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# Systolic Blood Pressure Is Associated with Increased Brain Amyloid Load in Mild Cognitively Impaired Participants: Alzheimer's Disease Neuroimaging Initiatives Study

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**Keywords**
Alzheimer's disease · Apolipoprotein · Blood pressure · A-beta-amyloid · Mild cognitive impairment

**Abstract**
***Background:*** Cardiovascular disease (CVD), including elevated blood pressure (BP), is known to promote Alzheimer's disease (AD) risk. Although brain amyloid load is a recognized hallmark of pre-symptomatic AD, its relationship to increased BP is less known. The objective of this study was to examine the relationship of BP to brain estimates of amyloid-β (Aβ) and standard uptake ratio (SUVr). We hypothesized that increased BP is associated with increased SUVr. ***Methods:*** Using data from the Alzheimer's Disease Neuroimaging Initiative (ADNI), we stratified BP according to the Seventh Joint National Committee (JNC) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure Classification (JNC VII). Florbetapir (AV-45) SUVr was derived from the averaged frontal, anterior cingulate, precuneus, and parietal cortex relative to the cerebellum. A linear mixed-effects model enabled the elucidation of amyloid SUVr relationships to BP. The model discounted the effects of demographics, biologics, and diagnosis at baseline within APOE genotype groups. The least squares means procedure was used to estimate the fixed-effect means. All analyses were performed using the Statistical Analysis System (SAS). ***Results:*** In non-ε4 carrier MCI subjects, escalating JNC categories of BP was associated with increasing mean SUVr using JNC-4 as a reference point (low-normal (JNC1) $p = 0.018$; normal (JNC-1) $p = 0.039$; JNC-2 $p = 0.018$ and JNC-3 $p = 0.04$). A significantly higher brain SUVr was associated with increasing BP despite adjustment for demographics and biological variables in non-ε4 carriers but not in ε4-carriers. This observation supports the view that CVD risk may promote increased brain amyloid load, and potentially, amyloid-mediated cognitive decline. ***Conclusion:*** Increasing levels of JNC classification of BP is dynamically associated with significant

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changes in brain amyloid burden in non-ε4 carriers but not in ε4-carrier MCI subjects. Though not statistically significant, amyloid burden tended to decrease with increasing BP in ε4 homozygote, perhaps motivated by increased vascular resistance and the need for higher brain perfusion pressure.


## Introduction

Epidemiological studies have shown that risk factors for vascular diseases, such as diabetes mellitus and hypertension (HTN), are also associated with increased risk for cognitive decline [1–4]. Evidence for an association between late-life high blood pressure (HBP) and cognition is mixed [5]. However, most have reported that HBP in mid-life is associated with more significant late-life cognitive decline, particularly in executive function and attention, and with the development of dementia [6–8]. Similarly, HTN in healthy adults is associated with poorer cognitive performance [9], increased rate of brain shrinkage [10], degraded white matter connectivity [11], and greater regional brain iron concentration [12]. Thus as an age-related cerebrovascular risk factor, HBP promotes white matter alterations and potentially Alzheimer's disease (AD) [13]. However, whether and how it influences amyloid deposits in the brain, therefore, AD development is less understood.

Amyloid-β (Aβ) accumulation in the brain [14] is a pathological feature of AD and underlies cognitive impairment and dementia. Transport of Aβ across the blood-brain barrier is one of the mechanisms regulating the concentration of Aβ in the central nervous system [15]. Also, peripheral Aβ interacts with the cerebral vasculature to modulate Aβ deposition in the brain [16]. Elevated levels of Aβ or the intracellular soluble Aβ protein correlate with the loss of neuronal synapses and cognitive impairment [17]. Brain amyloid load is the hallmark of pre-symptomatic AD, such as mild cognitive impairment (MCI). Notably, increasing evidence suggests that HBP may directly impact Aβ accumulation. In a recent review, Hughes et al. (2018) provided an overview revealing the complex relationship between increased blood pressure (BP), cognition, and AD [18]. However, Arvanitakis et al. (2018) found little evidence that increased BP increased the odds of amyloid pathology [19]. In another study examining the relationship among HTN, beta-amyloid, and neurodegeneration biomarkers of AD, Jeon et al. [20] concluded that regardless of APOE ε4 status, AD patients with HTN had significantly lower Aβ deposition than those without HTN. Collectively, though several studies support the view that HBP may enhance the accumulation of Aβ in the brain [12, 21], the relationship remains inconsistent, and modulating factors need more nuanced understanding [22–25].

