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Serum Brain-Derived Neurotrophic Factor and the Risk for Dementia:

The Framingham Heart Study

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Abstract

IMPORTANCE—In animal studies, brain-derived neurotrophic factor (BDNF) has been shown to impact neuronal survival and function and improve synaptic plasticity and long-term memory. Circulating BDNF levels increase with physical activity and caloric restriction, thus BDNF may mediate some of the observed associations between lifestyle and the risk for dementia. Some prior studies showed lower circulating BDNF in persons with Alzheimer disease (AD) compared with control participants; however, it remains uncertain whether reduced levels precede dementia onset.

OBJECTIVE—To examine whether higher serum BDNF levels in cognitively healthy adults protect against the future risk for dementia and AD and to identify potential modifiers of this association.

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DESIGN, SETTING, AND PARTICIPANTS—Framingham Study original and offspring participants were followed up from 1992 and 1998, respectively, for up to 10 years. We used Cox models to relate BDNF levels to the risk for dementia and AD and adjusted for potential confounders. We also ran sensitivity analyses stratified by sex, age, and education, as well as related BDNF genetic variants to AD risk. This community-based, prospective cohort study involved 2131 dementia-free participants aged 60 years and older (mean [SD] age, 72 [7] years; 56% women).

MAIN OUTCOMES AND MEASURES—Ten-year incidence of dementia and AD.

RESULTS—During follow-up, 140 participants developed dementia, 117 of whom had AD. Controlling for age and sex, each standard-deviation increment in BDNF was associated with a 33% lower risk for dementia and AD ($P = .006$ and $P = .01$, respectively) and these associations persisted after additional adjustments. Compared with the bottom quintile, BDNF levels in the top quintile were associated with less than half the risk for dementia and AD (hazard ratio, 0.49; 95%CI, 0.28–0.85; $P = .01$; and hazard ratio, 0.46; 95%CI, 0.24–0.86; $P = .02$, respectively). These associations were apparent only among women, persons aged 80 years and older, and those with college degrees (hazard ratios for AD: 0.65, [95%CI, 0.50–0.85], $P = .001$; 0.63 [95%CI, 0.47–0.85], $P = .002$; and 0.27 [95%CI, 0.11–0.65], $P = .003$, respectively). Brain-derived neurotrophic factor genetic variants were not associated with AD risk.

CONCLUSIONS AND RELEVANCE—Higher serum BDNF levels may protect against future occurrence of dementia and AD. Our findings suggest a role for BDNF in the biology and possibly in the prevention of dementia and AD, especially in select subgroups of women and older and more highly educated persons.

The lifetime risk[1] for developing Alzheimer disease (AD) is 1 in 5, and with increasing life expectancy, the number of affected people is projected to increase.[2] Despite intensive investigation in recent years, there is still an incomplete understanding of the etiology and pathophysiology of this disabling and costly disease; therefore, the best strategies for prevention and treatment are not known.

Brain-derived neurotrophic factor (BDNF) may explain some of the variation in dementia risk, and because it is inducible by factors such as reduced caloric intake[3] and increased physical activity,[4,5] it is thought to mediate the association between healthy lifestyle and successful aging. In animal models, BDNF is highly expressed and widely distributed throughout the central nervous system especially in the hippocampus and cerebral cortex[6,7] and is important in the survival and function of hippocampal and cortical, as well as cholinergic and dopaminergic, neurons.[8–11] In addition, BDNF is critical for synaptic plasticity and memory processing in the adult brain.[12,13] Erickson et al[14] demonstrated a relationship between reduced serum BDNF and smaller hippocampal volume, as well as poorer memory, in a sample of 142 dementia free individuals aged 59 to 81 years. Similarly, in a Finnish population-based study of 1389 men and women aged 57 to 79 years, plasma BDNF was positively associated with cognitive performance; however, these associations were apparent only in women.[15] Reduced levels of BDNF have been observed in the hippocampus and parietal lobe,[16,17] as well as in the serum,[18–20] of people with mild cognitive impairment and AD compared with cognitively intact individuals or people with

vascular dementia.[21] Nevertheless, other studies have found no association with AD.[22] However, because of the cross-sectional design of these studies, it is not clear whether changes in BDNF levels preceded or followed the cognitive decline and onset of clinical dementia.

In the present study, we examined whether serum BDNF levels were prospectively associated with 10-year risks for incident dementia and AD in a large population-based sample from the Framingham Heart Study (FHS). Because factors such as age, sex, smoking status,[23,24] and education[25,26] may influence both BDNF levels and dementia risk,[27] we explored whether these factors modify the association between BDNF and the risk for incident dementia or AD.

