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Observed Hearing Loss and Incident Dementia in a Multiethnic Cohort

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Abstract

Background/Objectives—Hearing loss (HL) may be a risk factor for incident dementia; however, this finding needs replication and extension to ethnically diverse samples for generalizability. The objective of this study was to determine whether observed hearing loss (OHL) is associated with incident dementia in a multiethnic population.

Design—Prospective epidemiologic cohort study

Setting—Community of Northern Manhattan

Participants—Subjects of the Washington Heights-Inwood Columbia Aging Project (WHICAP), a longitudinal study on aging and dementia in an ethnically diverse community (n=1,881).

Measurements—OHL was defined when observed by the examiner or by self-reported hearing aid use. Diagnoses of dementia were made by a consensus panel using standard research criteria. A Cox proportional hazards model was used to examine the relation of OHL at baseline to risk of incident dementia (mean 7.3 years, range, 0.9-20, SD=4.4).

Results—OHL was associated with 1.69 (95% CI=1.3-2.3; p<0.01) times the risk of incident dementia adjusting for demographics, cardiovascular risk factors, *APOE4* genotype, and stroke.

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When stratifying by race, the association of OHL with incident dementia was elevated in all groups but was statistically significant only among African Americans (HR=2.62, 95% CI=1.5-4.5; $p<0.01$).

Conclusion—OHL was associated with an increased risk of incident dementia in a multiethnic cohort. More study is needed to determine if HL contributes to dementia, and if treating HL can reduce the risk of dementia.

Keywords

observed hearing loss; dementia; Alzheimer's; aging; presbycusis

INTRODUCTION

Hearing loss (HL), long considered primarily a quality of life issue, has recently been recognized as a public health concern¹ Age-related hearing loss (ARHL), the most common form, results from idiopathic loss of the inner ear sensorineural epithelium. Several studies now note independent associations between ARHL and more severe conditions. This includes falls², hospitalization³, social isolation⁴, frailty², and even mortality^{5,6}. These associations are still present after adjustment for confounders such as age, diabetes, cardiovascular disease, and education.

One of the more concerning potential associations is with dementia, particularly given the high prevalence of ARHL. Independent associations of HL have been seen with both prevalent⁷ and incident⁸⁻¹¹ dementia. Dose-dependent relationships, whereby increasing HL levels lead to greater risk of incident dementia, have also been observed. In one study, subjects with mild HL had 1.9 times the risk of incident dementia, rising to 4.9 times for those with severe HL, after adjusting for confounders.⁸

HL may cause dementia through several mechanisms including increased cognitive load¹², change in brain structure/function^{13,14}, or reduced social engagement¹⁵. Conversely, HL and dementia may both result from a common etiology, such as vascular disease or other unknown factors.¹ If a causal relationship exists, treating HL would potentially reduce the risk of dementia.

Studies on the association between ARHL and dementia have been limited to primarily white populations. African Americans have been rarely studied, and even less common is inclusion of Hispanics.^{7-11,16-19} This limits the generalizability of findings in both the United States and world populations. The goal of this study was to examine the relation of baseline observed HL (OHL) with incident dementia in a multiethnic longitudinal cohort.

METHODS

Subjects and Data Source

Participants were drawn from the Washington Heights-Inwood Columbia Aging Project (WHICAP), an ongoing prospective epidemiologic cohort study. Begun in 1992, the study follows adults 65 years and older who are residents of Northern Manhattan. Additional

participants were recruited in 1999. Participants were identified through an ethnicity and age stratification process using a probability sample of Medicare beneficiaries aged 65 or older residing in three contiguous zip codes. After a baseline visit, participants were followed at 18-24 month intervals. At each follow-up visit, they received a comprehensive neuropsychological battery that included a dementia assessment. If testers noted observed hearing loss (OHL), they spoke louder or used hearing amplifiers when available. The procedures for cognitive testing were not otherwise modified.

The flowchart of enrollment and inclusion is detailed in Figure 1. A total of 4309 subjects were recruited from the 1992 and 1999 cohorts. If baseline covariate data were missing, they were filled, when possible, with values from the first through third follow-up visits. Those with no longitudinal follow-up (1269), continued missing covariate data (927), and baseline dementia (197) were sequentially excluded. The majority of missing covariate data (773 subjects) was from lack of *APOE* genotyping because not all participants agreed to provide a blood sample. This left 1881 subjects in the baseline cohort for analysis. These subjects were followed for a mean of 7.4 years (range: 0.9 to 22 years, SD: 4.6 years), during which time 377 developed incident dementia. Follow-up was truncated at 20 years to control for the small sample size at the later follow-up periods.

