A Summary Risk Score for the Prediction of Alzheimer Disease in Elderly Persons

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Abstract

Objective—To develop a simple summary risk score for the prediction of Alzheimer disease in elderly persons based on their vascular risk profiles.

Design—A longitudinal, community-based study.

Setting—New York, New York.

Patients—One thousand fifty-one Medicare recipients aged 65 years or older and residing in New York who were free of dementia or cognitive impairment at baseline.

Main Outcome Measures—We separately explored the associations of several vascular risk factors with late-onset Alzheimer disease (LOAD) using Cox proportional hazards models to identify factors that would contribute to the risk score. Then we estimated the score values of each factor based on their βcoefficients and created the LOAD vascular risk score by summing these individual scores.

Results—Risk factors contributing to the risk score were age, sex, education, ethnicity, *APOE* ε4 genotype, history of diabetes, hypertension or smoking, high-density lipoprotein levels, and waist to hip ratio. The resulting risk score predicted dementia well. According to the vascular risk score quintiles, the risk to develop probable LOAD was 1.0 for persons with a score of 0 to 14 and increased 3.7-fold for persons with a score of 15 to 18, 3.6-fold for persons with a score of 19 to 22, 12.6-fold for persons with a score of 23 to 28, and 20.5-fold for persons with a score higher than 28.

Conclusions—While additional studies in other populations are needed to validate and further develop the score, our study suggests that this vascular risk score could be a valuable tool to identify elderly individuals who might be at risk of LOAD. This risk score could be used to

identify persons at risk of LOAD, but can also be used to adjust for confounders in epidemiologic studies.

Late-onset Alzheimer disease (LOAD) is the most frequent cause of dementia in Western societies. It is estimated that approximately 5 million people in the United States and 17 million worldwide have the disease.[1] By age 85 years and older, 15% to 30% are affected, and the incidence rate increases from approximately 1% among people aged 65 to 70 years to approximately 6% to 8% for people aged 85 years and older.[1,2] It is expected that these numbers will quadruple by the year 2040, by which time 1 of 45 Americans will be affected, leading to a considerable public health burden.[3] As there is no curative treatment available, extensive efforts for the prevention of dementia in persons at risk are needed. Delaying LOAD onset, by modifying risk or lifestyle, could significantly decrease the prevalence and public health burden. For example, a delay in onset of 1 year would translate to almost 1 million fewer prevalent cases in the United States.[3]

Valuable tools for targeting preventive measures to those at risk of the disease are risk scores.[4] They have been frequently used in population-based settings, in particular to predict the risks of vascular disorders such as stroke, cardiovascular events, diabetes, and mortality from vascular causes.[4–10] They commonly include few known risk factors that are easily measurable to calculate the subsequent risk of an event or disease within a given time frame. Although the absolute risk of an event may differ across populations, risk ranking by use of risk scores is consistent.[11,12] An additional benefit of risk scores is that they can be used to transmit easily understandable information about risk factors to the general population.

Although vascular disease and vascular risk factors including stroke, diabetes, hypertension, smoking, heart disease, dyslipidemia, and obesity have been implicated in the risk of LOAD, [13] only Kivipelto et al[14] have published a score for predicting dementia based on common and easily measurable risk factors[14]; this score was based on risk factor profiles present in middle age.

Barnes et al[15] developed a dementia risk index for use in late life that can accurately stratify older adults into those with a low, moderate, or high risk of developing dementia within 6 years. However, it includes measures that may not be readily available, such as cerebral magnetic resonance imaging and Doppler sonography of the carotid arteries.

We previously reported associations of stroke, diabetes, hyperinsulinemia, hypertension, smoking, obesity, and dyslipidemia with cognitive impairment and dementia in the elderly. [13,16–23] In this study, we developed a tool for predicting dementia risk in elderly individuals that is based on easily available measures and can be used to identify persons at risk as well as to adjust for confounders in epidemiologic studies of risk factors for LOAD.

METHODS

SUBJECTS

Participants were enrolled in a community-based, longitudinal cohort study of Medicare recipients aged 65 years or older residing in northern Manhattan, New York.[24] Each participant underwent an interview of general health and function, medical history, a neurological examination, and a neuropsychological battery.[25] Baseline data were collected from 1999 through 2007. Follow-up data were collected at sequential intervals of 18 months.