Methods

Study Sample

The FHS is a longitudinal community-based cohort study that was initiated in 1948 with the enrollment of 5209 participants aged 28 to 62 years (original cohort). In 1971, the offspring and their spouses were enrolled as the offspring cohort. Since the study's inception, participants have had serial examinations including standardized interviews, physician examinations, and laboratory testing. Data were obtained under a protocol approved by the institutional review board of the Boston University Medical Center, and written informed consent was obtained from all participants. More details of the study design have been provided elsewhere.[28,29]

Of the original cohort, 1026 participants attended examination 23 (mean age, 82 years; 33% males) and from the offspring cohort, 3539 participants attended examination 7 (mean age, 62 years; 46% males). In total, BDNF levels were measured in 3689 participants (669 in the original and 3020 in the offspring cohorts). After exclusion of 1407 offspring participants who were younger than age 60 years, 9 participants with prevalent dementia, and 142 who did not have complete follow-up information, 2131 participants were available for the analyses of association with dementia/AD (655 in the original and 1476 in the offspring cohorts).

Laboratory Measurements of BDNF

Serum BDNF concentrations were measured on previously frozen (stored at −70°C) blood samples drawn in the fasting state from persons who attended the 23rd original cohort examination and the 7th offspring examination. Assays used enzyme-linked immunosorbent assay kits from R&D Systems. The intra-assay and interassay coefficients of variation were 4.8% and 7.6%, respectively.

Ascertainment of Dementia and AD

All FHS participants are under continuous surveillance for impairment in cognitive function. We have previously outlined our screening and surveillance methods for the development of dementia.[30] Dementia was diagnosed according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition)[31] and AD based on the criteria of

the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer Disease and Related Disorders Association for definite, probable, or possible AD.[32,33]

Definition of Covariates

The study covariates included previously described components of the Framingham Stroke Risk Profile[34] including age in years, systolic blood pressure in millimeters of mercury, history of diabetes mellitus, cardiovascular disease and atrial fibrillation, and current smoking status. Educational achievement was defined as a 3-class variable (no high-school degree, high-school degree only, or at least a college degree). Total plasma homocysteine (tHcy) was measured using high-performance liquid chromatography with fluorometric detection,[35] and depressive symptoms were evaluated with the Center for Epidemiological Studies Depression Scale (CES-D).[36] The Physical Activity Index (PAI) was calculated as a composite score based on information collected from a structured questionnaire.[37] Total plasma homocysteine, CES-D, and PAI were all log-transformed for analysis. Information on covariates was obtained from the visit in which BDNF was measured except for tHcy, CES-D, and PAI in the original cohort that were obtained from examination 20.

Single-Nucleotide Polymorphism Selection and Genotyping

Genome wide genotyping was available for all participants with good-quality DNA. Genotyping was performed on the Affymetrix GeneChip Human Mapping 500K Array Set and 50K Human Gene Focused Panel through the SHARe Project (SNP-Health Association Resource), and these data were used to impute to the 2.5 million nonmonomorphic, autosomal single-nucleotide polymorphisms (SNPs) described in the HapMap (CEU population). Genotyping, quality control, and imputation methods have been described previously.[38] Of 2131 participants available for the analysis of plasma BDNF levels and dementia/AD, 1819 also had adequate genotypic data after quality control, and there were 115 cases of incident AD in this subsample. Mean BDNF levels in this subsample (mean [SD], 23 270 [8144.95] pg/ml) were similar to that of the larger sample studied. We extracted information on 133 SNPs that were within the genomic region up to 60 kb on either side (chr11:27573018–27760181) of the BDNF gene (defined as chr11:27633018–27700181) and related these SNPs to serum BDNF levels and to the risk for AD.

