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Differential Effect of APOE ε4 Status and Elevated Pulse Pressure on Functional Decline in Cognitively Normal Older Adults

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Abstract.
Background/Objective: The APOE ε4 allele and increased vascular risk have both been independently linked to cognitive impairment and dementia. Since few studies have characterized how these risk factors affect everyday functioning, we investigated the relationship between APOE ε4 genotype and elevated pulse pressure (PP) on functional change in cognitively normal participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI).
Methods: 738 normally aging participants underwent APOE genotyping, and baseline PP was calculated from blood pressure indices. The Functional Activities Questionnaire (FAQ) was completed by participants' informant at baseline and 6, 12, 24, 36, and 48-month follow-up visits. Multiple linear regression and multilevel modeling were used to examine the effects of PP and APOE ε4 genotype on cross-sectional and longitudinal FAQ scores, respectively.
Results: Adjusting for demographic and clinical covariates, results showed that both APOE ε4 status and elevated PP predicted greater functional difficulty trajectories across four years of follow-up. Interestingly, however, elevated PP was associated with greater functional decline over time in ε4 non-carriers versus carriers.
Conclusion: Results show that, although APOE ε4 status is the prominent predictor of functional difficulty for ε4 carriers, an effect of arterial stiffening on functional difficulty was observed in non-carriers. Future studies are needed in order to clarify the etiology of the association between PP and different brain aging processes, and further explore its utility as a marker of dementia risk. The present study underscores the importance of targeting modifiable risk factors such as elevated PP to prevent or slow functional decline and pathological brain aging.

Keywords: Activities of daily living, aging, apolipoprotein E4, arterial stiffness, genetic susceptibility

[1]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of the ADNI and/or provided data but did not participate in analysis or writing of this article. 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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INTRODUCTION

Alzheimer's disease (AD) is a chronic neurodegenerative disease and a growing global health concern, with its prevalence expected to triple over the next 50 years due to demographic increases in older populations and longer life expectancies [1]. In addition to cognitive decline, a central component of AD—both with respect to diagnosis and its devastating individual and societal effects—is the progressive loss of everyday functioning skills. Functional skills are normally classified into basic activities of daily living (ADL) which comprise various self-maintenance skills (e.g., bathing, dressing, grooming, and eating) and instrumental ADL (IADL) which involve more complex activities (e.g., managing finances, preparing meals, and using public transportation). Impairment in functional abilities significantly reduces independence and quality of life, while increasing caregiver burden and healthcare costs [2–4]). Moreover, the loss of functional independence due to cognitive impairment is a central criterion for AD diagnosis [5]. As such, identification of objective factors that predict functional decline among older adults has become a clinical and public health imperative.

More recently, arterial stiffness has been established as an important risk factor for cardiovascular events and maladaptive brain aging [6–8]. Arterial stiffness is marked by the degeneration of compliant elastin fibers and concomitant deposition of collagens, and thus increases steadily with advanced age [9]. The resulting decrease in arterial elasticity reduces the ability of arteries to accommodate the blood ejected from the heart during systole, and therefore increases the propagation of pulsatile pressure into the vascular structure of peripheral organs. These changes to arterial pulsatility ultimately result in damage to vulnerable microvascular tissue due to hypoperfusion and ischemia [10, 11]. As the brain has an especially high metabolic demand, it is particularly susceptible to the detrimental effects of these vascular alterations [12]. Accordingly, several studies have linked elevated pulse pressure (PP)—a proxy for arterial stiffness—to the presence of AD biomarkers [6, 7, 13], cognitive decline [8], and progression to dementia [7, 14]. It remains unclear, however, how PP relates to functional difficultly and decline in cognitively normal older adults.

It is well known that the presence of the ε4 allele of the apolipoprotein E (APOE) gene—the most prominent susceptibility gene for late onset AD—is associated with cognitive impairment and decline over time [15, 16]. Moreover, brain volumetric changes and white matter decrements associated with APOE ε4 status have been noted across the aging spectrum, often in the presence of one or more vascular risk factors [17–19]. Given established associations between APOE and neurocognitive impairment [20, 21], several studies have attempted to explore the relationship between APOE ε4 status and functional decline. Findings are mixed, with some studies showing direct links between APOE genotype and functional outcomes [22], while others have reported that the effect of APOE ε4 status exists only in the presence of other risk factors for decline such as female sex or baseline functional difficulties [23]. Still, others have found no effect of APOE ε4 on functional outcome [24]. These varied findings are likely explained by wide-ranging methodologies and samples across studies. For example, the extant literature has focused on several different populations (e.g., cognitively normal, MCI, and AD; high versus low "AD risk"), employed various different study designs, and has used functional assessment methods with ranging reliabilities.

Although PP and the APOE ε4 allele have both been independently linked to cognitive impairment and pathological brain changes across the aging spectrum, it remains unclear how these risk factors may interact to affect functional decline. Thus, we investigated the longitudinal relationship between APOE ε4 genotype and elevated PP on changes in functional abilities in a well-characterized sample of cognitively normal older adults from the Alzheimer's Disease Neuroimaging Initiative (ADNI). We hypothesized that individuals with elevated PP would show poorer everyday functioning over time, and that this rate of functional decline would be more pronounced in APOE ε4 carriers than non-carriers.

