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## Pulse Pressure in Relation to Tau-Mediated Neurodegeneration, Cerebral Amyloidosis, and Progression to Dementia in Very Old Adults

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### Abstract

**IMPORTANCE**—Increased pulse pressure associated with age-related arterial stiffening increases risk for Alzheimer dementia but the mechanism responsible for this association remains unclear.

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**Author Contributions:** Dr Nation had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Nation, Edmonds, Bangen, Delano-Wood, Scanlon, Edland, Salmon, Galasko, Bondi.

**Acquisition, analysis, or interpretation of data:** Nation, Bangen, Delano-Wood, Scanlon, Han, Salmon, Bondi.

**Drafting of the manuscript:** Nation, Bangen, Bondi.

**Critical revision of the manuscript for important intellectual content:** All authors.

**Statistical analysis:** Nation.

**Administrative, technical, or material support:** Nation, Bangen, Delano-Wood, Scanlon, Han, Salmon, Bondi.

**Study supervision:** Bondi.

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**Additional Information:** Alzheimer's Disease Neuroimaging Initiative data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California. The study was coordinated by the Alzheimer's Disease Cooperative Study at the University of California, San Diego.

**OBJECTIVES**—To determine the relationship between pulse pressure and cerebral spinal fluid biomarker profiles of preclinical Alzheimer disease, investigate whether observed relationships are stronger in adults with more advanced arterial age (> 80 years of age), and examine the relationship between pulse pressure and progression to dementia.

**DESIGN, SETTING, AND PARTICIPANTS**—In this retrospective cohort study, 877 participants without dementia (55–91 years of age) from the Alzheimer’s Disease Neuroimaging Initiative underwent baseline health assessment, including blood pressure assessment and lumbar puncture for determination of cerebral spinal fluid phosphorylated tau (P-tau) and  $\beta$ -amyloid 1–42. Participants have been followed up longitudinally since 2005. The last date of examination was October 15, 2013. Clinical follow-up between 6 and 96 months tracked progression to dementia.

**MAIN OUTCOMES AND MEASURES**—Regression and analysis of covariance analyses investigated relationships between pulse pressure and distinct cerebral spinal fluid biomarker profiles. Very old participants (80 years or older) were compared with younger participants (55–79 years of age) on clinical measures and pulse pressure  $\times$  age group interactions were investigated. Survival analysis examined the effect of baseline pulse pressure on progression to dementia. Covariates were age, sex, apolipoprotein E genotype, body mass index, vascular risk factors, and antihypertensive medication use.

**RESULTS**—Individuals with a P-tau-positive biomarker profile exhibited mean (SD) elevated pulse pressure regardless of age (62.0 [15.6]mmHg for a P-tau-positive biomarker vs 57.4 [14.0]mmHg for P-tau-negative biomarker;  $P = .04$ ). In very old participants, a further increase in pulse pressure was observed in those exhibiting both P-tau elevation and  $\beta$ -amyloid 1–42 reduction vs either biomarkers alone (69.7 [16.0]mmHg for both positive biomarkers vs 63.18 [13.0]mmHg for P-tau alone vs 60.1 [16.4]mmHg for  $\beta$ -amyloid 1–42 alone vs 56.6 [14.5]mmHg for negative biomarkers;  $P = .003$ ). Those with higher baseline pulse pressure progressed to dementia more rapidly (95% CI, 1.000–1.048;  $P = .05$ ; hazard ratio = 1.024). Systolic pressure exhibited similar relationships with Alzheimer disease biomarkers and progression to dementia in the very old subgroup ( $P < .05$ ) but showed no associations in the young old subgroup ( $P > .10$ ). Diastolic pressure was reduced in young old participants with isolated phosphorylated tau elevation ( $P = .04$ ).

**CONCLUSIONS AND RELEVANCE**—Pulse pressure, an index of vascular aging, was associated with neurodegenerative change prior to the onset of dementia across a broad age range. Among those with more advanced age, higher pulse pressure was also associated with cerebral amyloidosis in the presence of neurodegeneration and more rapid progression to dementia. Diastolic contributions to these biomarker associations were limited to young old participants whereas systolic contributions were found only in very old participants.

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Vascular risk factors are well-established susceptibilities for Alzheimer dementia<sup>1</sup> but their exact role in the pathophysiology of Alzheimer disease (AD) remains unclear.<sup>2</sup> Several studies have demonstrated associations between AD biomarkers and markers of vascular aging and aortic stiffening, including brachial artery pulse pressure.<sup>3–5</sup> These findings suggest a direct link between vascular aging and AD pathophysiology during the earliest stages of the disease.

A recent study found that markers of age-related arterial stiffening were associated with amyloid retention in very old adults (80 years of age and older),<sup>6</sup> a finding consistent with studies linking pulse pressure elevation to cognitive decline in this age group.<sup>7,8</sup> Growing evidence indicates that although vascular pathology is highly prevalent in AD,<sup>9,10</sup> it is even more common in the very old population,<sup>11</sup> suggesting that vascular aging may underlie or exacerbate the pathogenesis of AD in very old adults. Very old adults represent the fastest growing segment of the population at risk for dementia<sup>12</sup>; however, less is known about AD in these individuals, making the further characterization of prodromal markers in this group an important area of research focus.

