Age of onset of hypertension and risk of dementia in the oldest-old: The 90+ Study

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Abstract

\textbf{Introduction:} We investigated the association between age of onset of hypertension and dementia risk in an oldest-old cohort.

\textbf{Methods:} Participants are from The 90+ Study, a population-based longitudinal study of people aged 90+ who are survivors from the Leisure World Cohort Study. We estimated hypertension onset age using self-reported information from The 90+ Study and Leisure World Cohort Study, collected about 20 years earlier. A total of 559 participants without dementia were followed every 6 months for up to 10 years.

\textbf{Results:} A total of 224 participants developed dementia during follow-up (mean = 2.8 years). Compared with those without hypertension, participants whose hypertension onset age was 80 to 89 years had a lower dementia risk (hazard ratio = 0.58, \( P = .04 \)) and participants with an onset age of 90+ years had the lowest risk (hazard ratio = 0.37, \( P = .004 \)).

\textbf{Discussion:} Developing hypertension at older ages may protect against dementia. Understanding the mechanisms for this lower risk is important for determining ways to prevent dementia in the very elderly.

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1. Introduction

Numerous studies have shown that midlife hypertension is associated with increased dementia risk in later life \cite{1-4}. The effects of developing hypertension in late old age, however, are uncertain and its association with dementia may change with age \cite{5,6}. In the Adult Changes in Thought (ACT) Study \cite{6}, increased systolic blood pressure (BP) was associated with increased dementia risk at ages <75 but with nonsignificant decreased risk at ages \( \geq 85 \). Most studies have not explored these relationships in the oldest-old (people aged 90+ years). As the oldest-old is the fastest growing segment of the population in the United States \cite{7} and other countries \cite{8}, dementia threatens to become a public health epidemic. Elucidating associations between potentially modifiable factors and dementia is crucial to reduce this burden in the oldest-old.

Our objective was to evaluate the association between hypertension and the risk of all-cause dementia in a population-based cohort of individuals aged 90+ years. We evaluated...
self-reported history of hypertension including age at first diagnosis as well as measured BP to stage hypertension and accounted for antihypertensive medication intake in our analyses.

2. Methods

2.1. Subjects

The 90+ Study is a population-based longitudinal study of aging and dementia. Participants are surviving members of the Leisure World Cohort Study (LWCS) [9], an epidemiological health study of a California retirement community established in 1981. The 13,978-member cohort was mostly female, Caucasian, and highly educated. Survivors aged 90 or older on January 1, 2003, on January 1, 2008, and on or after January 1, 2009 were invited to join The 90+ Study. As of July 17, 2013, a total of 1872 surviving members had been invited to participate and 1554 individuals (83%) had joined The 90+ Study (Fig. 1). Of the 891 who agreed to in-person longitudinal evaluations, 601 did not have dementia at baseline. Our analyses include the 559 participants who had an in-person evaluation, did not have dementia at baseline, and had additional follow-up. All participants provided informed consent, and the University of California, Irvine, institutional review board approved all procedures.

2.2. Assessments

Assessments (including neurological examination, neuropsychological testing, review of medical history, and medication use) took place between January 1, 2003 and July 17, 2013. Trained neuropsychological testers administered the neuropsychological test battery [10] including the mini-mental state examination (MMSE) [11] and modified MMSE (3MS) [12]. Neurological examiners (trained physicians or nurse practitioners) administered the Clinical Dementia Rating scale [13] and assessed functional abilities using the Functional Activities Questionnaire [14]. Assessments were repeated every 6 months at the research center or the participant’s home.

2.3. Cognitive status evaluation

Baseline cognitive status was determined from the neurological evaluation or MMSE score. Neurological examiners used MMSE and 3MS results and information from their examination to determine the presence or absence of dementia, applying Diagnostic and Statistical Manual of Mental Disorders, 4th edition criteria [15]. On the few occasions when MMSE scores alone were used to determine cognitive status, we used age- and education-specific cutoffs for dementia derived from this cohort [16].

Follow-up cognitive status was usually determined from in-person visits. When an in-person visit was not possible, follow-up occurred by telephone or mail with the participant or an informant. Information from informants included the Dementia Questionnaire [17,18] administered by telephone and a mailed questionnaire regarding the participant’s cognitive status [19] and functional abilities [14,20]. Participants who were followed-up by telephone completed the short version of the Cognitive Abilities Screening Instrument [21]. The diagnostic methods and incidence rates for dementia in this cohort have been previously presented and discussed [22].