Among the multiple genetic variants identified as risk factors for AD, the apolipoprotein E ε4 allele (APOE ε4) is the most consistent genetic polymorphism [26] associated with increased risk for cognitive decline and dementia [27–32]. Individuals with two copies of the APOE ε4 allele have a 10–12-fold risk for AD compared with ε3 homozygotes [33]. Interestingly, the APOE ε4 polymorphism is also a risk factor for vascular disease [34, 35]. Although the APOE gene regulates the levels of the multifunctional lipid transporter, its relationships to levels of systolic BP (SBP), diastolic BP (DBP), and Pulse Pressure (PPR) need a more nuanced understanding. Similarly, the differential effects of the APOE gene on the relationship of BP with brain Aβ accumulation need improved understanding. Thus, genetic and vascular risk factors, including Aβ, may work synergistically to influence the neuropathological changes that result in cognitive decline. To test our hypothesis that BP affects Aβ standard uptake ratio (SUVr) in MCI subjects, we examined the relationship of BP to SUVr using Alzheimer's Disease Neuroimaging Initiative (ADNI) data. We hypothesized that increased BP is associated with increased SUVr in patients with MCI. We also determined whether alleles of the APOE gene differentially influenced BP effects on SUVr.

## Materials and Methods

Data for this analysis were downloaded from the ADNI database (http://adni.loni.usc.edu) on December 10, 2012. The ADNI was designed to improve methods for clinical trials by providing an extensive, publicly available database to inform cognitive deterioration leading to AD at an early stage and mark its progress through biomarkers [36]. In part, the goal of ADNI was to test whether neuroimaging, other biological markers, clinical measures, and neuropsychological assessments can be combined to inform cognitive deterioration from cognitively normal to MCI and AD. Participants in the ADNI study underwent baseline and periodic physical and neurological examinations and standardized neuropsychological assessments and provided biological samples [36]. The physical examinations included height, weight, SBP, and DBP measurements. Seated brachial artery SBP and DBP were obtained using the standard of care approach, and PPR was calculated as SBP minus DBP [37]. Our analysis was a cross-sectional study of longitudinally obtained data from the ADNI cohort.

The ADNI study also provided a rich set of amyloid positron emission tomography (PET) and several clinical and neuropsychological measures acquired from MCIs and other diagnostic categories in participants [38, 39]. Whereas our analysis is limited to

24-month data, the study followed participants over several years with additional years of data acquired in the ADNI-GO, ADNI-2, and now ADNI-3 projects [38]. Participants were classified as meeting the MCI inclusion criteria premise on the following: Mini-Mental State Examination (MMSE) [40] scores between 24 and 30 (inclusive), objective memory loss measured according to education-adjusted scores on the Wechsler Memory Scale Logical Memory II [41], Clinical Dementia Rating of 0.5 [36], absence of significant levels of impairment in other cognitive domains, essentially preserved activities of daily living, and absence of dementia.

Details of the ADNI study, including the acquisition of amyloid PET, have been previously published [41–44]. The analyses included participants who had brain amyloid PET scans at baseline and at 12 and 24 months and 2-year follow-up clinical evaluations. The time of the first amyloid PET scan underscored the baseline visit for each participant.