We hypothesized that vascular aging may play a substantial role in the pathogenesis of AD and that this would be most apparent in the very old participants compared with the young old participants. Therefore, we investigated the relationship between pulse pressure, a well-established and easily obtained marker of vascular aging, and both cerebrospinal fluid (CSF)-based AD biomarker profiles and progression to dementia in young old (55–79 years of age) vs very old (80–91 years of age) participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI) Study.

## Methods

Data were obtained from the ADNI database (<http://adni.loni.usc.edu>). The primary goal of ADNI is to test whether neuroimaging, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early AD. The ADNI is the result of efforts of many coinvestigators from a range of academic institutions and private corporations. Participants have been recruited from more than 50 sites across the United States and Canada via newsletters, Internet-based communication, direct mail, and press releases. Inclusion criteria include the following: being 55 to 91 years of age, taking permitted medications for 4 weeks, having a study partner who can accompany the participant to visits, a Geriatric Depression Scale score of less than 6, a Hachinski Ischemic Scale score of less than or equal to 4, adequate visual and auditory acuity, good general health, 6 grades of education or equivalent work history, and the ability to speak English or Spanish fluently. Exclusion criteria for cognitively healthy participants and participants with MCI include any significant neurologic disease or history of significant head trauma. For more information, see <http://www.adni-info.org>. Institutional review board approval was obtained at each performance site for ADNI (more than 50 sites). Approval for this retrospective data analysis was obtained from the University of Southern California.

## Participants

Participants included 877 participants from ADNI1, ADNI Grand Opportunity, and ADNI 2 who underwent lumbar puncture at their baseline evaluation and completed a clinical evaluation that included blood pressure assessment, medical history, and a cognitive examination. All participants were classified as either cognitively healthy or having MCI at baseline. Progression to dementia was ascertained for a large subset of participants (n = 849) who were followed up with serial clinical assessments at varying intervals for different

lengths of time ranging from 6 months to 96 months (mean = 28.4 months). Criteria for MCI and dementia defined by the ADNI study are described in detail elsewhere.<sup>13</sup>

### Blood Pressure Assessment

Seated brachial artery systolic and diastolic blood pressures were obtained and pulse pressure was calculated as systolic pressure minus diastolic pressure. Mean arterial pressure was calculated as diastolic pressure plus one-third the pulse pressure.

### Vascular Risk Factors

Participant vascular risk factor burden was determined during clinical interviews and physical examinations at the study entry. For purposes of the present study, participant medical history data was screened for vascular risk factors until the date of baseline blood pressure using criteria derived from the Framingham Stroke Risk Profile.<sup>14</sup> Vascular risk factors included the following: a history of cardiovascular disease (ie, myocardial infarction, intermittent claudication, angina, heart failure, or other evidence of coronary disease), dyslipidemia (ie, hypercholesterolemia, low levels of high-density lipoprotein cholesterol, or hypertriglyceridemia), hypertension, type 2 diabetes mellitus, atrial fibrillation, evidence of carotid artery disease, and transient ischemic attack or minor stroke. Body mass index was calculated as weight in kilograms divided by height in meters squared. Medications were reviewed at the time of baseline evaluation and participants were divided into those who were taking antihypertensive medications vs those who were not. All major classes of antihypertensive medications were included.

### CSF and Genetic Biomarkers

All participants underwent lumbar puncture and AD biomarkers were assayed from obtained CSF samples, including  $\beta$ -amyloid 1–42 ( $A\beta$ 1-42), phosphorylated tau (P-tau), and total tau (T-tau).<sup>15</sup> When available, data from multiple assays of a single sample were averaged to provide more robust estimates. Biomarker profiles were determined using the following previously reported cutoff values for CSF AD biomarkers in ADNI<sup>15</sup>:  $A\beta$ 1-42 ( $< 192$  pg/mL), P-tau ( $< 23$  pg/mL), and T-tau ( $< 93$  pg/mL). All but 2 participants who were T-tau positive were also P-tau positive. Only the P-tau status was used in determining biomarker profiles. Participants were divided into those whose test results were biomarker negative for both  $A\beta$ 1-42 and P-tau ( $A\beta$ -Ptau-),  $A\beta$ 1-42 positive only ( $A\beta$ +Ptau-), P-tau positive only ( $A\beta$ -Ptau+), or both  $A\beta$ 1-42 and P-tau positive ( $A\beta$ +Ptau+).

Participants also underwent venipuncture. Blood samples were used to determine apolipoprotein E (APOE)- $\epsilon$ 4 carrier status and participants were divided into those with 1 or more copy of the APOE- $\epsilon$ 4 allele vs those without 1 or more copy of the APOE- $\epsilon$ 4 allele. Those carrying the APOE  $\epsilon$ 2/ $\epsilon$ 4 genotype ( $n = 12$ ) were excluded given the ambiguity associated with the presence of both an allele imparting increased risk ( $\epsilon$ 4) and an allele with a possible protective impact ( $\epsilon$ 2).