2.4. History and age of onset of hypertension

As part of the LWCS questionnaire participants were asked, “Has a doctor ever told you that you had high blood pressure? If yes, please indicate how old you were when you were first told this.” Similarly, at The 90+ Study baseline visit, participants were asked, “Have you ever been diagnosed with high blood pressure. If yes, please give the approximate year when you were first diagnosed with this condition.” We estimated hypertension onset age by combining information from the LWCS collected about 20 years earlier (range, 16–31 years) and from the baseline visit from The 90+ Study. If a participant said “YES” in the LWCS, we used that age of onset. If a participant said “NO” in the LWCS but YES in The 90+ Study, we used the age of onset reported in The 90+ Study. Before analysis, people were classified into six “age of onset” categories representing age decades: “no hypertension,” “<70 years,” “70 to 79 years,” “80 to 89 years,” “90 years or older,” and “unknown age” for those with hypertension but who did not report an age.

2.5. Hypertension stage by blood pressure classification

At the 90+ baseline evaluation, BP was measured in a sitting position after several minutes of rest using standard sphygmomanometers and cuffs. BP was classified into four...
stages as determined by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [23]: “normal BP” (systolic <120 mm Hg and diastolic <80 mm Hg), “prehypertension” (systolic between 120 and 139 mm Hg or diastolic between 80 and 89 mm Hg), “stage 1 hypertension” (systolic between 140 and 159 mm Hg or diastolic between 90 and 99 mm Hg), and stage 2 hypertension (systolic ≥160 or diastolic ≥100 mm Hg). The “unmeasured” group includes people whose BP was not measured at baseline. Although developed for younger individuals, we used these stages for comparison with the literature.

2.6. Antihypertensive medications

Use of antihypertensive medications was assessed both in the LWCS questionnaire and during The 90+ Study baseline visit. The LWCS questionnaire asked whether participants had ever taken reserpine (Yes/No/Currently) or any other BP medicine (Yes/No/Currently). At the baseline visit of The 90+ Study, participants brought in their medication containers. The Cerner Multum Lexicon database was used to classify medications by drug type and to identify people taking the following categories of antihypertensive medications: β-blockers, diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, calcium channel blockers, antiadrenergic agents, and vasodilators.

2.7. Additional variables

Other medical histories reported at the 90+ baseline visit and considered as potential confounders included stroke, transient ischemic attack, diabetes, heart disease, and depression. Heart disease included any of the following diseases or surgeries: coronary artery disease, myocardial infarction, atrial fibrillation or other arrhythmias, heart valve disease, congestive heart failure, coronary artery bypass, or pacemaker placement. The highest level of education attained was also recorded.

2.8. Statistical approach

To examine the association between hypertension and dementia risk, we used Cox regression methods with age as the fundamental time scale. Participants were considered at risk for dementia and contributed person-years from age at baseline evaluation until either age at follow-up evaluation when first determined to have dementia or age at the last follow-up evaluation when determined not to have dementia. To decide which medical histories to include, we examined the bivariate associations between stroke, transient ischemic attack, heart disease, diabetes, and depression and our main independent variables (age of onset of hypertension and hypertension stage) using chi-square tests. We also examined the same variables in relation to dementia risk using Cox regression.

We first examined the association between a history of hypertension and risk of dementia. We analyzed hypertension history as reported at the LWCS and at The 90+ Study baseline visit. We then estimated the association between age of onset of hypertension and dementia risk using no hypertension as the reference group. As hypertension history may increase mortality, we also analyzed age of onset of hypertension with a Fine and Gray model [24] where dementia was the event of interest and death was a competing event (Supplementary Materials). Finally, we estimated the association between hypertension stage at baseline and dementia risk using normal BP as the reference. Hazard ratios (HRs) for dementia were estimated and adjusted for age (using age as the time scale), sex, education, and significant medical history variables. All analyses were repeated with adjustment for antihypertensive medications (user vs. nonuser) at the time of the LWCS or The 90+ Study. We also evaluated the potential for survival bias as described in Supplementary Materials. We used SAS 9.4 (SAS Institute, Cary, NC) for analyses.