Statistical Analyses

We used multivariable Cox regression analysis to examine the associations of BDNF with incident dementia and AD, modeling BDNF as a continuous variable and also examining the trend across quintiles. In addition, we tested for interaction of BDNF levels with age, sex, smoking status, and education in determining the risk for dementia by including these interaction terms in the Cox regression model. If a significant interaction was found, we ran a stratified model. For age stratification, we chose the cutoff of 80 years. All primary analyses were first adjusted for age, sex, and cohort (original or offspring). In model B, we additionally adjusted for education and for the following vascular covariates previously associated in FHS with stroke and brain injury: systolic blood pressure, prevalent cardiovascular disease, atrial fibrillation and diabetes mellitus, current smoking status, and apolipoprotein ε4 genotype. In model C, we additionally adjusted for other metabolic

covariates that have been related to cognitive outcomes outside FHS: total cholesterol, body mass index (calculated as weight in kilograms divided by height in meters squared), and use of statins. In model D, we also included lifestyle and biomarker measures of CES-D and PAI scores and tHcy, in addition to the covariates in model C. The additional covariates adjusted for in model D were available for all offspring participants but only for participants in the original cohort who attended examination 20. The associations of SNPs contained within the BDNF region with serum BNDF levels were examined using linear regression and their association with the risk for AD was examined using Cox models. Both analyses used additive genetic models and adjusted for age, sex, and occult population stratification and familial relationships within the Framingham cohorts. We additionally examined the association with AD within sex-specific strata (using models adjusted only for age and family relationships).

Results

At baseline, the mean (SD) serum BDNF of the sample was 23 043 (8274) pg/mL, the mean (SD) age was 72 (7) years, and 932 (44%) were men. The baseline characteristics according to BDNF levels are presented in Table 1. Participants with BDNF levels at the bottom 2 quintiles were significantly older, and they were more likely to be males, to have a college degree or higher, and to have a history of atrial fibrillation compared with those with higher BDNF levels. Moreover, they were less likely to be current smokers and their total cholesterol was lower.

During a median of 10 years of follow-up, 140 participants developed dementia, 117 of whom had AD. After controlling for age, sex, and cohort, each 1-SD increment of serum BDNF level was associated with a 23% lower risk for future dementia ($P = .006$) and AD ($P = .01$) (Table 2). There was a significant trend toward a lower risk for dementia and AD with increasing quintiles of BDNF levels (P for trend = .002 and .01 for dementia and AD, respectively), and compared with the lowest quintile, the top quintile of BDNF level was associated with less than half the risk for developing dementia (hazard ratio [HR], 0.49; 95%CI, 0.28–0.85; $P = .01$) and AD (HR, 0.46; 95% CI, 0.24–0.86; $P = .02$) (Table 2 and Figure). The results remained significant after further adjustment for education, systolic blood pressure, history of cardiovascular disease, atrial fibrillation, diabetes mellitus, smoking status, and apolipoprotein ε4, as well as for total cholesterol, body mass index, and statin use (Table 3). Additional adjustment for tHcy, CES-D, and PAI resulted in a HR of 0.80 (95% CI, 0.64–0.99; $P = .04$) for dementia and 0.80 (95%CI, 0.63–1.01; $P = .05$) for AD (data not tabulated). As previously mentioned, these variables were available only for a subset of participants from the original cohort who attended examination 20 in addition to examination 23, and thus they may be subject to bias.

We found significant interactions of age and sex with BDNF in determining the risk for AD ($P = .03$ and $P = .048$ for age and sex, respectively) and for education (college degree or higher vs others) with BDNF in determining both the risks for dementia ($P = .003$) and AD ($P = .01$). The associations between BDNF levels and the risk for incident dementia and AD were significant only in women (HR, 0.70; 95%CI, 0.55–0.89; $P = .003$, and HR, 0.65; 95%CI, 0.50–0.85; $P = .001$, for dementia and AD, respectively), in people aged 80 years or

older (HR, 0.66; 95% CI, 0.50–0.87; $P = .003$, and HR, 0.63; 95% CI, 0.47–0.85; $P = .002$, for dementia and AD, respectively), and in participants with a college degree or higher (HR, 0.31; 95% CI, 0.16–0.60; $P < .001$, and HR, 0.27; 95%CI, 0.11–0.65; $P = .003$, for dementia and AD, respectively (Table 4, model A). We did not find any interaction between BDNF and smoking status in determining the risk for AD or dementia. These stratum-specific associations remained unchanged after additional adjustment for vascular risk factors, apolipoprotein ε4, and education, where appropriate (Table 4, model B).

There were 133 SNPs contained within the BDNF region and none of them were significantly associated with AD risk, both overall and separately, in men and women (eTable and eFigure 1 in the Supplement) after correction for multiple testing. Moreover, BDNF SNPs explained only a small proportion of the variability in serum BDNF levels (eFigure 2 in the Supplement).

Discussion

In our community-based cohort, dementia-free individuals with higher BDNF levels were less likely to develop dementia and AD, independent of other risk factors. The association between BDNF and the risk for incident dementia and AD was apparent only in women, older persons, and those with at least a college degree.