### Statistical Analyses

Data were initially screened for influential outliers and departures from normality using indices of skewness and kurtosis. The CSF  $A\beta$ 1-42, P-tau, and T-tau distributions exhibited

significant kurtosis, which was corrected by log transformation. Log-transformed values were used in all analyses. Age groups were compared on clinical, demographic, and CSF biomarker values using *t* tests for continuous variables and  $\chi^2$  analyses for categorical variables. Biomarker profile analyses investigated differences in pulse pressure across profiles using an analysis of covariance design ( $2 \times 4$  analysis of covariance; 2 age groups were young old vs very old) to examine the interaction between biomarker profiles and age group. Follow-up simple main effects analyses and least significant difference post hoc tests were conducted. Although there is no well established cutoff for determining pulse pressure elevation, prior studies used a cutoff of more than 63 mm Hg owing to its association with poor cardiovascular prognosis.<sup>16</sup> Thus, post hoc  $\chi^2$  analyses examined proportional differences in biomarker profiles between individuals with normal vs elevated pulse pressure using this cutoff. Multiple linear regression was used to determine continuous cross-sectional interactions and main effects for pulse pressure in association with biomarkers by age group. Cox regression investigated the relationship between baseline pulse pressure and progression to dementia using months to dementia diagnosis as the time variable.

All analyses were 2-tailed with significance set at  $P < .05$  for main effects and  $P < .10$  for interaction effects. All analyses controlled for age (except for age group interaction analyses), sex, APOE- $\epsilon 4$  carrier status, body mass index, cardiovascular disease, hypertension, type 2 diabetes mellitus, dyslipidemia, atrial fibrillation, carotid artery disease, transient ischemic attack/minor stroke, and use of antihypertensive medications. Given the relatively circumscribed number of analyses based on a priori hypotheses, multiple comparison correction was not applied.

Although the a priori focus of the present study was pulse pressure, given its importance as a marker of vascular aging and prior findings using this measure,<sup>3-5</sup> we repeated all primary analyses examining systolic, diastolic, and mean arterial blood pressure to determine whether findings were specific to pulse pressure. We did this because of its high correlation with systolic blood pressure and to disambiguate the relative contributions of systolic and diastolic pressure to the study findings, which may have provided mechanistic insight. Statistical methods for systolic, diastolic, and mean arterial pressure analyses were identical to those used in pulse pressure analyses.

## Results

### Demographic and Clinical Data

Results of participant age group comparisons on clinical, demographic, and biomarker profiles are presented in the Table. Compared with the young old group, the very old group contained proportionally more men ( $P = .03$ ) and individuals taking antihypertensive medications ( $P = .001$ ) as well as fewer APOE- $\epsilon 4$  carriers ( $P < .001$ ) and individuals with type 2 diabetes mellitus ( $P = .002$ ). The very old group also exhibited elevated systolic pressure ( $P = .007$ ) and reduced diastolic pressure ( $P = .02$ ), resulting in a more profound increase in pulse pressure ( $P < .001$ ), but there was no group difference in mean arterial pressure ( $P = .85$ ). The very old group contained a greater proportion of individuals whose test results were both A $\beta$ 1-42 and P-tau positive (A $\beta$ +Ptau+;  $P = .02$ ) but neither biomarker

alone ( $A\beta+P\tau-$  or  $A\beta-P\tau+$ ). There were no significant differences in individual CSF biomarker values between the groups.

### Biomarker Profiles

Results of the age group  $\times$  biomarker profile analysis ( $2 \times 4$  analysis of covariance) revealed a significant interaction in association with pulse pressure values ( $F_{3,834} = 2.23; P = .08$ ). Age-stratified analyses are displayed in Figure 1. In the young old age group, there were significant pulse pressure differences among biomarker profiles ( $F_{3,688} = 2.64; P = .05$ ) so that the  $A\beta-P\tau+$  group exhibited significantly higher mean (SD) pulse pressure compared with the  $A\beta+P\tau-$  group ( $P = .01$ ) and a nonsignificant trend toward higher levels than the  $A\beta-P\tau-$  group ( $P = .07$ ). Additionally, those whose test results were  $A\beta+P\tau+$  exhibited elevated mean (SD) pulse pressure compared with the  $A\beta+P\tau-$  group ( $P = .04$ ).

In the very old age group, there were greater pulse pressure differences among biomarker profiles ( $F_{3,133} = 5.30, P = .002$ ) so that the  $A\beta+P\tau+$  group displayed higher mean (SD) pulse pressure compared with the  $A\beta-P\tau-$  group ( $P = .003$ ) and a nonsignificant trend toward higher levels compared with the  $A\beta+P\tau-$  group ( $P = .06$ ).

Post hoc  $\chi^2$  analyses indicated that pulse pressure elevation ( $>63$  mm Hg) was associated with a 10% increase in the proportion of  $A\beta+P\tau+$  cases in the total sample ( $P = .001$ ) owing to a 9% increase in the young old group ( $P = .02$ ) and a greater than 15% increase in the very old group ( $P = .05$ ).