*Statistical Analysis*

The ADNI sample of 1,697 participants (at the time of download) consisted of 809 subjects genotyped at the APOE locus (non-ε4 carriers = 465; ε4 heterozygote = 277; and ε4 homozygote = 67). Among these subjects, 466 MCI participants identified for this analysis had data on SUVr. BP data from the ADNI studies were stratified according to the Seventh Joint National Committee (JNC) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure Classification (JNC VII). To discern the effects of low BP, the JNC1 was subdivided into two categories: low-normal and normal; and used univariate analysis to discern unique data characteristics and validate the assumption of normality. The Aβ SUVr was derived from the averaged frontal, anterior cingulate, precuneus, and parietal cortex relative to the cerebellum. We implemented a linear mixed-effects model (proc mixed) with restricted maximum likelihood to elucidate the relationships of amyloid SUVr to BP while accounting for demographics (age, gender, race, education) and biological effects (DBP, PPR, pulse rate, body mass index (BMI), and diagnosis at baseline), variables within APOE genotype groups. To discern fixed-effect means, we employed the least squares means (LS-means) procedure. All analyses were performed using the Statistical Analysis System (SAS), Research Triangle North Carolina [45].

## Results

To delineate categories of BP, we used the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) Classification for SBP and DBP measurements (Table 1). The BP measurements were classified as low-normal, normal, pre-HTN, stage I and II HTN.

The characteristics of the 860 ADNI participants are presented in Table 2 by BP categories; low-normal (56); normal (152); pre-HTN (360); stage I HTN (240), and stage II HTN (52). The mean age of the participants at baseline ranged from 71 to 75 years. The low-normal group was more educated (mean years of education = 16.55 (SD = 2.68)) compared to the stage II HTN category (mean years of education = 15.62 (SD = 3.02)). Men had greater representation in all categories than women, and the overall sample is ~87% whites. The sample included non-ε4 carriers (48.39%); ε4 heterozygotes (39.95%); ε4 homozygotes (11.66%). Among those with low-normal BP, the majority were ε4 heterozygotes (45.10%) compared to non-ε4 carriers (43.14%) and ε4 homozygotes (11.76%). The low-normal BP group had a normal mean BMI of 24.52 (3.69). As expected, the sample BMI increased as the BP categories increased, with stage II HTN having a mean BMI of 28.24 (5.77). However, the mean pulse rate was similar across the BP categories, with greater variability (14.26) among stage II HTN than in the other categories. In addition, cognitive scores (MMSE and ADAS 13) and AV-45 SUVr were similar across the different BP categories.

**Table 1.** Classification of BP (mm Hg)

| Classification | SBP, mm Hg | DBP, mm Hg |
|---|---|---|
| Low-normal (JNC 1) | <100 | <60 |
| Normal (JNC 1) | 100–120 | 60–80 |
| Pre-HTN (JNC 2) | 120–139 | 80–89 |
| Stage I HTN (JNC 3) | 140–159 | 90–99 |
| Stage II HTN (JNC 4) | ≥160 | ≥100 |

JNC, Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure Classification.

To test the relationship between SUVr and the different BP categories by APOE ε4 status, we performed a linear mixed-effects model (Table 3). To discount the effect of important confounders, all fixed-effects estimates included adjustments for demographics (age, gender, race, education), biologics (DBP, SBP, pulse rate, BMI), and diagnosis at baseline. Among non-ε4 carriers ($n$ = 256), with the stage II HTN as a reference, the low-normal group had a statistically significant lower SUVr than the stage II HTN group SUVr ($p$ value = 0.018). Similarly, the remaining BP groups had a statistically significantly lower SUVr than the stage II HTN group: normal ($p$ value = 0.036), pre-HTN ($p$ value = 0.017), and stage I HTN ($p$ value = 0.036) among non-ε4 carriers.