Our findings add to the previous literature by demonstrating that BDNF is not only reduced in persons with AD,[18–20] but may also be reduced in healthy people who are destined to develop dementia or AD. The prodromal phase of AD is long and characterized by cognitive deficits[39,40] and structural brain magnetic resonance image changes.[41–43] Furthermore, findings of associations between some risk factors for dementia, such as hypertension and obesity, could only be demonstrated in prospective studies where these risk factors were measured at mid-life rather than in cross-sectional studies or when the risk factor was assessed closer to the time when the disease became apparent.[44,45] Hence, it is to be expected that if BDNF has an active pathophysiologic role in mediating the association of these risk factors with AD, reduced levels will be already apparent at these early stages. This finding is in accordance with a previous study that observed lower BDNF levels in mild cognitive impairment,[46] a condition recognized as a prodromal stage of AD. The fact that BDNF levels predicted dementia and AD independently of putative risk factors further suggests that it may be an active participant in the mechanism underlying these conditions rather than an incidental risk marker.

Little data exists on factors that may modify the association between BDNF levels and the risk for dementia. Sex, age, and smoking status may be associated with BDNF levels,[23,24] as well as dementia risk, and thus we examined whether they also modify the association between BDNF levels and the risk for incident dementia/AD. Our finding that high BDNF levels predict lower risk for dementia/AD only in women is consistent with previous studies. In a Japanese sample, polymorphism in *Val66Met*, a BDNF gene, was associated with AD only in women.[47] Other data suggest that plasma BDNF is a biomarker of impaired memory and general cognitive function in aging women but not men.[15] These findings may support the hypothesis that BDNF interaction with estrogen,[48] other sex hormones,[49] or another sex-

specific mechanism may underlie the development of AD. The finding of an association only in older individuals may be explained by the decline in BDNF levels with age.[23] Because younger individuals have relatively high levels of BDNF, it is possible that their dementia/AD events are due to other processes. Because BDNF plays a role in synaptic plasticity and functional efficiency, it is postulated that it mediates the influence of educational attainment on cognitive reserve. Persons sensitive to the effects of BDNF may achieve greater education but also be more susceptible to the adverse impact of a decline in BDNF with increasing age. Our finding that the risk for dementia and AD is related to BDNF levels only in highly educated people needs to be tested in subsequent studies. If this and the former interactions are confirmed, they may provide insight into some of the complex mechanisms underlying dementia and AD and may set the road for future observational and experimental studies focusing on specific subpopulations. They may also explain inconsistencies between prior reports owing to different distributions of these variables in different study samples and pooled analyses that might obscure real associations in subsamples.

The absence of a significant association between BDNF SNPs and the risk for AD is not inconsistent with the association we show between serum BDNF levels and the risk for AD in women since genetic variation does not appear to explain a substantial proportion of the variation in BDNF levels. Rather, environmental factors, such as mood, diet, and physical activity,[3,4] likely alter BDNF levels and BDNF may be a biological intermediate between these lifestyle factors and their impact of AD pathology and risk, a hypothesis that needs further exploration in additional studies.

The strengths of this study were its community-based prospective design, the large dementia-free sample, and the careful surveillance for end points. We were able to adjust for multiple potential confounders; however, we could not exclude the possibility that some other unknown factors may have affected the results. In addition to this limitation, the number of people in some stratified categories was small and the over-whelmingly European origin of the study sample limits the generalizability of our results.