Participants were without dementia or cognitive impairment at baseline and had complete information on demographics and vascular risk factors. Of the 2190 persons who were initially recruited, 146 (6.7%) were excluded owing to prevalent dementia, 350 (16.1%)

owing to loss to follow-up over the mean follow-up period of 4.0 years (SD, 1.36 years), and 643 (29.4%) owing to a lack of complete data on all vascular risk factors included in the final analytic model. The final analytic sample included 1051 individuals. The final sample was younger and included more white and fewer Hispanic individuals than the original sample (eTable 1, http://www.archneurol.com).

CLINICAL ASSESSMENTS

Data were available from medical, neurological, and neuropsychological evaluations.[25] All participants underwent a standardized neuropsychological test battery examining multiple domains at baseline and subsequent assessments using the Mini-Mental State Examination, the Boston Naming Test, the Controlled Word Association Test, category naming, the Complex Ideational Material and Phrase Repetition subtests from the Boston Diagnostic Aphasia Evaluation, the Wechsler Adult Intelligence Scale–Revised Similarities subtest, the Mattis Dementia Rating Scale, the Rosen Drawing Test, the Benton Visual Retention Test, the multiple choice version of the Benton Visual Retention Test, and the Selective Reminding Test.[25]

DIAGNOSIS OF DEMENTIA

The diagnosis of dementia was established on the basis of all available information gathered from the initial and follow-up assessments and medical records. Dementia was diagnosed by consensus of neurologists, psychiatrists, and neuropsychologists based on *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) criteria.[26] The diagnosis of LOAD was based on the National Institute of Neurological Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria.[27] A diagnosis of probable LOAD was made when the dementia could not be explained by any other disorder. A diagnosis of possible LOAD was made when the most likely cause of dementia was LOAD, but there were other disorders that could contribute to the dementia, such as stroke and Parkinson disease. A diagnosis of dementia associated with stroke was made when the dementia started within 3 months of the stroke.

VASCULAR RISK FACTORS

APOE genotypes were determined as described by Hixson and Vernier[28] with slight modification. We classified persons as homozygous or heterozygous for the *APOE* ε4 allele or as not having any ε4 allele. At baseline, all participants were asked whether or not they had a history of hypertension any time during their life. If affirmative, they were asked whether or not they were under treatment and the specific type of treatment. Blood pressure was also recorded at each visit. The blood pressure cuff was placed on the right arm while the individual was seated, and a recording was obtained every 3 minutes over 9 minutes. The third measurement was recorded in the database. Values above 140 mm Hg (systolic) and 90 mm Hg (diastolic) were used as criteria for hypertension. Diabetes mellitus was also defined by self-report at baseline and at each follow-up interval and by the use of disease-specific medications. Heart disease was defined as a history of arrhythmia, myocardial infarction, congestive heart failure, or angina pectoris at any time during life. Waist to hip ratio (WHR) was calculated by measuring the waist circumference and dividing by the hip circumference at its widest part. Fasting plasma total cholesterol and triglyceride levels were determined using standard techniques. High-density lipoprotein cholesterol (HDL-C) levels were determined after precipitation of apolipoprotein B containing lipoproteins with phosphotungstic acid. Low-density lipoprotein cholesterol was recalculated using the formula of Friedewald et al.[29] Non-HDL cholesterol levels were calculated using the following formula: non-HDL-C=total cholesterol-HDL-C. At baseline, all participants were asked if they had ever been treated with statins. For assessment of smoking habit, a trigger question asked whether or not the individual ever smoked at least 1 cigarette per day for a

period of 1 year or more. If the answer to the trigger question was no, the subject was classified as a nonsmoker and no further questions were asked. Participants who answered the question affirmatively were classified as current smokers if they were still smoking or past smokers if they had quit smoking. Current and past smokers were additionally asked at what age they began smoking and how many cigarettes on average they had smoked or still smoked per day. Past smokers were also asked at what age they stopped smoking. Stroke was defined according to the World Health Organization criteria.[30] At baseline, the presence of stroke was ascertained from an interview with participants and their informants. Persons with stroke were confirmed through their medical records, 85% of which included results of brain imaging. The remainder were confirmed by direct examination.