In a similarly adjusted fixed-effects model, participants' age was associated with increasing SUVr only among the non-ε4 carriers ($p$ = 0.008) and ε4 heterozygotes ($p$ < 0.0001). Further, DBP was significantly associated with decreased SUVr ($p$ value = 0.014) among the non-ε4 carriers. However, we observed no

**Table 2.** Characteristics of participants by BP classification

| Characteristics | Low-normal (*N* = 56) | Normal (*N* = 152) | Pre-HTN (*N* = 360) | Stage I HTN (*N* = 240) | Stage II HTN (*N* = 52) |
|---|---|---|---|---|---|
| Age at baseline (years) | 70.94 (8.46) | 72.21 (8.14) | 72.79 (7.60) | 73.90 (6.99) | 75.00 (7.79) |
| Education (years) | 16.55 (2.68) | 15.87 (2.89) | 15.96 (2.88) | 15.85 (2.76) | 15.62 (3.02) |
| Gender (% men) | 35 (62.50) | 87 (57.24) | 221 (61.39) | 136 (56.67) | 32 (61.54) |
| Race (% white) | 51 (91.07) | 147 (96.71) | 336 (93.33) | 221 (92.08) | 47 (90.38) |
| Race (% black) | 4 (7.14) | 3 (1.97) | 12 (3.33) | 8 (3.33) | 3 (5.77) |
| APOE ε4 status (%) | | | | | |
| Non-ε4 carriers | 22 (43.14) | 80 (53.33) | 168 (47.06) | 130 (54.17) | 23 (44.23) |
| ε4 heterozygote | 23 (45.10) | 54 (36.00) | 147 (41.18) | 89 (37.08) | 21 (40.38) |
| ε4 homozygote | 6 (11.76) | 16 (10.67) | 42 (11.76) | 21 (8.75) | 8 (15.38) |
| BMI | 24.52 (3.69) | 25.78 (3.74) | 27.33 (4.80) | 26.94 (4.47) | 28.24 (5.77) |
| Systolic (mm Hg) | 92.78 (4.52) | 110.99 (6.19) | 128.88 (6.28) | 145.76 (6.60) | 168.69 (11.29) |
| Diastolic (mm Hg) | 54.89 (3.95) | 66.04 (6.07) | 73.26 (7.63) | 77.76 (9.31) | 84.37 (10.04) |
| Pulse pressure (mm Hg) | 37.89 (6.57) | 44.95 (8.08) | 55.63 (9.46) | 68.00 (11.61) | 84.32 (14.26) |
| Pulse rate (beats/min) | 65.00 (12.01) | 64.52 (9.16) | 64.44 (9.71) | 66.55 (11.60) | 65.67 (11.26) |
| MMSE | 27.63 (1.72) | 27.84 (1.75) | 27.59 (1.83) | 27.51 (1.76) | 27.19 (2.09) |
| ADAS 13 | 17.47 (7.40) | 15.64 (6.66) | 16.41 (6.79) | 16.87 (6.70) | 17.64 (6.47) |
| Amyloid load (AV45 SUVr) | 1.27 (0.26) | 1.17 (0.23) | 1.18 (0.22) | 1.24 (0.21) | 1.19 (0.25) |

Values are mean ± SD when appropriate; MMSE, Mini-Mental State Examination; BMI, body mass index; ADAS 13, Alzheimer's Disease Assessment Scale; HTN, hypertension.

**Table 3.** Amyloid SUVr and JNC categories of BP in MCI by APOE ε4 status

| | Fixed effects | Standard error | *p* value |
|---|---|---|---|
| Non-ε4 carriers (*N* = 256) | | | |
| Overall model (residual) | | | 0.0004 |
| Intercept | 1.731 | 0.389 | <0.0001 |
| JNC 1: low-normal | −0.456 | 0.192 | 0.018 |
| JNC 1: normal | −0.275 | 0.131 | 0.036 |
| JNC 2: pre-HTN | −0.243 | 0.101 | 0.017 |
| JNC 3: stage I HTN | −0.165 | 0.078 | 0.036 |
| JNC 4: stage II HTN | – | – | – |
| ε4 heterozygote (*N* = 168) | | | |
| Overall model (residual) | | | 0.002 |
| Intercept | 0.447 | 0.492 | 0.366 |
| JNC 1: low-normal | −0.009 | 0.255 | 0.971 |
| JNC 1: normal | 0.049 | 0.164 | 0.763 |
| JNC 2: pre-HTN | 0.099 | 0.124 | 0.423 |
| JNC 3: stage I HTN | 0.096 | 0.095 | 0.317 |
| JNC 4: stage II HTN | – | – | – |
| ε4 homozygote (*N* = 42) | | | |
| Overall model (residual) | | | 0.131 |
| Intercept | −0.724 | 1.181 | 0.545 |
| JNC 1: low-normal | 0.736 | 0.488 | 0.143 |
| JNC 1: normal | 0.528 | 0.303 | 0.092 |
| JNC 2: pre-HTN | 0.287 | 0.228 | 0.219 |
| JNC 3: stage I HTN | 0.165 | 0.180 | 0.366 |
| JNC 4: stage II HTN | – | – | – |