Nineteen percent of whites, 23% of blacks, and 20% of Hispanics did not have any longitudinal followup data (significantly different among groups, $p=0.04$). Length of followup was not significantly different in those with dementia versus those without dementia among whites (7.0 years vs 7.2 years, respectively; $p=0.75$) or blacks (6.5 years versus 6.9 years, respectively; $p=0.41$). Length of followup was actually longer in those with dementia versus without dementia among Hispanics (9.0 years versus 7.6 years, respectively, $p=0.01$). Twenty eight percent of whites, 37% of blacks, and 32% of Hispanics were missing covariate data (significantly different among groups, $p<0.001$). However, when ignoring those with missing *APOE* genotyping, there were no significant differences in missing covariate data among groups (14% of whites, 15% of blacks, 17% of Hispanics; $p=0.32$).

Exposure

The primary exposure was OHL. OHL was defined as a binary variable (present/absent) and was created from 5 other hearing-related variables based on examiner observations at different times during the visit: (1) hearing normal/abnormal (2) hearing normal/abnormal [repeat of first variable occurring later during the visit] (3) no impairment in hearing/some difficulty hearing/must speak loudly/must shout/can't rate (4) auditory ability adequate/inadequate (5) has hearing aid: no/yes. If any hearing loss was noticed in any of the variables, or if the subject wore hearing aids, OHL was considered present. If no hearing loss was noted in any of the variables, and if the subject did not wear hearing aids, OHL was considered absent. Otherwise, OHL was coded as missing.

OHL was analyzed both as a time-constant variable (defined only at baseline) and time-varying variable. For the time-varying analysis, OHL was considered prevalent for the remaining duration of the study after it was initially observed.

Outcome

The primary outcome was all-cause dementia (present/absent). A neuropsychological battery²⁰ was performed at baseline and all follow-up visits. The battery included measures of memory (Selective Reminding Test, Benton Visual Retention Test), orientation (10 items from the Mini-Mental State Examination), language (multiple tests²⁰), abstract reasoning (subtests of the Wechsler Adult Intelligence Scale-Revised and the Mattis Dementia Rating Scale) and construction/visuospatial functioning (Rosen Drawing Test, Benton Visual Retention Test Matching). Consistent with the *DSM, 3rd Edition*²¹, memory was the key-defining feature; impairment was required in 2 of 3 memory areas. In addition, impairment was required in at least 2 of the orientation, language, abstract reasoning, and construction domains.²⁰ Dementia was then applied using previously defined cutoff scores via a consensus panel of neurologists, neuropsychologists, and psychiatrists.²² We also examined Alzheimer's dementia and vascular dementia as secondary outcomes. The dementia subtype was based on research criteria for probable Alzheimer's disease (NINCDS-ARDA Work Group)²³ versus vascular dementia subtype (NINDS-AIREN Workshop)²⁴. Other dementia subtypes were uncommon and not analyzed as separate outcomes in this study.

Covariates

Age (in years) was calculated from birthdate and the date of the study visit. Other demographic variables were collected by self-report. This included gender (male/female) and ethnic/racial group (Hispanics, non-Hispanic black, non-Hispanic white). Only 1% of individuals were of "other" race and were excluded. Education was included as years of education. Joint monthly income was recorded categorically as US dollars, ranging from \$450 or less to \$4000 or more. Cohort was defined by the enrollment wave (1992 or 1999).

Hypertension (present/absent) was assessed by a combination of blood pressure measurement and self-report. Other cardiovascular risk factors were collected by self-report. This included history of diabetes mellitus (present/absent), heart disease (present/absent), and smoking (present/absent). Heart disease was defined by presence/absence of either myocardial infarction or congestive heart failure. Cardiovascular risk factors were chosen as covariates because they may increase the risk of both HL and dementia, thus potentially confounding the relationship between HL and dementia.^{8,25} To address possible multicollinearity of vascular risk factors, a composite cardiovascular disease variable was created. One point was assigned for each of the four individual cardiovascular disease variables that were present (hypertension, congestive heart failure, diabetes mellitus, and myocardial infarction) as previously used in this cohort.²⁶

APOE genotyping was conducted using the approach by Hixson and Vernier²⁷ with slight modification. *APOE-ε4* genotype was considered present if the subject was homo- or heterozygous for the *APOE-ε4* allele. Stroke (present/absent) was assessed by self-report.