### Continuous Biomarker Relationships

Linear regression analyses indicated no significant age group  $\times$  pulse pressure interaction for P-tau ( $R^2 = 0.001; \beta = 0.015; P = .43$ ) or T-tau ( $R^2 < .001; \beta = 0.011; P = .95$ ) but there was a significant interaction for  $A\beta 1-42$  ( $R^2 = 0.004; \beta = -0.35; P = .04$ ). Age-stratified analyses indicated pulse pressure was significantly associated with reduced  $A\beta 1-42$  in the very old group ( $R^2 = 0.035; \beta = -0.20; P = .01$ ) but not the young old group ( $R^2 < .001; \beta = -0.007; P = .85$ ).

For the total sample, significant main effects were found for the association between pulse pressure and both P-tau ( $R^2 = 0.008; \beta = 0.094; P = .005$ ) and T-tau ( $R^2 = 0.008; \beta = 0.093; P = .004$ ).

### Cognitive Status

There was no significant difference in pulse pressure between the MCI and cognitively healthy groups at baseline after correcting for covariates ( $F_{1,839} = 1.37; P = .24$ ) and no significant interaction between cognitive status and biomarker profile in association with pulse pressure levels ( $F_{3,833} = 0.53; P = .67$ ). Length of clinical follow-up did not differ significantly between age groups ( $P = .20$ ). Cox regression analyses revealed very old participants with higher baseline pulse pressure showed more rapid progression to dementia compared with those with lower pulse pressure (95% CI, 1.000–1.048;  $P = .05$ ; hazard ratio = 1.024; Figure 2).

## Systolic, Diastolic, and Mean Arterial Blood Pressure

Systolic pressure results revealed similar age group  $\times$  biomarker profile interactions (Figure 3) but systolic pressure was not significantly related to biomarker profiles in the young old participants. Diastolic pressure analysis revealed evidence for an age group interaction in association with P-tau levels, with the  $A\beta$ -Ptau+ biomarker profile associated with reduced diastolic pressure in the young old group but not the very old group. Mean arterial pressure exhibited the same pattern of association with biomarkers found in the diastolic analysis in the young old participants but showed a statistically significant pattern in the very old participants similar to the systolic analysis. Systolic and mean arterial pressures were similarly predictive of more rapid progression to dementia. There were no significant relationships between blood pressure measures and progression to dementia in the young old group (see eAppendix 2 in the Supplement for statistical details).

## Discussion

The overall study findings indicated a clear relationship between the progressive increase in pulse pressure observed in advanced age and CSF P-tau elevation indicative of ongoing neurodegeneration. These findings were consistent across a broad age range (55–91 years of age) and cognitive spectrum (healthy cognition to MCI) and could not be accounted for by age, sex, APOE- $\epsilon$ 4 carrier status, body mass index, traditional vascular risk factors, or the use of antihypertensive medications. Results in this larger sample confirmed those of our previous study, indicating that increased pulse pressure is associated with neurodegenerative changes prior to the onset of major cognitive dysfunction.<sup>5</sup> Previous studies have largely focused on associations between pulse pressure and amyloid markers,<sup>3,4,6</sup> although examination of individual biomarker values in isolation can be misleading owing to high intercorrelations among different biomarkers (eg, P-tau and  $A\beta$ 1-42). The present study was able to disentangle these associations to examine independent relationships between pulse pressure and specific CSF biomarker profiles. Findings indicated that pulse pressure was related primarily to P-tau elevation and its interaction with  $A\beta$ 1-42 reduction rather than  $A\beta$ 1-42 reduction itself.

Until recently, the prevailing model of preclinical AD has held that cerebral amyloidosis indexed by  $A\beta$ 1-42 reduction is the first event marking the preclinical stage of AD followed by subsequent neurodegenerative change indexed by P-tau elevation.<sup>17,18</sup> However, previous work has called into question this sequence of events<sup>19</sup> because nearly one-quarter of older adults exhibit a profile of P-tau elevation in the absence of amyloidosis.<sup>20</sup> It is now recognized that AD neurodegeneration may not depend on prior amyloidosis.<sup>21</sup>

The updated model indicates that neurodegeneration reflected as tau pathology may emerge independently and ahead of amyloid pathology and may be accentuated by the later development of amyloidosis.<sup>22,23</sup> The association between pulse pressure and biomarker profiles observed in the present study was consistent with its potential role in this sequence of events. Findings from both linear regression and biomarker profile analyses agreed that the relationship between pulse pressure and  $A\beta$ 1-42 was only observed in the very old group and in participants whose test results were also P-tau positive. Pulse pressure elevation was associated with a 15% increase in the number of very old individuals exhibiting both  $A\beta$ 1-42



reduction and P-tau elevation. The very old participants were more likely to exhibit the A $\beta$  +Ptau+ profile, displaying the highest pulse pressure in the sample, with a mean higher than 13mmHg compared with the biomarker negative group. Although we cannot conclude causality from these cross-sectional associations, findings support the possibility that vascular aging may play a role in the pathogenesis and/or progression of AD through an amyloid-independent relationship with neurodegeneration and also facilitate the interaction between amyloid and tau pathologies. This possibility is further supported by the fact that higher pulse pressure predicted a more rapid progression to dementia in the very old group, where for every 5–mm Hg increase in pulse pressure there was a 12% increase in the odds of progressing to dementia across a 5-month period.