Fixed-effects estimates modeling adjusted for demographics (age, gender, race, education), biologics (DBP, SBP, pulse rate, body mass index (BMI)), and diagnosis at baseline.

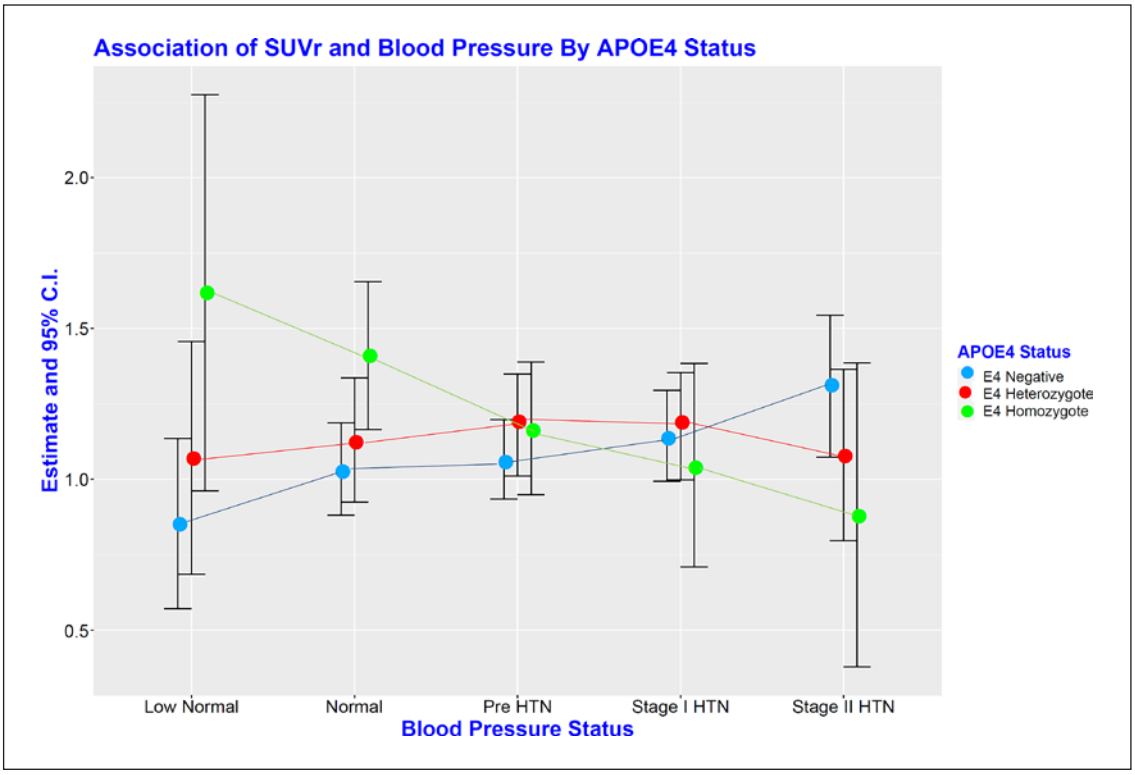


**Fig. 1.** Least squares mean (LS-mean) estimates from a linear mixed-effects model showing estimates and 95% CI of the association of SUVr with categories of blood pressure by APOE ε4 status. HTN, hypertension; APOE ε4, apolipoprotein ε4.

consistently discernable relationship of JNC-7 BP categories to SUVr among ε4 heterozygote ($n$ = 168) and ε4 homozygote ($n$ = 42).