STATISTICAL ANALYSIS

We chose an approach similar to that of Kivipelto et al.[14] First, we evaluated the distributions of vascular risk factors, demographic variables, and clinical characteristics at baseline. To calculate the risk scores, all vascular risk factors were first included separately in a Cox proportional hazards model adjusting for age, sex, education, and ethnicity. Factors that reached $P \leq .1$ were then simultaneously placed in a Cox proportional hazards model, first adjusting for age and sex (model 1) and subsequently for age, sex, education, ethnicity, and *APOE* ε4 genotype (model 2). Using the βcoefficients from these models, we then assigned a risk score for each factor. To make the scores approach an integer and easier to understand for the user, all coefficients were standardized so that the lowest had a value of 1. Since the lowest value was 0.14, all β coefficients were multiplied by 7.14 and then rounded to the closest integer. Subsequently, the risk score for an individual was obtained by summing the scores of each of the risk factors. Because of the large range of possible scores (0–60), we subsequently explored the risk of dementia based on the risk score categorized into 5 groups (quintiles). To minimize misclassification of vascular dementia as LOAD, we first used probable and possible LOAD as the outcome and then repeated all analyses using probable LOAD only. We performed all analyses using SPSS for Windows, version 16.0.

RESULTS

There were 92 cases of incident probable and possible LOAD and 80 cases of probable LOAD during 4182 person-years of follow-up. The general characteristics of the sample are shown in Table 1. Compared with persons who did not develop LOAD during follow-up, persons who became demented were older, less educated, more often Hispanic, and had a higher prevalence of diabetes, a higher WHR, and lower HDL-C levels at baseline (Table 2).

Of the risk factors assessed, age, sex, diabetes, hypertension, current smoking, HDL-C levels, WHR, education, ethnicity, and *APOE* ε4 genotype were associated with LOAD in individual Cox models at $P<.1$ (Table 3) and were included in a single model for the subsequent analyses simultaneously. Table 4 shows the β coefficients and odds ratios for probable and possible LOAD and probable LOAD only derived from this model and the risk scores assigned to each factor. Table 5 shows the risk of LOAD according to the 5 categories (quintiles) of the risk scores. The probability of LOAD increased with increasing risk score, and the increase was clearly highest in the highest risk score category. Compared with analyses in which we used probable and possible LOAD, the results did not change appreciably when we used probable LOAD only as the outcome. When only age and vascular risk factors were included in the score (eTable 2), the associations were attenuated but still showed an increase of LOAD risk with increasing risk score, with strongest risk in the highest category.

Based on this risk score, an 84-year-old man who has low HDL-C levels, does not smoke, has a low WHR, and does not have a history of diabetes or hypertension has a 3.7-fold

increased risk of LOAD. In contrast, an 84-year-old woman who smokes and has a high WHR, low HDL-C, and a history of diabetes has a 20.5-fold increased risk of dementia.

COMMENT

In the past decade, vascular disease and vascular risk factors, in particular diabetes, hypertension, smoking, heart disease, dyslipidemia, and obesity, have been implicated in the risk of LOAD.[13] While the specific mechanisms through which they affect the risk of LOAD are largely unclear, vascular risk factors may directly affect the deposition of amyloid-βprotein—the main putative culprit—in the brain[32,33] or they could be related through cerebrovascular disease. However, there is also evidence that they may act through other mechanisms. Diabetes may increase the risk of dementia via oxidative stress or protein glycosylation.[34] Type 2 diabetes is associated with hyperinsulinemia, and peripheral insulin is transported to the central nervous system across the blood-brain barrier.[35,36] Insulin receptors have been found in the hippocampus,[37] the part of the brain first affected by AD,[38] indicating the potential for peripheral insulin to cause direct injury in AD. Insulin-degrading enzyme in the brain is a regulator of extracellular amyloid-βlevels[39] inhibited by insulin.[40] Insulin also has a role in the regulation of phosphorylation of tau protein, the main component of neurofibrillary tangles.[37] Heart disease can lead to cognitive impairment through cerebral hypoperfusion or embolism[41] and is also known to be linked with the *APOE* ε4 allele, a known risk factor for AD.[42,43] Smoking may augment cholinergic metabolism by upregulation of cholinergic nicotinic receptors in the brain.[44] Cholinergic deficits, characterized by reduced levels of acetylcholine and nicotinic receptors, are found in AD.[45] Hypertension may also contribute to a blood-brain barrier dysfunction, which has been suggested to be involved in the etiology of AD[46] or through the formation of free oxygen radicals.[46] In addition, vascular risk factors increase the risk of cerebrovascular disease, and cerebrovascular disease seems to lower the threshold of amyloid pathology necessary to manifest dementia.[47]