Statistical Analysis

Differences in baseline subject characteristics according to baseline OHL were assessed with the chi-squared test for categorical variables or the T-test for continuous variables. All mean values were presented with standard deviations.

Survival analysis was used to assess the trajectory of incident dementia over time by HL status, without adjustment for confounders. Cox proportional hazard models were employed to study the relation of baseline OHL to onset of all-cause dementia, incident Alzheimer's dementia, or incident vascular dementia. Models were also stratified by race. Duration of follow-up was used as the time-to-event variable. Duration of follow-up was calculated using the subject's date of last follow-up minus the date at study entry (baseline). In a separate analysis, age was used as the time-to-event variable.

For one set of Cox analyses, all covariates, including OHL, were defined at baseline and used as time-constant variable in several models. In an additional analysis, all covariates were analyzed as time-varying variables.

To address the concern that OHL could be confused with cognitive impairment, we performed two additional analyses. First, all subjects with baseline memory impairment (worse than one standard deviation below mean on a memory battery) were eliminated. The memory battery included total immediate recall, delayed recall, and delayed recognition from the Selective Reminding Test²⁸. Second, participants who developed dementia within a 2-, 4-, or 6-year washout period from baseline were censored.

Multivariable Cox models included the covariates described previously. The proportionality assumptions of the Cox model were assessed graphically and by using the Schoenfeld residuals method.

Significance was considered at $p < 0.05$. Analyses were conducted with Stata 14.1 (StataCorp, College Station, TX). Institutional review board approval was obtained through Columbia University Irving Medical Center.

RESULTS

Baseline subject characteristics are detailed in Table 1. Eleven percent (204/1881) of subjects had OHL at baseline. Subjects with no baseline OHL were significantly more likely to be younger, female, and less likely to have congestive heart failure. The racial makeup was also significantly different ($p < 0.05$), in that African Americans were less likely to have OHL. Among those with OHL, 27% went on to develop dementia versus 19% in those without OHL ($p < 0.01$).

We compared the ethnic distribution of those with and without OHL who developed incident dementia and there was no significance difference ($p = 0.62$) (Of the 56 subjects with OHL who developed dementia, the racial makeup was 54% Hispanic, 29% black, and 18% white. Of the 321 of subjects without OHL who developed dementia, the racial makeup was 60% Hispanic, 27% black, and 14% white.)

The Kaplan-Meier failure curve appears in Figure 2. Participants with OHL at baseline developed dementia earlier and had a higher cumulative incidence than those without OHL. In all models, subjects were observed for 13,150 person-years.

Cox proportional hazard models were created to assess the risk of developing dementia over time, and to allow adjustment for covariates. (Table 2) There were a total of 377 cases. Adjusting for demographic factors (age, gender, ethnicity/race, education), the risk of incident dementia was 1.66 (95% CI=1.2-2.3; $p<0.001$) times higher in those with OHL compared with those without OHL. Additionally adjusting for cardiovascular risk factors did not appreciably change the hazard ratio (HR=1.65; 95% CI=1.2-2.2; $p<0.01$). Further adjusting for the *APOE-ε4* allele produced a modest change on the effect estimate (HR=1.71, 95% CI 1.3-2.3; $p<0.01$). Finally, additionally adjusting for stroke produce a modest change as well (HR=1.69, 95% CI=1.3-2.3; $p<0.01$) This latter model was defined as the working model.

In a sensitivity analysis, we treated all covariates as time-varying, instead of being only defined at baseline. The risk of incident dementia was similar to the risk observed in the working model (HR=1.53; 95% CI=1.2-1.9; $p<0.001$). In an additional sensitivity analysis, age was used as the time scale instead of time-on-study. The risk of dementia was slightly attenuated and remained significant (HR=1.52, 95% CI=1.1-2.0; $p<0.01$). Finally, adjusting for cohort did not greatly change the risk of dementia (HR=1.62, 95% CI=1.2-2.4; $p<0.01$). There was no interaction between cohort and OHL ($p=0.63$ for interaction term) or between carrying an *APOE-ε4* allele and OHL ($p=0.30$ for interaction term).