Figure 1 shows LS-mean estimates from the linear mixed-effects model on the association of SUVr with categories of BP by APOE ε4 status. Among the non-ε4 carriers, the SUVr LS-mean tended to increase with increasing JNC-7 BP categories from low-normal to stage II HTN. This trend was reversed among the ε4 homozygotes with LS-means decreasing from low-normal to stage II HTN participants, though not significant in the fixed-effect model. Among ε4 heterozygotes, we observed no directional relationship between SUVr LS-means and BP.

## Discussion

In the current study, increasing JNC-7 classification of BP levels is dynamically associated with significant changes in brain amyloid burden (measured by SUVr) in non-ε4 carriers but not in ε4-carrier MCI subjects. This relationship of BP to brain amyloid burden is similarly influenced by ε4 carrier status, suggesting that increasing BP may enable increased amyloid accumulation in APOE non-ε4 carriers at the transitional stage of neurodegeneration. Paradoxically, and evidenced by the LS-mean, increasing BP may be advantageous in ε4 homozygote, though the threshold is undetermined. Increased vascular resistance promoted by amyloid deposition and the need for higher brain perfusion pressure may underlie this effect up to a specific BP threshold [21]. This finding is consistent with our previously published observation that changes in brachial artery pulse pressure (PPR), SBP, and DBP differentially influenced hippocampal volumes depending on the cognitive phenotype and APOE genotypic categories [46].

Data are scanty on the relationship of BP to brain amyloid load, and evidence on the relationship of BP to the cognitive phenotype is inconsistent. For example, Faraco, Park et al. reported that the effects of Aβ on both mean diffusivity alterations and global white matter hyperintensity were independent of HTN status [47]. The implication is that mediators besides hypertensive small vessel

disease may account for the observed effects [47] in APOE ε4 carriers. Therefore, APOE ε4 may overwhelmingly motivate amyloid deposition in ε4 carriers, while HTN likely promotes increased amyloid burden in non-ε4 carriers. Thus, increasing BP may harm the brain by enabling increased amyloid accumulation in non-ε4 carriers at the MCI transitional stage of neurodegeneration but not in ε4 carriers. Another study [48], with a relatively large sample size ($n$ = 1,406, aged 60–95 years), investigated the relationship between HTN and the modulating effects of APOE ε4. Their findings suggested that HTN was not associated with either ε2 or ε4 alleles in the model adjusted for age and gender or with the inclusion of other confounders. However, the investigators did not study the interaction between Aβ and APOE. Further, Rodrigue et al. showed that hypertensive APOE ε4 carriers did not have significantly different amyloid burdens compared to normotensive non-carriers [21]. Because their result is congruent with our current findings in MCI subjects (Fig. 1), it is possible that in APOE ε4 carriers with Aβ-mediated elevated vascular resistance, increased BP may promote perfusion and potentially mitigate Aβ effect on brain function.

Yet, studies reporting conflicting observations must be noted. In contrast to our observations in APOE ε4 carriers, Oberlin et al. [49] noted that the combined role of APOE ε4 and elevated SBP may synergistically compromise memory function long before the appearance of clinically significant impairment. These observations suggest that interventions targeting BP in APOE ε4 carriers during mid-life may reduce the risk of cognitive decline in APOE ε4 carriers [49]. Likewise, in a cross-sectional study to discern risk factors for Aβ deposition in cognitively healthy middle-aged and older adults (aged 47–89 years), Rodrigue et al. reported that HTN interacts with APOE ε4 allele to increase amyloid deposition in cognitively healthy middle-aged and older adults [21]. Accordingly, the mean cortical amyloid level was lowest in the normotensive APOE ε4-positive group, followed closely by the normotensive APOE ε4-negative group and the hypertensive APOE ε4-negative group. The hypertensive APOE ε4-positive group (mean age = 75 years) had significantly greater amyloid deposition than all other groups ($p$ = 0.05), implying an association between vascular risk and APOE ε4-positive in the elderly. However, in contrast to our analysis of the ADNI data, the study had a small sample size and did not include participants with MCI.