We aimed to develop a risk score that allows clinicians to determine the risk of developing dementia in elderly populations and that can be used in genetic research to adjust for a compound variable of nongenetic risk factors. The dementia risk score we developed in the present study was based on the regression coefficients of age, sex, education, ethnicity, *APOE* ε4 genotype, and several common vascular risk factors that were individually associated with LOAD risk in our study (ie, age, sex, education, ethnicity group, *APOE* ε4 genotype, diabetes, hypertension, HDL-C levels, and WHR). The resulting risk score predicted dementia in this elderly population well: the probability of LOAD increased with a higher vascular risk score and a greater number of risk factors.

It is important to note that inclusion of additional factors on which we did not have information such as plasma amyloid-β measurements, cerebrospinal fluid biomarkers, neuroimaging markers, inflammation markers, or homocysteine levels may have further improved the predicitivity of the dementia risk score. There is evidence that changes in plasma amyloid β,[48] regional cerebral blood flow,[49] cerebral blood volume,[50–52] hippocampal volumes, posterior cingulate gyrus 1H protein magnetic resonance spectroscopy metabolites, white matter hyperintensity load,[53] presence of cortical and subcortical infarctions,[54] hyperhomocysteinemia,[55–58] atrial fibrillation,[59,60] and inflammation are associated with an increased risk of dementia,[61–68] and inclusion of some or all of these factors in future risk scores may improve predicitivity of the score. However, our score uses variables that are readily available in most studies and easy to calculate.

The score values were derived from βcoefficients of the logistic regression model. A more accurate reflection of risk would be the sum of the original coefficients. However, this

calculation would be less practical for clinical use. In our study the area under the curve was comparable with that of the model with original βcoefficients, suggesting that our simple scoring method did not result in an important loss of information.

Another important consideration in the use of our score is that the study sample was derived from participants in an urban multiethnic elderly community with a high prevalence of risk factors for mortality and dementia. They were aged 65 years or older at baseline and were followed up on average for 4.2 years. Thus, the score is applicable to the prediction of dementia risk in approximately 4 years only among elderly people who survive for about the next 4 years. It is possible that survival bias has affected our results, as it is reasonable to postulate that those who died before inclusion in the study had worse risk factor profiles than persons surviving up to inclusion in the study. If dementia were more prevalent during life in persons who died before enrollment in the study than in persons who were included in the study, our score would underestimate the effects of the individual risk factors. If those who died before inclusion in the study had worse risk factor profiles while dementia was less prevalent, the specificity of our risk score could be reduced. It is also important to note that there is a potential of misclassification of other types of dementia as LOAD. The diagnosis of LOAD was a consensus diagnosis based on clinical information that includes strokes and other features of clinical presentation such as time of dementia in relation to stroke. While imaging was used to confirm the clinical diagnosis of stroke in most cases, we did not have information on subclinical infarcts or white matter hyperintensities. However, we addressed the issue of misclassification of vascular dementia as LOAD by conducting sensitivity analysis using probable LOAD only. Compared with analyses in which we used probable and possible LOAD, the results did not change, indicating that misclassification of vascular dementia as LOAD is unlikely to explain our findings. The main reason we considered LOAD and not vascular dementia or all dementia as an outcome is that the purpose of this score is to be used as a simple summary score for adjusting for known risk factors in epidemiologic studies of LOAD, including LOAD genetics.

This study has important strengths. It is a prospective cohort study designed for the diagnosis of cognitive decline that has complete clinical and neuropsychological evaluation at each interval. Our study has sensitive measures of cognitive change in several specific domains including memory. In addition, we had the ability to diagnose dementia and cognitive impairment without dementia at baseline, thus allowing us to observe an unbiased sample.