The Zlokovic<sup>24</sup> 2-hit hypothesis states that vascular disease may influence AD pathophysiology through the breakdown of the blood-brain barrier leading to leakage of neurotoxic blood products into the parenchyma or through chronic hypoperfusion. These cerebrovascular abnormalities may directly cause neurodegeneration independent of cerebral amyloidosis, a hypothesis consistent with the findings of the present study. We previously reported that pulse pressure elevation in the context of reduced cerebral blood flow is associated with AD, cerebrovascular disease, and cognitive dysfunction<sup>25</sup> and that these findings are particularly salient in the very old population.<sup>26</sup> Together, these studies further support a potential role for chronic hypoperfusion. Future work is needed to further investigate these possible mechanisms linking age-related vascular stiffening to neurodegeneration.

It has also been hypothesized that pulse pressure elevation may impair A $\beta$ 1-42 clearance through the disruption of paravascular drainage.<sup>27</sup> The present study findings suggest this mechanism may be primarily operating in individuals with very advanced age and ongoing neurodegenerative change. Thus, we speculate that pulsatile hemodynamics associated with advanced age may impair paravascular clearance of A $\beta$ 1-42 in the context of an aged and inelastic cerebrovasculature. It remains unclear whether pulse pressure itself plays a causal role or whether pulse pressure elevation represents an indirect index of age-related cerebrovascular stiffness. The present study findings may also be consistent with the hypothesis that AD is characterized by a general failure to clear misfolded proteins,<sup>23</sup> with the greater–molecular weight proteins (P-tau) impacted at lower doses of pulse pressure and smaller proteins (A $\beta$ 1-42) affected at higher doses.

The pattern of associations observed between pulse pressure and T-tau was similar to that of P-tau but somewhat attenuated. Prior work has suggested that P-tau and T-tau similarly index AD neurodegeneration<sup>15</sup>; however, it is also possible that T-tau levels may be more specific to axonal injury.<sup>28</sup> In this case, the observed relationships between pulse pressure and T-tau may be secondary to the previously described impact of pulsatile hemodynamics on white matter integrity.<sup>29,30</sup>

Although pulse pressure was the primary focus of the study, we examined systolic and diastolic pressure in relation to biomarkers to determine their contributions to the pulse pressure findings. Increased systolic blood pressure was associated with P-tau in the very old group but not the young old group while decreased diastolic pressure was associated

with P-tau in the young old group but not the very old group. This pattern of results was consistent with the hypothesized relationship between vascular aging and neurodegeneration because low diastolic pressure and widening pulse pressure in the young old group was likely owing to the emergence of age-related arterial stiffening. In the very old group, low diastolic pressure may be more indicative of cardiac dysfunction and the prevalence of isolated systolic hypertension increases owing to continued arterial stiffening.<sup>31</sup> Finally, the pattern of associations between mean arterial pressure and biomarker profiles was similar to that of diastolic pressure in the young old group and systolic pressure in the very old group. This likely reflects the greater relative contributions of diastolic and systolic pressures to mean arterial pressure in the young old group and very old group, respectively.

The present study focused on cross-sectional blood pressure values. Although higher blood pressure is associated with increased risk of dementia, there is actually a decline in blood pressure associated with the onset and progression of dementia.<sup>32</sup> Thus, the relationship between relative changes in blood pressure and biomarker profiles may differ from findings related to the absolute blood pressure values reported in the present study. These differences may pertain to bidirectional effects of blood pressure and AD pathophysiology because neurodegeneration and amyloidosis may alter blood pressure through their effects on brain stem regions involved in cerebral control of circulation.<sup>33</sup>

A strength of the present study was the large sample size, which allowed for examination of independent associations between pulse pressure and specific biomarker profiles, as well as longitudinal clinical follow-up that allowed for the investigation of progression to dementia. Another strength was our ability to statistically control for a variety of potential confounds. The principal study limitations included the cross-sectional and retrospective nature of the biomarker analyses. There was not a sufficient number of cases with serial biomarker data to generate biomarker profiles during the follow-up period. Future studies should investigate the relationship between blood pressure and biomarker profiles across time. We did note several clinicodemographic differences between our young old and very old age groups that should be considered in the interpretation of the study findings. Although we statistically controlled for relevant sample characteristics, the very old participants were more likely to be men and taking antihypertensive medications and less likely to be APOE-ε4 carriers or have type 2 diabetes mellitus. These demographic differences are atypical of those found in community-dwelling young old and very old adults and likely reflect ADNI sampling biases that may have differed substantially across the more than 50 centers contributing to the study. Additionally, ADNI inclusion/exclusion criteria yielded a sample with relatively low levels of cerebrovascular disease as well as other health issues. These considerations limit the generalizability the present study findings, suggesting that the replication of these results in a more representative community sample is warranted. An additional limitation was the uncontrolled and varying length of clinical follow-up in our progression to dementia analysis, although we did statistically control for this factor.