It is possible that other unknown factors may yet modulate the interaction of BP and the APOE gene on brain amyloid burden. Further, whether treatment of HTN influences the combined effect of APOE ε4 status and HTN on cognitive function is a subject of an ongoing investigation. For example, Kim et al. (2019) examined the interaction between APOE genotypes in both treated and untreated HTN on cognitive function in a recent analysis of Nurses' Health Study data [50]. Women with HTN and at least one APOE ε4 allele had poorer cognitive function than ε3/ε3 genotyped women without HTN; an observation amplified among APOE ε4 allele carriers with untreated HTN. Unfortunately, the study did not discern the interactive effect of amyloid load. In our current study, adjusting for age and DBP were associated with increased brain amyloid burden in non-ε4. The association of DBP with SUVr in the context of age was observed only among the non-ε4 carriers, suggesting that having the homozygote allele may exert effects over and beyond the effects of aging and brain amyloid burden.

We conclude that the disadvantageous effects of BP were most noticeable in non-ε4 carriers, were attenuated in ε4 heterozygote, and may be compensatory in ε4 homozygote to enhance perfusion pressure and potentially Aβ clearance in the groups at the highest risk of AD. This observation suggests the existence of an interaction between the APOE ε4 allele and HBP, which, if controlled in subjects with MCI, may delay the onset or risks of AD. Analysis of larger sample sizes is needed to validate our findings and address determinants of amyloid deposition in the aging brain and AD. In addition, similar studies in cognitively healthy persons might provide further insight into the relationship between SUVr and BP. Such studies will further inform additional mediating risk factors such as treatment of HTN and duration and inflammation.

### Strengths and Limitations

The approach used in this study enhances the understanding of the relationship between brain amyloid load, recognized as the hallmark of AD, with increased BP in MCI subjects. Potential limitations of this study include a small sample size in the ε4 homozygote group. In addition, BP was not an a priori outcome in the ADNI study; hence, assessing BP did not employ a unified procedure but followed current JNC 1–4 clinical standards. Furthermore, the inclusion of a diverse population in such studies may improve the generalization of the results. Nonetheless, our observation is unique and provides important insight into the field's current understanding. Future work on the longitudinal relationship between HTN,

APOE, and cerebral amyloidosis would undoubtedly increase our current understanding of the impact of SUVr and HTN on AD.


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## Statement of Ethics

According to ADNI protocols, all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee. The standards were also in accord with the 1964 Helsinki Declaration and its ensuing amendments. Before the enrollment of participants, written informed consent forms approved by the participating Institutional Review Boards were used to inform and obtain consent from prospective participants. Details can be found at https://adni.loni.usc.edu/ (no studies with human participants were performed by any of the authors included in this manuscript).

## Conflict of Interest Statement

The authors have no commercial associations that might be a conflict of interest in this article.


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## Author Contributions

Thomas V. Fungwe, Julius S. Ngwa, and Thomas O. Obisesan conceived, designed, and conducted the analyses of the study. Steven P. Johnson, Jilian V. Turner, Mara I. Ramirez Ruiz, and Oludolapo O. Ogunlana read and edited the manuscript. Fikru B. Bedada, Sheeba Nadarajah, and Oyonumo E. Ntekim assisted with the interpretation of the results and provided subject matter expertise. The ADNI collaborators were responsible for the collection and processing of the data.

## Data Availability Statement

Data used to prepare this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (https://adni.loni.usc.edu/). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and provided data but did not participate in the analysis or writing of this report. A complete listing of ADNI investigators can be found at http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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