Today there is no curative treatment for LOAD, which emphasizes the importance of primary prevention. In particular, vascular risk factors have been implicated in the risk of LOAD, suggesting that, at least partly, the same measures of primary prevention are implicated for the prevention of both LOAD and cardiovascular events. Our dementia risk score, which is based on the vascular risk profile in late life, predicts dementia well in our data set. For all vascular risk factors included in the score (diabetes, hypertension, dyslipidemia, and obesity), therapeutic interventions are widely available. While additional studies in other populations are needed to validate and further develop the score, our study suggests that this score could be a valuable tool to identify individuals in late life who might be at risk and benefit from lifestyle and therapeutic interventions. In addition, it could be used in genetic research of dementia to adjust for nongenetic confounding.

Acknowledgments

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Table 1

Demographic and Clinical Characteristics of the Study Population

Characteristic	No. (%) of Participants (n=1051)[a]
Age, mean (SD), y	75.66 (6.32)
Female sex	696 (66.2)
Education, mean (SD), y	10.97 (4.65)
Ethnicity[b]	
White	359 (34.2)
Black	322 (30.6)
Hispanic	350 (33.3)
≥1 APOE allele	259 (24.6)
Diabetes	176 (16.7)
Hypertension	687 (65.4)
Heart disease	278 (26.5)
Current smoking	91 (8.7)
HDL-C, mean (SD), mg/dL	48.47 (14.53)
Waist to hip ratio, mean (SD)	0.87 (0.07)

Abbreviation: HDL-C, high-density lipoprotein cholesterol.

SI conversion factor: To convert HDL-C to millimoles per liter, multiply by 0.0259.

[a] Some percentages are based on an incomplete sample owing to small amounts of missing data.

[b] Classified by self-report using the format of the 1990 US census.[31]

Table 2

Comparison of Characteristics Among Persons With and Without Incident LOAD

Characteristic	No. (%)[a]	
	Persons Without LOAD (n=959)	Persons Developing LOAD (n=92)
Age, mean (SD), y	75.27 (6.14)	79.74 (6.88)[b]
Female sex	636 (66.3)	60 (65.2)
Education, mean (SD), y	11.30 (4.50)	7.54 (4.77)[b]
Ethnicity[c]		
White	346 (36.1)	13 (14.1)[b]
Black	294 (30.7)	28 (30.4)
Hispanic	301 (31.4)	49 (53.3)[b]
≥1 *APOE* allele	232 (24.2)	27 (29.3)
Diabetes	152 (15.8)	24 (26.1)[b]
Hypertension	622 (64.9)	65 (70.7)
Heart disease	253 (26.4)	25 (27.2)
Current smoking	83 (8.7)	8 (8.7)
HDL-C, mean (SD), mg/dL	48.75 (14.58)	45.47 (13.79)[b]
Waist to hip ratio, mean (SD)	0.88 (0.07)	0.89 (0.08)[b]

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LOAD, late-onset Alzheimer disease.

[a] Significant at $P \leq .05$ vs persons not developing LOAD during follow-up.

[b] Some percentages are based on an incomplete sample owing to small amounts of missing data.

[c] Classified by self-report using the format of the 1990 US census.[31]

Table 3

Individual Risk Factors Related to Risk of Developing LOAD

Characteristic	β Coefficient	HR (95% CI)	P Value
Female sex	−0.035	0.90 (0.63–1.49)	.8
Age, y	0.118	1.125 (1.092–1.159)	<.001
Education, y	−0.19	0.83 (0.79–0.89)	<.001
Ethnicity			
White		1 [Reference]	
Black	1.10	2.96 (1.52–5.75)	.001
Hispanic	1.84	6.27 (3.35 to 11.72)	<.001
APOE ε4 allele			
None		1 [Reference]	
≥1	0.42	1.52 (0.96–2.39)	.07
Type 2 diabetes	0.71	2.04 (1.28–3.25)	.003
Hypertension	0.34	1.41 (0.90–2.22)	.1
Heart disease	−0.05	0.95 (0.59–1.52)	.83
Current smoking	0.62	1.85 (0.85–4.04)	.1
HDL-C, per unit increase, mg/dL	−0.03	0.97 (0.96–0.99)	.003
WHR, per unit increase	0.12	1.13 (1.09–1.16)	<.001

Abbreviations: CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LOAD, late-onset Alzheimer disease; WHR, waist to hip ratio.