3. Results

Average baseline age was 93.2 years (range, 90–103), most participants were women (71%), Caucasian (99%), and had greater than high school education (75%) (Table 1). During the follow-up period (average, 2.8 years; range, 0.4–10.2 years), 224 participants (40%) were diagnosed with dementia representing an incidence of 14.1% per year. The source of cognitive status determination at last follow-up was most often neurological examination (81%), followed by informant questionnaires (10%), telephone Cognitive Abilities Screening Instrument (7%), and MMSE score (3%).

Reported history of hypertension was 30% at the time of the LWCS and increased to 58% at the 90+ baseline visit (Table 1). With the combined information to estimate age of hypertension onset, 61% of participants reported having been diagnosed with hypertension. The most common age of onset was <70 years (28%) but 109 participants (19%) reported an age of onset of 80+ years. About half of participants (52%) had either stage 1 or stage 2 hypertension. At the 90+ baseline visit, approximately three-quarters of participants (73%) were taking at least one antihypertensive medication (Table 1); the most common types were diuretics (42%), β-blockers (29%), calcium channel blockers (26%), and ACE inhibitors (22%).

Evaluations of the association between medical histories and the main independent and dependent variables revealed that history of heart disease was associated with an increased dementia risk (HR = 1.30, P = .04) and with age of onset of hypertension (P < .001) but not with BP stage (P = .79). Histories of stroke (HR = 1.72, P = .01) or depression (HR = 1.53, P = .04) were associated with increased dementia risk but not with age of onset of hypertension or hypertension stage (all P > .50). Thus, heart disease was the only medical history included as a potential confounder.
Table 1
Characteristics of participants: The 90+ Study

| Characteristic                                | Mean (SD) [range]|
|-----------------------------------------------|------------------|
| Age at 90+ Study baseline, years              | 93.2 (2.5) [90–103]|
| Follow-up time for dementia, years            | 2.8 (2.0) [0.4–10.2]|
| Age at LWCS survey, years                     | 69.6 (4.4) [60–84]|
| Interval between LWCS and 90+ baseline, years | 23.6 (3.0) [16–31]|

| Number (%)|
|-----------|------------------|
| Women     | 398 (71.2)       |
| Caucasian | 553 (98.9)       |
| Education |                 |
| ≤High school | 139 (24.9) |
| Vocational/some college          | 189 (33.8) |
| College or higher degree         | 231 (41.3) |
| Hypertension history at LWCS     | 169 (30.2) |
| Antihypertensive medication use at LWCS | 126 (22.5) |
| Hypertension history at 90+ baseline| 321 (58.1) |
| Age of onset of hypertension     |               |
| No hypertension                  | 217 (38.8)     |
| <70 years                        | 157 (28.1)     |
| 70–79 years                      | 50 (8.9)       |
| 80–89 years                      | 68 (12.2)      |
| 90+ years                        | 41 (7.3)       |
| Unknown age                       | 26 (4.7)       |
| Hypertension stage at 90+ baseline* |             |
| Normal blood pressure            | 43 (7.7)       |
| Prehypertension                  | 162 (29.0)     |
| Stage 1 hypertension             | 164 (29.3)     |
| Stage 2 hypertension             | 125 (22.4)     |
| Unmeasured                       | 65 (11.6)      |
| Antihypertensive medication use at 90+ baseline* | | |
| All participants                 | 403 (73.4)     |
| According to age of onset of hypertension |               |
| No hypertension                  | 87 (41.1)      |
| <70 years                        | 145 (93.6)     |
| 70–79 years                      | 47 (94.0)      |
| 80–89 years                      | 65 (95.6)      |
| 90+ years                        | 36 (87.8)      |
| Unknown age                       | 23 (92.0)      |
| According to hypertension stage   |               |
| Normal blood pressure            | 30 (69.8)      |
| Prehypertension                  | 124 (78.5)     |
| Stage 1 hypertension             | 122 (74.9)     |
| Stage 2 hypertension             | 92 (74.8)      |
| No blood pressure measurement    | 35 (56.5)      |
| Medical history at 90+ baseline    |               |
| Heart disease1                    | 265 (47.4)     |
| Stroke                           | 53 (9.5)       |
| Transient ischemic attack        | 83 (15.4)      |
| Diabetes                         | 33 (5.9)       |
| Depression                       | 58 (10.5)      |
| Incident dementia during follow-up| 224 (40.1)     |
| Source of cognitive diagnosis at last follow-up |         |
| Neurological examination         | 451 (80.7)     |
| MMSE                             | 14 (2.5)       |
| Informant questionnaires          | 56 (10.0)      |
| Telephone CASI                   | 38 (6.8)       |

Abbreviations: LWCS, Leisure World Cohort Study; MMSE, mini mental state examination; CASI, cognitive abilities screening instrument.