We conducted two additional analyses to address possible biased ascertainment of OHL because of cognitive impairment. First, elimination of subjects with baseline memory impairment did not attenuate the risk of incident dementia in those with OHL (HR=1.92, CI=1.4-2.7, $p<0.001$). Second, excluding subjects who developed dementia within a 2 (HR=1.67, CI=1.19-2.34, $p<0.01$), 4 (HR=1.84, CI=1.2-2.8, $p<0.01$), or 6 (HR=1.97, CI=1.1-3.4, $P<0.05$) year washout period also did not attenuate the risk.

Ethnic/racial group was a significant predictor of incident dementia as previously reported in WHICAP²⁹, even after adjustment for covariates ($p<0.001$). The interaction between OHL and ethnicity/race was not significant ($p=0.19$ for interaction term). However, ethnic/racial disparities in hearing health care have been previously demonstrated³⁰. Because our *a priori* hypothesis was that hearing loss may differentially impact people of different race/ethnicities, we stratified the working model by ethnicity/race. An increased risk of dementia with OHL was seen in all race/ethnic groups but reached statistical significance only among blacks (HR for blacks=2.62, 95% CI=1.5-4.5, $p<0.01$; HR for Hispanics 1.43, 95% CI=1.0-2.1, $p=0.08$; HR for whites=1.61, 95% CI=0.7-3.5, $p=0.23$). Risk changed slightly when additionally including joint monthly income into the model, however this did not affect the significance of associations (HR for blacks=2.89, 95% CI=1.7-5.0, $p<0.001$; HR for Hispanics 1.24, 95% CI=0.8-1.9, $p=0.31$; HR for whites=1.29, 95% CI=0.5-3.6, $p=0.63$.)

Finally, we looked separately at incident Alzheimer's dementia and incident vascular dementia (Table 2). In the full model, which adjusted for demographics, cardiovascular risk factors, and *APOE4* status, the risk of incident Alzheimer's dementia was 1.85 times higher in those with OHL (95% CI=1.3-2.6; $p<0.001$; 254 cases). This was higher than for vascular dementia, which did not reach statistical significance (HR=1.34 95% CI=0.51-3.5; $p=0.55$; 46 cases), although the number of incident cases was much smaller (46), which could have

decreased the power to detect a significant association. This association remained non-significant if vascular risk factors were not adjusted for (HR=1.39, 95% CI 0.5-3.6; p=0.50).

DISCUSSION

In this multiethnic cohort, OHL was associated with a 1.7 times increased risk of incident dementia. This association was independent of potential confounders including demographics (age, ethnicity/race, sex, and education), vascular risk factors, *APOE4* genotype, and stroke. These associations also were robust and remained in different models and sensitivity analyses, including different time scales and considering time varying covariates. These findings add to the growing body of literature associating ARHL with dementia, and extend the investigations to a more diverse population.

Our study is one of the few to study the relation of ARHL with dementia in multiple ethnic groups. Nearly 50% of participants were Hispanic, followed by blacks and whites. In prior studies, the percentage of white participants has ranged from 67-91%^{8,9,16,17} or, when unreported, has been in regions that are predominantly white^{7,10,11,18,19}. One study included a biracial group including 67% white and 33% African Americans, however Hispanics were not included.⁹ Extending finding to multiethnic groups is important to allow generalizability of findings.

The observed association between HL and incident dementia in our study (HR=1.69) was stronger (HR=1.27-1.55)^{9,10} than two similar longitudinal studies, although with overlapping confidence intervals, suggesting the magnitude of association may be similar. The association is weaker, however, than two other longitudinal studies (HR=4.94 for severe HL, or OR=2.40 per 10 dB rise in HL).^{8,11} Difference in magnitudes are not surprising as several variables differed between the studies, including the hearing construct (observed versus audiometric) and length of follow-up. Nonetheless, it is possible that our association was either underestimated or overestimated. One possible explanation for an underestimated association is that HL was not defined by formal audiometry, but rather by the examiner noticing hearing difficulty. This less accurate measure may bias the results towards the null hypothesis. Our finding could have overestimated the association if OHL biased the ascertainment of prevalent cognitive impairment differentially. However, sensitivity analyses excluding people with memory impairment and those who developed dementia within several years of OHL showed similar findings, suggesting that overestimation was unlikely.