Table 4

Cox Proportional Hazards Models Relating the Risk Factors Profiles With Risk of LOAD

Characteristic	Probable and Possible LOAD (n=92)				Probable LOAD (n=80)			
	β	P Value	HR (95% CI)	Risk Score	β	P Value	HR (95% CI)	Risk Score
Sex								
M	0		1 [Reference]	0	0		1 [Reference]	0
F	0.14	.66	1.15 (0.61–2.21)	1	0.13	.7	1.14 (0.51–2.54)	1
Age, y								
65–70	0		1 [Reference]	0	0		1 [Reference]	0
>70–75	0.809	.14	2.246 (0.76–6.62)	6	0.776	.22	2.174 (0.623–7.587)	6
>75–80	1.12	.04	3.065 (1.03–9.09)	8	1.559	.01	4.754 (1.447–15.614)	12
>80–85	1.862	.001	6.433 (2.07–20.03)	13	1.861	.006	6.433 (1.710–24.204)	14
>85	2.892	<.001	18.023 (5.93–54.77)	21	3.295	<.001	26.991 (7.797–93.434)	25
Diabetes								
No	0		1 [Reference]	0	0		1 [Reference]	0
Yes	0.461	.16	1.586 (0.83 to 3.01)	3	0.216	.58	1.241 (0.577–2.671)	2
Hypertension								
No	0		1 [Reference]	0	0		1 [Reference]	0
Yes	0.147	.63	1.158 (0.64–2.11)	1	0.027	.93	1.027 (0.540–1.953)	0
Current smoking								
No	0		1 [Reference]	0	0		1 [Reference]	0
Yes	0.684	.10	1.981 (0.88–4.49)	5	0.925	.04	2.521 (1.027–6.191)	7
Low HDL-C								
No	0		1 [Reference]	0	0		1 [Reference]	0
Yes	0.47	.21	1.6 (0.77–3.32)	3	0.466	.26	1.58 (0.711–3.541)	4
High WHR								
No	0		1 [Reference]	0	0		1 [Reference]	0
Yes	0.967	.003	2.629 (1.39–4.97)	7	1.139	.002	3.124 (1.542–6.327)	9
Education, y								
>9	0		1 [Reference]	0	0		1 [Reference]	0
7–9	1.103	.009	3.014 (1.32–6.87)	8	1.074	.02	2.928 (1.187–7.226)	8
0–6	1.506	0	4.507 (2.09–9.74)	11	1.325	.002	3.761 (1.612–8.773)	10

Characteristic	Probable and Possible LOAD (n=92)				Probable LOAD (n=80)			
	β	P Value	HR (95% CI)	Risk Score	β	P Value	HR (95% CI)	Risk Score
Ethnicity								
White	0		1 [Reference]	0	0		1 [Reference]	0
Black	0.664	.12	1.942 (0.84–4.52)	5	0.598	.23	1.819 (0.686–4.822)	5
Hispanic	0.522	.27	1.685 (0.67–4.22)	4	0.897	.08	2.451 (0.895–6.715)	7
APOE ε4 allele								
None	0		1 [Reference]	0	0		1 [Reference]	0
≥1	0.604	.04	1.829 (1.02–3.29)	4	0.616	.07	1.851 (0.961–3.566)	5

Abbreviations: CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LOAD, late-onset Alzheimer disease; WHR, waist to hip ratio.

Table 5

Risk of LOAD Based on Risk Score Categories

Risk Score	No. at Risk	Cases, No. (%)	HR (95% CI)	*P* Value
Probable and Possible LOAD (n=92)				
0–14	315	7 (2.2)	1 [Reference]	
15–18	225	13 (5.8)	3.74 (1.42–9.88)	.008
19–22	193	11 (5.7)	3.55 (1.31–9.62)	.01
23–28	187	33 (17.6)	12.57 (5.26–30.08)	<.001
>28	131	28 (21.4)	20.47 (8.38–49.99)	<.001
P value for trend				<.001
Probable LOAD (n=80)				
0–16	250	1 (0.4)	1 [Reference]	
17–21	189	7 (3.7)	3.381 (0.87–13.13)	.07
22–26	222	7 (3.2)	4.98 (1.36–18.19)	.01
27–32	184	15 (8.2)	14.01 (4.06–48.39)	<.001
>32	206	35 (17.0)	35.81 (10.81–118.61)	<.001
P value for trend				<.001

Abbreviations: CI, confidence interval; HR, hazard ratio; LOAD, late-onset Alzheimer disease.