Conclusions

We suggest that serum BDNF may play a role in the development of AD, especially in older women, the group at highest risk for AD. This is of particular interest because serum BDNF levels can be elevated through simple lifestyle measures such as increased physical activity. Brain-derived neurotrophic factor may also serve as a novel predictor of dementia and AD in healthy adults and as a biomarker of dementia risk and prognosis. Finally, BDNF might also have a potential therapeutic effect in AD. This effect could be reached by noninvasive means, such as physical activity and caloric-restricted diet, or by the administration of exogenous BDNF and/or by stimulating its receptor expression.[50] Lee et al[51] recently showed that inhibition of specific microRNA enhances BDNF protein levels, synaptogenesis, and neurogenesis, as well as improves memory function in mice. They concluded that this inhibitor may be therapeutically effective for AD. Future clinical trials and observational studies should consider the possibilities of a compensation effect in early disease and of an effect modification by various demographic and lifestyle factors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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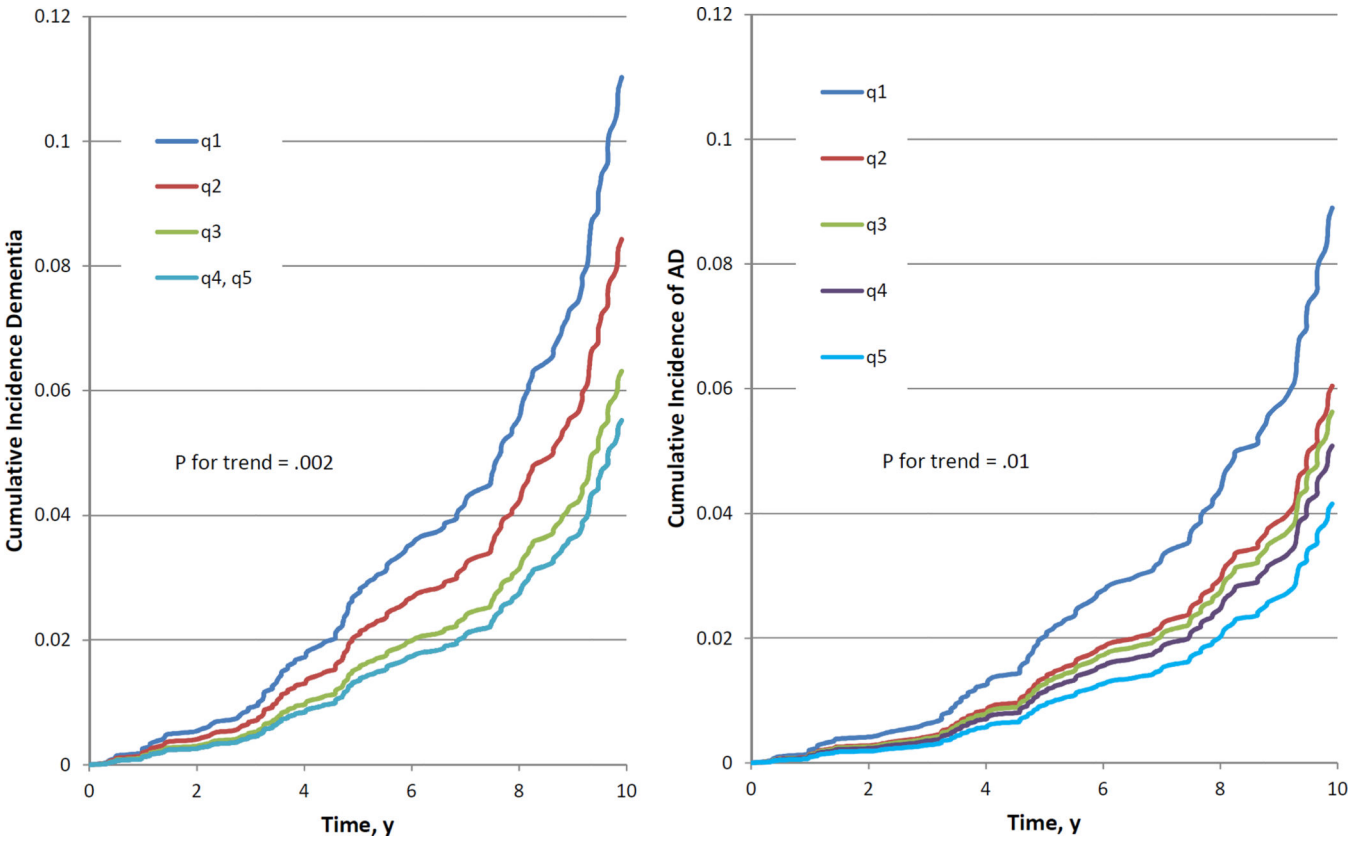

Figure.

Cumulative Incidence of Alzheimer Disease by Quintiles of Serum Brain-Derived Neurotrophic Factor Levels

Table 1

Baseline Characteristics

Characteristic	No. (%)		*P* Value
	Quintiles 1–2	Quintiles 3–5	
Total No.	852	1279	
BDNF, mean (SD), ng/mL	15 242 (4033)	28 240 (5972)	
Age, mean (SD), y	72.8 (7.6)	72.1 (7.5)	.03
Women	242 (50)	775 (61)	<.001
College degree	231 (28)	296 (24)	.04
Systolic blood pressure, mean (SD), mm Hg	135 (20)	136 (20)	.56
Antihypertensive medication	389 (45.8)	584 (45.8)	.99
Current smoker	52 (6)	115 (9)	.02
Diabetes mellitus	145 (17)	185 (15)	.11
Prevalent cardiovascular disease	192 (23)	255 (20)	.15
Atrial fibrillation	77 (9)	66 (5)	<.001
Total cholesterol, mean (SD), mg/dL	195 (36)	204 (37)	<.001
Total homocysteine, median (IQR), μmol/L	9.0 (4.3)	9.0 (3.9)	.09
Depression (CES-D score), median (IQR)	3.0 (6.0)	3.0 (6.0)	.23
Physical Activity Index, median (IQR)	35.7 (8.0)	35.8 (8.2)	.18

Abbreviations: BDNF, brain-derived neurotrophic factor; CES-D, Center for Epidemiological Studies Depression Scale; IQR, interquartile range.