The reason that increased risk of dementia with OHL was significant only among blacks is unknown. This finding was not explained by years of education or monthly income. Our study replicated several others demonstrating that African Americans are less likely to have ARHL.^{31,32} Because of this reduced susceptibility, it is possible that HL among African Americans represents a more severe exposure to a common cause. However, it is important to note that the p value for the interaction term for ethnic group and OHL was nonsignificant, and it is possible these ethnic differences are a chance finding.

We did not find an association between OHL and dementia among whites, which is contrary to prior studies in predominantly white populations⁸⁻¹¹. While our white population was

fairly large, it was still smaller than most other studies. Whites also had a lower rate of developing incident dementia overall compared with blacks and Hispanics. Our study thus may have been underpowered.

Finally, there is a concern that different degrees of missing data among ethnic groups could affect associations between OHL and dementia. Because subjects with dementia might be less likely to have continued followup, there is a particular concern of differential exclusion due to differential longitudinal followup. This is unlikely to have meaningfully affected our results, however, because subjects with baseline dementia were intentionally excluded from the analysis and participants who developed dementia were censored in the Cox time-to-event model at the visit at which they were classified as demented. In addition, sensitivity analysis excluding subjects who developed dementia years after study onset also did not affect results. Finally, among all three races, length of followup was not significantly shorter in those who developed dementia compared with those who did not develop dementia.

Only 4% of subjects reported using hearing aids. Furthermore, the amount of hearing aid use was not quantified.^{33,34}

One methodologic concern is that impaired cognition/dementia may have appeared to examiners as OHL, since both conditions may result in asking questions to be repeated or not following instructions. In addition, poor hearing could result in lower performance in cognitive testing independent of cognitive abilities. These explanations for our findings seem unlikely for several reasons. First, the association between OHL and incident dementia was not weakened even after eliminating subjects with baseline cognitive impairment, or after censoring subjects who developed dementia within a 2-, 4-, or 6-year washout period. The study examiners were also trained to observe specific signs of HL. The diagnosis of dementia was rigorous and made via a consensus panel, taking into account both cognitive and functional performance, although it is possible that HL could have affected both. Finally, the neuropsychological battery was conducted in a relatively quiet one-on-one office, or a home environment. Unless HL was profound, subjects should have been able to follow clearly spoken instructions.

There are several mechanisms that could link ARHL to dementia. (1) Increased attention required to decode a degraded auditory signal may monopolize cognition, leaving fewer resources available for processing the content of the message and for making memories.¹² (2) Prolonged ARHL may lead to a change in brain structure and function, for example, through atrophy of the auditory cortex^{13,14}. (3) ARHL may reduce social engagement, which in turn, may lead to a cascade of events that reduce cognitive stimulation, cognitive function, and increase risk of dementia¹⁵. The important implication of the aforementioned scenarios is that treating ARHL would potentially reduce the risk of dementia.

It is also possible that ARHL and dementia may share a common etiology, such as vascular disease.¹ This study attempted to control for this possibility by adjusting for cardiovascular confounders, and the associations remained robust. However, we cannot rule out that our findings could be explained by residual or unmeasured confounding. For example, HL could be an indicator of other features of advanced physiologic age that could be related to

dementia. Lastly, ARHL and dementia could have a common neurodegenerative etiology. However, neuropathological findings of Alzheimer's have not been found in the peripheral auditory pathways.^{35,36}

This study has limitations. A subject was considered to have HL when the examiner noticed that the patient had difficulty hearing. This was a subjective observation, and thus was a relatively insensitive measure. The true prevalence of HL in those aged 70 years and older has been estimated at nearly two-thirds.³⁷ The prevalence in this study, which included participants mostly aged 70 years and older, was far lower. This is not surprising, since mild HL is usually unrecognized in a quiet one-on-one examination setting. Therefore, OHL in this study was most likely moderate or worse. Failure to detect HL would have had the effect of attenuating our relative risk estimates.

This study has several advantages. The study population was multiethnic, allowing greater generalizability of findings. We defined HL both at baseline, and also as a time-varying variable (i.e., changing over time.) Studies that employ audiometry have not looked at changes in hearing over time^{8,9,11}, but we examined HL at baseline and also as a time-varying variable.