NOTE. Missing data: antihypertensive medication use at 90+ baseline n = 10, stroke history n = 2, transient ischemic attack history n = 20, diabetes n = 3, and depression n = 5.

*Hypertension stages defined as normal = systolic <120 mm Hg and diastolic <80 mm Hg, prehypertension = systolic between 120 and

3.1. History of hypertension and dementia risk

We first examined the association between history of hypertension and dementia risk (Table 2). Hypertension at the time of the LWCS was unrelated to dementia risk (HR = 1.09, P = .56). In contrast, hypertension at the baseline 90+ visit was associated with a lower dementia risk (HR = 0.68, P = .005).

3.2. Age of onset of hypertension and dementia risk

Given the previous result regarding history of hypertension at two time points, we examined the association between age of onset of hypertension and risk of dementia (Table 3). Participants with onset at 80 to 89 years had a significantly lower risk of dementia compared with those with no history (HR = 0.58, P = .04) and those with onset at 90+ years had the lowest risk (HR = 0.37, P = .004). A test for trend showed a significant decreasing risk with increasing age of hypertension onset (P = .002) (Table 3). The HRs were virtually unchanged when analyses were adjusted for baseline use of any antihypertensive medication (Table 3) or for individual classes of antihypertensive medications (Supplementary Table 1), suggesting that the association between older age of hypertension and lower dementia risk is independent of antihypertensive medication use. A competing risk analysis showed similar results (Supplementary Fig. 1).

3.3. Hypertension stage and dementia risk

Compared with people with normal BP, people in all stages of hypertension showed lower, although nonsignificant, risks for dementia (Table 4). A trend for decreasing risk with increasing levels of hypertension was observed (P = .07) (Table 4). Results for analyses with adjustment for baseline use of any antihypertensive medication (Table 4) or for individual classes of antihypertensive medications (Supplementary Table 2) were almost identical, suggesting that the association between the BP stage and dementia risk is independent of antihypertensive medication use.

4. Discussion

In this cohort study of 559 participants aged 90+, history of hypertension reported at entry into The 90+ Study was related to a lower dementia risk compared with those with no history of hypertension. This reduced risk was limited to participants who reported onset of hypertension after

139 mm Hg or diastolic between 80 and 89 mm Hg, stage 1 hypertension = systolic between 140 and 159 mm Hg or diastolic between 90 and 99 mm Hg, and stage 2 hypertension = systolic \( \geq 160 \) or diastolic \( \geq 100 \) mm Hg.

1Heart disease includes a history of any of the following: coronary artery disease, myocardial infarction, atrial fibrillation or other arrhythmias, heart valve disease, congestive heart failure, coronary artery bypass, or pacemaker.
the age of 80 years. In addition, there was a trend for lower dementia risk with increasing severity of hypertension. These associations were independent of antihypertensive medication use. To our knowledge, our study is the first to report in the oldest-old and to include hypertension by age of onset.

Observational studies have consistently reported that hypertension during midlife (measuring BP directly) is related to an increased dementia risk and Alzheimer disease [1–4]. This association, however, changes with age and hypertension appears to no longer be a risk factor at very advanced ages [25]. The changing association with increasing age is evident in the ACT Study [6] and in a pooled analysis of the Rotterdam and Gothenburg H-70 studies [5]. In the ACT Study, a high systolic BP (>160 mm Hg) was associated with a greater dementia risk in the youngest group (65–74 years) but with a nonsignificant lower dementia risk (HR = 0.64) in the oldest group (≥85 years) [6]. In the Rotterdam and Gothenburg H-70 studies, higher systolic BP was not associated with dementia risk at younger ages (55–74 years, HR = 0.96 per 10 mm Hg; 75–84 years, HR = 0.95 per 10 mm Hg) but was associated with a decreased dementia risk at ages ≥85 years (HR = 0.89 per 10 mm Hg) [5]. Although significance of results is somewhat different, the interpretation is the same as ours: at older ages, dementia risk is lowest in people with the highest BP.

