2.75)	1.62 (0.99, 2.62)
Continuous (Per SD)	0.90 (0.72, 1.11)	0.89 (0.66, 1.21)	0.86 (0.73, 1.00)
Doubling	0.71 (0.45, 1.12)	0.70 (0.35, 1.38)	0.74 (0.54, 1.03)
Men			
Q1 (vs. Q5)	0.95 (0.45, 2.00)	0.51 (0.14, 1.88)	1.22 (0.68, 2.17)
Continuous (Per SD)	1.00 (0.79, 1.26)	1.02 (0.74, 1.42)	0.98 (0.80, 1.19)
Doubling	1.01 (0.62, 1.63)	1.14 (0.57, 2.29)	0.91 (0.62, 1.35)
IGF1			
Overall			
Q1 (vs. Q5)	1.19 (0.75, 1.90)	2.04 (0.94, 4.44)	1.38 (0.93, 2.06)
Continuous (Per SD)	0.94 (0.80, 1.11)	0.75 (0.55, 1.02)	0.92 (0.80, 1.06)
Doubling	0.84 (0.62, 1.13)	0.60 (0.37, 0.97)	0.84 (0.65, 1.07)
Women			
Q1 (vs. Q5)	1.54 (0.82, 2.89)	1.95 (0.81, 4.70)	1.32 (0.83, 2.12)
Continuous (Per SD)	0.85 (0.68, 1.06)	0.85 (0.57, 1.27)	0.92 (0.76, 1.11)
Doubling	0.73 (0.50, 1.06)	0.72 (0.39, 1.33)	0.82 (0.61, 1.12)
Men			
Q1 (vs. Q5)	0.92 (0.45, 1.90)	4.56 (0.99, 21.0)	1.16 (0.61, 2.22)
Continuous (Per SD)	1.03 (0.81, 1.30)	0.57 (0.35, 0.92)	0.93 (0.76, 1.15)
Doubling	0.97 (0.59, 1.62)	0.36 (0.17, 0.77)	0.87 (0.57, 1.33)
Aldosterone			
Overall			
Q1 (vs. Q5)	1.33 (0.80, 2.22)	1.25 (0.58, 2.67)	1.13 (0.78, 1.63)
Continuous (Per SD)	0.97 (0.83, 1.14)	1.01 (0.81, 1.25)	0.97 (0.85, 1.10)
Doubling	0.97 (0.80, 1.18)	0.98 (0.74, 1.30)	0.96 (0.82, 1.11)
Women			
Q1 (vs. Q5)	1.70 (0.85, 3.38)	2.09 (0.72, 6.01)	1.36 (0.81, 2.29)
Continuous (Per SD)	0.89 (0.72, 1.11)	0.85 (0.58, 1.23)	0.94 (0.77, 1.14)
Doubling	0.87 (0.67, 1.12)	0.79 (0.56, 1.11)	0.91 (0.74, 1.10)

	16-year Incident Cognitive Impairment ^a	5-year Incident MCI/Dementia ^b	5-year Incident Cognitive Decline ^c
BDNF	HR (95% CI)*	RR (95% CI)*	RR (95% CI)*
Men			
Q1 (vs. Q5)	0.73 (0.34, 1.58)	0.68 (0.21, 2.21)	0.96 (0.59, 1.57)
Continuous (Per SD)	1.07 (0.87, 1.31)	1.28 (1.01, 1.62)	1.02 (0.87, 1.20)
Doubling	1.10 (0.83, 1.48)	1.43 (0.89, 2.29)	1.04 (0.83, 1.31)

^aAdjusted for age, sex, education, alcohol consumption, smoking status, mean intima-media thickness, C-reactive protein level, and tumor necrosis factor-alpha level.

^bAdjusted for age, sex, education, alcohol consumption, interleukin-6 level, and tumor necrosis factor-alpha level.

^cAdjusted for age, sex, education, alcohol consumption, smoking status, history of cardiovascular disease, exercise, and C-reactive protein level.

MCI=Mild Cognitive Impairment, BDNF= Brain-derived neurotrophic factor, IGF1= Insulin-like growth factor, Q=Quintile, SD=Standard Deviation