Table 2

Association of Serum Brain-Derived Neurotrophic Factor Levels and Risk for Incident Dementia and Alzheimer Disease[a]

	Dementia 140/2131		Alzheimer Disease 117/2131	
Group	**Hazard Ratio (95% CI)**	***P* Value**	**Hazard Ratio (95% CI)**	***P* Value**
Per SD	0.77 (0.64–0.93)	.006	0.77 (0.63–0.95)	.01
Quintile 1	1 [Reference]		1 [Reference]	
Quintile 2	0.75 (0.47–1.20)	.24	0.67 (0.39–1.14)	.14
Quintile 3	0.56 (0.34–0.92)	.02	0.62 (0.37–1.06)	.08
Quintile 4	0.49 (0.29–0.81)	.006	0.56 (0.33–0.96)	.04
Quintile 5	0.49 (0.28–0.85)	.01	0.46 (0.24–0.86)	.02
P value for trend		.002		.01

[a]Model A: Adjusted for age, sex, and cohort.

Table 3

Association Between Serum Brain-Derived Neurotrophic Factor Levels (Per SD) and Risk for Incident Dementia and Alzheimer Disease

	Dementia		Alzheimer Disease	
Model	**Hazard Ratio (95% CI)**	***P* Value**	**Hazard Ratio (95% CI)**	***P* Value**
B[a]	0.77 (0.63–0.93)	.006	0.78 (0.63–0.95)	.02
C[b]	0.77 (0.63–0.94)	.008	0.77 (0.63–0.95)	.02

[a]Model B: Adjusted for age; sex; cohort; education; systolic blood pressure; history of cardiovascular disease, atrial fibrillation, and diabetes mellitus; smoking status; and apolipoprotein ε4.

[b]Model C: Model B + total cholesterol, body mass index, and statin use.

Table 4

Association Between Serum Brain-Derived Neurotrophic Factor Levels and Risk for Incident Dementia and Alzheimer Disease Stratified by Sex, Age, and Education[a,b]

	Dementia		Alzheimer Disease	
Variable	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value
Women				
Total No.	86/1199		76/1199	
Model A	0.70 (0.55–0.89)	.003	0.65 (0.50–0.85)	.001
Model B	0.69 (0.54–0.88)	.003	0.65 (0.50–0.84)	.001
Men				
Total No.	54/932		41/932	
Model A	0.88 (0.66–1.18)	.39	0.99 (0.72–1.38)	.97
Model B	0.88 (0.64–1.20)	.42	1.03 (0.73–1.47)	.85
<80 y				
Total No.	67/1792		55/1792	
Model A	0.92 (0.70–1.19)	.51	0.98 (0.73–1.31)	.88
Model B	0.92 (0.71–1.19)	.52	0.94 (0.71–1.24)	.65
≥80 y				
Total No.	73/339		62/339	
Model A	0.66 (0.50–0.87)	.003	0.63 (0.47–0.85)	.002
Model B	0.64 (0.49–0.85)	.002	0.65 (0.48–0.88)	.005
No college degree				
Total No.	120/1554		106/1554	
Model A	0.83 (0.68–1.01)	.07	0.83 (0.67–1.02)	.08
Model B	0.84 (0.68–1.02)	.08	0.83 (0.67–1.03)	.08
College degree				
Total No.	18/527		11/527	
Model A	0.31 (0.16–0.60)	<.001	0.27 (0.11–0.65)	.003
Model B	0.27 (0.13–0.57)	<.001	0.26 (0.10–0.69)	.007

[a] Model A: Adjusted for age, sex, and cohort.

[b] Model B: Adjusted for age (except for the age stratification); sex (except for the sex stratification); education (except for the education stratification); cohort; systolic blood pressure; history of cardiovascular disease, atrial fibrillation, and diabetes mellitus; smoking status; and apolipoprotein ε4.