Other studies in the very elderly have also found associations between hypertension and reduced dementia risk. In the Kungsholmen project (average age at baseline = 86), a high diastolic BP (>90 mm Hg) was associated with a lower risk of developing dementia 6 to 9 years later (HR = 0.55) [26]. In contrast, a high systolic BP (>160 mm Hg) was not associated with dementia risk (relative risk = 1.2).

The association between hypertension and reduced dementia risk in the oldest-old can be explained in several ways. Table 2 and Table 3 provide a detailed analysis of the risk factors associated with dementia.

### Table 2
Hazard ratios of developing all-cause dementia in relation to history of hypertension

| History of hypertension | Adjusted for age, sex, education, and history of heart disease* (n = 559) | Adjusted for age, sex, education, history of heart disease, and antihypertensive medication use† (n = 549) |
|-------------------------|---------------------------------------------------------------|---------------------------------------------------------------|
|                         | Hazard ratio (95 % CI) | *P* value | Hazard ratio (95 % CI) | *P* value |
| At LWCS                 |                           |          |                           |          |
| No                      | 1.00 (reference) | — | 1.00 (reference) | — |
| Yes                     | 1.09 (0.82–1.46) | .56 | 1.25 (0.83–1.90) | .29 |
| At 90+ baseline          |                           |          |                           |          |
| No                      | 1.00 (reference) | — | 1.00 (reference) | — |
| Yes                     | 0.68 (0.51–0.89) | .005 | 0.67 (0.48–0.94) | .02 |

Abbreviations: CI, confidence interval; LWCS, Leisure World Cohort Study.

*Cox regression models adjusted for age by using age as the time scale and adjusted for sex, education, history of heart disease, and antihypertensive medication by including them as covariates.

†Antihypertensive medication at the LWCS was used for the LWCS history of hypertension analysis, and antihypertensive medication at the 90+ baseline was used for the 90+ baseline history of hypertension analysis.

### Table 3
Hazard ratios of developing all-cause dementia in relation to age of onset of hypertension

| Age of onset of hypertension | Adjusted for age, sex, education, and history of heart disease* (n = 559) | Adjusted for age, sex, education, history of heart disease, and antihypertensive medication use† (n = 549) |
|-----------------------------|---------------------------------------------------------------|---------------------------------------------------------------|
|                             | Hazard ratio (95 % CI) | *P* value | Hazard ratio (95 % CI) | *P* value |
| No hypertension             | 1.00 (reference) | — | 1.00 (reference) | — |
| Unknown age                 | 0.96 (0.55–1.66) | .87 | 1.07 (0.60–1.90) | .82 |
| <70 years                   | 0.79 (0.56–1.11) | .17 | 0.79 (0.54–1.17) | .24 |
| 70–79 years                 | 1.09 (0.69–1.73) | .72 | 1.11 (0.67–1.84) | .68 |
| 80–89 years                 | 0.58 (0.34–0.98) | .04 | 0.60 (0.34–1.06) | .08 |
| 90+ years                   | 0.37 (0.19–0.73) | .004 | 0.38 (0.19–0.76) | .007 |
| Test for trend†             | 0.83 (0.74–0.94) | .002 | 0.84 (0.74–0.96) | .01 |

Abbreviation: CI, confidence interval.

*Cox regression models adjusted for age by using age as the time scale and adjusted for sex, education, history of heart disease, and antihypertensive medication by including them as covariates.

†Antihypertension medication at the 90+ baseline was used for analyses.

Test for trend excludes people with unknown age of hypertension onset (n = 26).
Hypertension stages defined as normal = systolic <120 mm Hg and diastolic <80 mm Hg, prehypertension = systolic between 120 and 139 mm Hg or diastolic between 80 and 89 mm Hg, stage 1 hypertension = systolic between 140 and 159 mm Hg or diastolic between 90 and 99 mm Hg, and stage 2 hypertension = systolic ≥160 or diastolic ≥100 mm Hg.