## Conclusions

The present study findings underscore the importance of the vascular contribution to neurodegeneration in the very old population and suggest a potential relationship between

vascular aging and both tau-mediated neurodegeneration and concomitant cerebral amyloidosis in this population. Future studies are needed to investigate the potential role of reduced cerebral blood flow, increased blood-brain barrier permeability, and reduced clearance of misfolded proteins as potential mechanisms linking vascular aging to AD pathophysiology.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Group Information

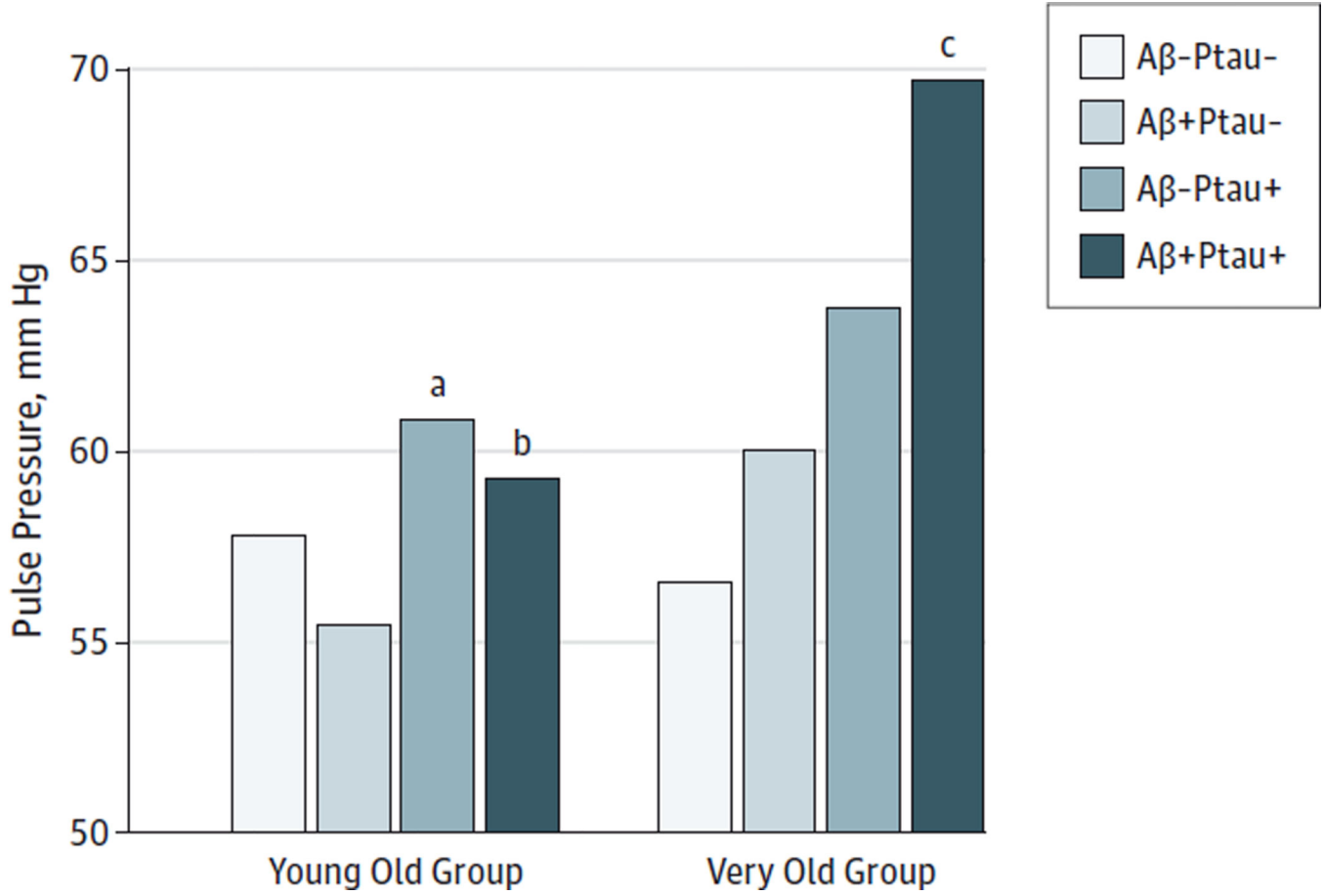
Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative database (<http://adni.loni.usc.edu>). As such, the investigators in the Alzheimer's Disease Neuroimaging Initiative contributed to the design and implementation of the Alzheimer's Disease Neuroimaging Initiative and/or provided data but did not participate in analysis or writing of this article. A complete listing of Alzheimer's Disease Neuroimaging Initiative investigators is in eAppendix 1 in the Supplement.