Future studies should use objective methods of assessing hearing, such as pure tone audiometry. Investigations of the mechanisms that may underlie the association between ARHL and dementia are also needed. Finally, whether treating ARHL can reduce incident dementia must be addressed.

In conclusion, ARHL was independently associated with incident dementia in a multiethnic population. The association was strongest in blacks. These relationships remained strong even when adjusting for vascular disease, a primary confounder in conceptual models. Future studies are needed to determine whether there is, in fact, a causal relationship between ARHL and dementia. HL is among the most common conditions affecting older adults, with a prevalence of 80% in those over 80 years old³⁸. Yet hearing aid use is low, under 25% for at least occasional use in this age group.³³ Should ARHL prove to be a modifiable risk factor for dementia, increasing its treatment rate could be one of the most effective strategies for risk reduction given its near-universal prevalence and low treatment levels.

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Figure 1.
Flowchart of enrollment and inclusion for the longitudinal analysis

Figure 2. Kaplan-Meier failure curve showing the cumulative incidence of dementia by observed hearing loss status (unadjusted for covariates). n=1881

Table 1Baseline Subject Characteristics According to Baseline Observed Hearing Loss Status^a

Characteristic	Total n=1881	No Baseline Observed Hearing Loss n=1677	Baseline Observed Hearing Loss n=204	P Value ^b
Age, mean (SD)	76 (6.3)	75 (6.0)	80 (7.1)	<0.001
Female gender, num (%)	1308 (70)	1179 (70)	129 (63)	<0.05
Race/ethnicity, num (%)				<0.01
Hispanic	752 (40)	670 (40)	82 (40)	
Black	576 (31)	531 (32)	45 (22)	
White	553 (29)	476 (29)	77 (38)	
Years of education, mean (SD)	10 (4.9)	10 (4.9)	9.8 (4.8)	0.33
Congestive heart failure, num (%)	83 (4.4)	64 (3.8)	19 (9.3)	<0.001
Diabetes mellitus, num (%)	325 (17)	288 (17)	37 (18)	0.73
Hypertension, num (%)	1142 (61)	1020 (61)	122 (60)	0.78
Myocardial infarction, num (%)	160 (8.5)	140 (8.4)	20 (9.8)	0.48
Development of dementia after baseline, num (%)	377 (20)	321 (19)	56 (27)	<0.01

^aBaseline cohort excluded those with dementia.^bP values are for comparison between no baseline observed hearing loss and baseline observed hearing loss. P values are from chi-squared test for categorical variables, or T-test for continuous variables.

Table 2

Cox Proportional Hazards Models for Incident Dementia Based on Observed Hearing Loss

	Primary Outcome: All-Cause Dementia		Secondary Outcome: Alzheimer's Dementia		Secondary Outcome: Vascular Dementia	
	Observed Hearing Loss	No Observed Hearing Loss	Observed Hearing Loss	No Observed Hearing Loss	Observed Hearing Loss	No Observed Hearing Loss
Cases/Total	56/204	321/1677	42/204	212/1677	41/204	5/1677
Model 1 Adjusted for demographics ¹	1.66 (1.2-2.3)	1.0	1.79 (1.3-2.5)	1.0	1.28 (0.5-3.3)	1.0
Model 2 Above + CV risk factors ²	1.65 (1.2-2.2)	1.0	1.78 (1.3-2.5)	1.0	1.24 (0.5-3.2)	1.0
Model 3 Above + <i>APOE4</i> genotype ³	1.71 (1.3-2.3)	1.0	1.85 (1.3-2.6)	1.0	1.34 (0.5-3.5)	1.0
Model 4 (Working Model) Above + stroke	1.69 (1.3-2.3)	1.0				

For all models, people without hearing loss are the reference group. All covariates were treated as time-constant variables (defined at baseline only) with duration of follow-up as the time-to-event variable. Ranges in parentheses represent 95% confidence intervals. All models used duration of follow-up as the time-to-event variable. CV=cardiovascular.

¹Demographic factors included age, gender, ethnicity/race, and years of education.

²CV risk factors included diabetes mellitus, hypertension, heart disease, and smoking.

³*APOE4* genotype was defined by homo- or heterozygosity for the *APOE4* allele.