Abbreviations: CI, confidence interval; BP, blood pressure.

Antihypertensive medication use at the 90+ baseline was used for analyses.

Test for trend excludes people with no BP measurement (n = 65).

ways. First, adequate cerebral perfusion may help maintain normal cognition. Individuals who develop hypertension very late in life may be successfully marshaling a physiological compensatory mechanism to maintain adequate cerebral perfusion in the face of age-associated vascular changes. In support of this hypothesis, individuals with lower cerebral blood flow have been found to have higher rates of cognitive decline [27] and prevalent dementia [28]. If increased BP is a compensatory mechanism, it would also help maintain adequate perfusion in other vital organs [29] and may explain the protective associations between increased BP and other outcomes such as mortality [30], frailty indicators [31], disability [32], and physical decline [33] in the very elderly.

Another explanation for the observed association may be that people with hypertension take medications that lower the risk of dementia. Studies of younger elderly have reported lower dementia risk in people taking different classes of antihypertensive medications [34–36]. These studies, however, have not included the oldest-old and we did not find similar effects (data not shown). Moreover, if antihypertensive medications were responsible for a lower risk, we would expect the lowest dementia risk in people taking medication for a long time (those with an early age of hypertension onset), rather than in people who have taken medications for a short time (those with oldest age of hypertension onset) as seen in our study. Furthermore, our results were essentially unchanged when adjusting for use of antihypertensive medications.

Our observed association could also be explained by reverse causality. Others have noted a BP decline a few years before dementia onset [26,37]. Thus, rather than lower BP being detrimental for cognition, decreasing BP may be a consequence of the neurodegenerative process. Although we cannot completely rule out this possibility, we previously observed in our cohort that BP declined at the same rate in those who died with and without dementia [38]. Thus, a decline in BP appears to be related to dying rather than to dementia onset.

Others have suggested selection bias as an explanation for the observed lower dementia risk in very elderly hypertensives [39]. This explanation rests on a scenario where hypertensives who are most likely to develop dementia imminently die at higher rates than hypertensives who are less likely to develop dementia imminently. If so, we would underestimate the incidence rates of dementia among hypertensives. To explore this possibility, we performed analyses that estimated the association between MMSE (as a surrogate for dementia risk) and death but found no evidence to support such selection bias as an explanation for our findings (see the Supplementary Material). Furthermore, if selection bias accounts for the observed protective effect of hypertension, other vascular diseases associated with increased mortality (such as stroke and heart disease) would be expected to have a similar protective effect, which was not the case in our study.

Our study has several limitations. First, The 90+ Study participants are mostly women (71%), Caucasian (99%), and well educated (75% high school graduates) and thus not representative of the oldest-old in the United States. These characteristics, however, reflect to some extent the demographics of the oldest-old in Orange County (76% women and 91% Caucasian) [40] and the United States (76% women and 88% Caucasian) [7]. Second, although our dementia follow-up was up to 10 years, our average follow-up was only 2.8 years because of the high mortality of participants. Third, as with all

Table 4
Hazard ratios of developing all-cause dementia in relation to hypertension stage

| Hypertension stage* | Adjusted for age, sex, education, and history of heart disease (n = 559) | Adjusted for age, sex, education, history of heart disease, and antihypertensive medication use (n = 549) |
|---------------------|-------------------------------------------------|-------------------------------------------------|
|                     | Hazard ratio (95% CI) | P value | Hazard ratio (95% CI) | P value |
| Normal BP           | 1.00 (reference)    | —       | 1.00 (reference)    | —       |
| No BP measurement   | 0.77 (0.41–1.46)    | .42     | 0.76 (0.40–1.45)    | .41     |
| Prehypertension     | 0.87 (0.50–1.53)    | .64     | 0.84 (0.48–1.48)    | .55     |
| Stage 1 hypertension| 0.75 (0.43–1.32)    | .32     | 0.75 (0.42–1.31)    | .31     |
| Stage 2 hypertension| 0.64 (0.35–1.15)    | .13     | 0.61 (0.34–1.11)    | .10     |
| Test for trend      | 0.86 (0.74–1.01)    | .07     | 0.86 (0.74–1.01)    | .07     |

Abbreviations: CI, confidence interval; BP, blood pressure.
Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jalz.2016.09.007.

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