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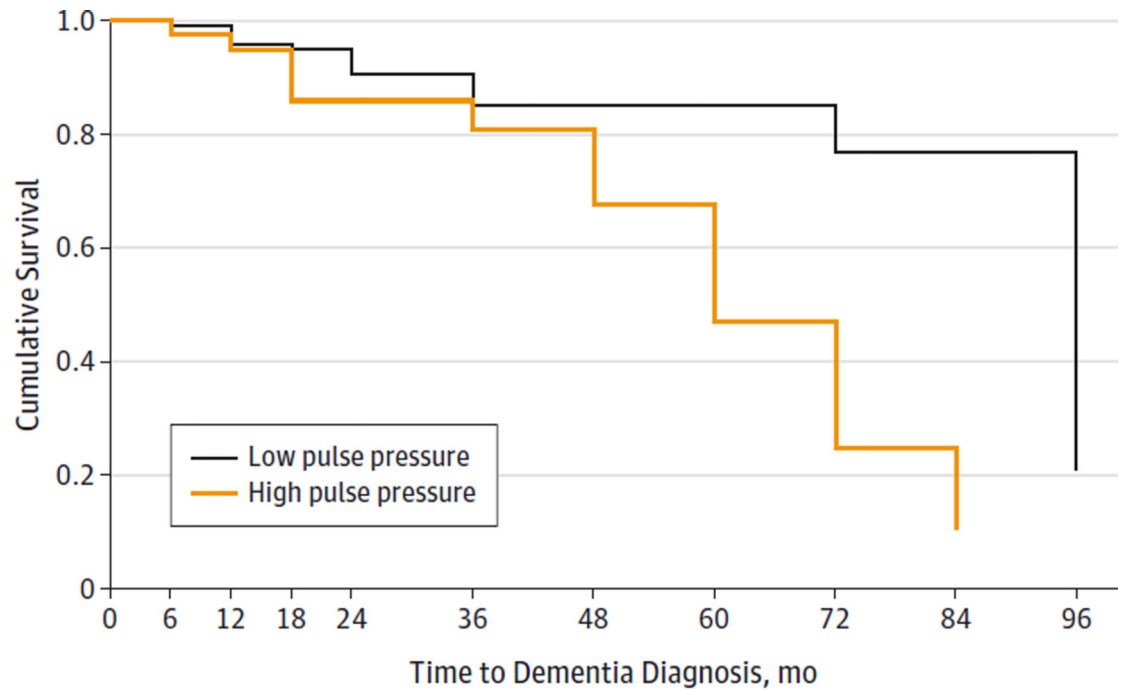
**Figure 1. Pulse Pressure by Alzheimer Disease Biomarker Profile in Young Old vs Very Old Participants**

Bar graphs display pulse pressure values (estimated marginal means) corresponding to different cerebrospinal fluid biomarker profiles in the young old and very old age groups. Aβ-Ptau+ indicates negative biomarkers for β-amyloid 1-42 and positive biomarkers for phosphorylated tau and Aβ+Ptau+, positive biomarkers for both Aβ1-42 and P-tau.

<sup>a</sup>*P* < .05 vs positive β-amyloid 1-42 only (Aβ+Ptau-).

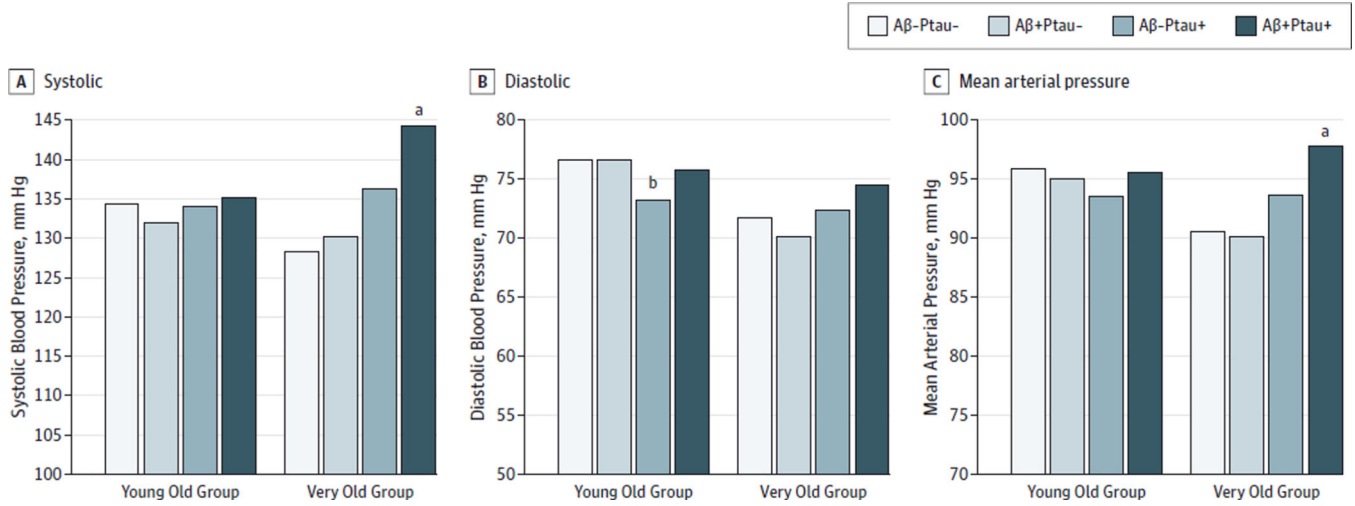
<sup>b</sup>*P* < .05 vs Aβ+Ptau- and *P* = .07 vs negative β-amyloid 1-42 and phosphorylated tau (Aβ-Ptau-).

<sup>c</sup>*P* < .001 vs Aβ-Ptau- and *P* = .06 vs Aβ+Ptau-.



No. at risk	0	6	12	18	24	36	48	60	72	84	96
Low pulse pressure	73	72	66	61	56	37	17	15	10	9	2
High pulse pressure	77	71	70	55	62	22	9	6	4	2	0

**Figure 2. Pulse Pressure Predicts More Rapid Progression to Dementia in Very Old Participants**  
 Cox regression indicating that higher pulse pressure was associated with more rapid progression to dementia in very old participants. For visual comparison, the survival plot displays results for high pulse pressure (>63 mmHg) in comparison with low pulse pressure (<63mmHg).



**Figure 3. Systolic, Diastolic, and Mean Arterial Blood Pressure by Alzheimer Disease Biomarker Profile in Young Old vs Very Old Groups**

Bar graphs display systolic, diastolic, and mean arterial pressure values (estimated marginal means) corresponding to different cerebrospinal fluid biomarker profiles in the young old and very old age groups. Aβ-Ptau+ indicates negative biomarkers for β-amyloid 1–42 and positive biomarkers for phosphorylated tau.

<sup>a</sup>*P* < .001 vs negative β-amyloid 1–42 and phosphorylated tau (Aβ-Ptau–) and *P* < .05 vs positive β-amyloid 1–42 only (Aβ+Ptau–).

<sup>b</sup>*P* < .05 vs Aβ+Ptau– and positive β-amyloid 1–42 and phosphorylated tau (Aβ+Ptau+) and *P* < .01 vs Aβ-Ptau–.



Clinical, Demographic, and Biomarker Data in Comparison With Young Old and Very Old Groups

Table

Clinical Demographics	Total (n = 877)	Young Old (n = 727)	Very Old (n = 150)	t	ory <sup>2</sup>	P Value
Age, y	72.6 (7.2)	70.4 (5.8)	83.1 (2.3)	NA	NA	NA
Education, y	16.1 (2.7)	16.1 (3.2)	16.2 (2.9)	-0.51		.58
Men, %	56.1	54.5	64.0	4.60		.03
APOE ε4+ genotype, %	41.0	44.1	26.2	16.44		.005
MCI diagnosis, %	68.6	68.7	68.0	.03		.88
BMI <sup>d</sup>	27.1 (4.7)	27.3 (4.8)	26.4 (4.4)	1.94		.06
Blood pressure, mm Hg						
Systolic	134.9 (16.9)	134.2 (16.3)	138.7 (19.1)	-2.73		.007
Diastolic	75.1 (9.8)	75.4 (9.8)	73.3 (9.3)	2.36		.02
MABP, mm Hg	95.0 (10.4)	95.0 (10.2)	95.1 (11.1)	-.181		.86
Pulse pressure, mm Hg	59.9 (15.1)	58.8 (14.7)	65.4 (15.9)	-4.97		<.001
Vascular risk factors, %						
Cardiovascular disease	9.3	9.1	10.7	0.38		.54
Dyslipidemia	37.3	37.7	35.3	0.30		.57
Hypertension	34.7	39.3	33.7	2.32		.19
Atrial fibrillation	1.8	3.3	1.5	1.72		.13
Type 2 diabetes mellitus	6.3	7.4	0.7	9.64		.002
Carotid artery disease	0.9	2.0	0.7	2.38		.12
TIA/minor stroke	3.3	3.0	4.7	1.06		.31
Taking antihypertensives	49.9	47.4	62.0	10.54		.001
CSF biomarkers, pg/mL						
Aβ1-42	180.5 (54.3)	181.2 (54.2)	176.9 (54.8)	0.87		.36
P-tau	36.2 (21.0)	36.3 (21.9)	35.3 (16.3)	0.54		.56
T-tau	84.5 (50.7)	83.5 (53.2)	89.4 (41.9)	-1.30		.20
Biomarker profiles, %						
Aβ-Ptau-	23.1	24.0	18.7	2.00		.15

Clinical Demographics	Total (n = 877)	Young Old (n = 727)	Very Old (n = 150)	$t$	$\text{or}\chi^2$	$P$ Value
A $\beta$ +Ptau-	9.2	9.7	6.7	1.40		.23
A $\beta$ -Ptau+	19.1	19.5	17.3	0.37		.53
A $\beta$ +Ptau+	48.6	46.8	57.3	5.55		.02

Abbreviations: A $\beta$ 1-42,  $\beta$ -amyloid 1-42; APOE, apolipoprotein E; CSF, cerebrospinal fluid; BMI, body mass index; MABP, mean arterial blood pressure; MCI, mild cognitive impairment; NA, not available; P-tau, phosphorylated tau; TIA, transient ischemic attack; T-tau, total tau.

<sup>a</sup>Calculated as weight in kilograms divided by height in meters squared.