MATERIALS AND METHODS

The ADNI dataset

Data used for the present study were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu). The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies, and non-profit organizations. The main goal of ADNI has been to determine

whether magnetic resonance imaging, positron emission tomography, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early AD. The Principal Investigator of ADNI is Michael W. Weiner, MD, VA Medical Center and University of California – San Francisco. ADNI is the result of efforts of many co-investigators from a broad range of academic institutions and private corporations, and participants have been recruited from over 50 sites across the U.S. and Canada. ADNI has been followed by ADNI-GO and ADNI-2. Subjects originally recruited for ADNI-1 and ADNI-GO had the option to be followed in ADNI-2. Data used in the present study were acquired in ADNI-2. For up-to-date information, see http://www.adni-info.org.

Participants

The sample comprised 738 cognitively normal older adults from ADNI. All participants were between the ages of 55 and 90 years old, had completed at least six years of education, were fluent in Spanish or English, and were free of any significant neurological or psychiatric disease. Additionally, all participants completed a neuropsychological assessment, APOE genotyping, and blood pressure assessment at baseline. Full criteria for ADNI eligibility and diagnostic classifications are described in detail at http://www.adni-info.org/Scientists/ADNIStudyProcedures.html.

Figure 1 shows participant selection for the present study sample. Of the 1,109 ADNI participants who completed baseline neuropsychological assessment, 749 participants were identified as cognitively normal (CN) since they were not classified by ADNI as having dementia and they did not meet criteria for MCI based on comprehensive neuropsychological criteria[2] [25, 26]. All individuals with the APOE ε2/ε4 genotype were excluded due to the unknown paired effects of the potential protective role of the ε2 allele combined with the known risk of the ε4 allele. Consistent with previous work, individuals with functional dependence at baseline were also excluded (i.e., Functional Activities Questionnaire (FAQ) score >5), as to ensure that that the final study sample consisted of older adults who could independently complete their activities of daily living at baseline [27]. Participants were not excluded for functional dependence at any subsequent visits. This yielded a final analytic sample of 738 cognitively normal older adults (ε4 carriers = 236; ε4 non-carrier = 502). Within the final analytic sample, 357 participants had complete data at the 48-month follow-up visit.

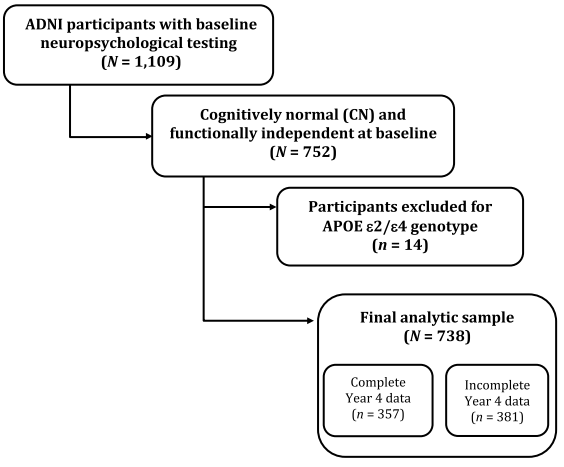

Fig. 1. Participant selection.

Assessment of everyday functioning

Everyday functioning was measured using the FAQ, which measures IADL difficulty, was completed by participants' informant at baseline, 6-month follow-up, and then annually. The FAQ consists of 10 items that assess an individual's level of performance of daily activities including: 1) writing checks, paying bills, or balancing a checkbook; 2) assembling tax records, business affairs, or other papers; 3) shopping alone for clothes, household necessities, or groceries; 4) playing a game of skill such as bridge or chess or working on a hobby; 5) heating water, making a cup of coffee, turning off the stove; 6) preparing a balanced meal; 7) keeping track of current events; 8) paying attention to and understanding a TV program, book, or magazine; 9) remembering appointments, family occasions, holidays, medications; 10) traveling out of the neighborhood, driving, or arranging to take public transportation. Each item is rated on a 4-point scale, with higher scores indicating greater dependence (dependent = 3; requires assistance = 2;

[2]The comprehensive neuropsychological criteria used in the current study are an empirically-based set of diagnostic criteria for MCI that have been demonstrated to produced fewer false-positive errors when used to identify cognitive impairment in older adult samples. The comprehensive criteria for MCI are as follows: 1) impaired performance on two or more tests in one cognitive domain, as defined as scores 1 standard deviation (SD) below normative expectations; 2) impaired performance on one test in each of the three measured cognitive domains; or 3) impairment in three or more daily activities (i.e., denoted by an FAQ score ≥6 [25]).

has difficulty but does by self = 1; normal = 0). The FAQ score ranges from 0 to 30, and is derived as the sum of the individual activity scores.

Pulse pressure assessment and genotyping

Blood pressure was measured for ADNI participants at all study visits. For the present study, PP was derived from baseline sitting brachial artery blood pressure data (systolic blood pressure-diastolic blood pressure). All arterial blood pressure measurements were taken using calibrated mercury sphygmomanometer and blood pressure cuff. Blood pressure readings were taken from the dominant arm while the participant was in a seated position, with their forearm held horizontally at the level of the fourth intercostal space at the sternum (i.e., the level of the heart). The presence or absence of the apolipoprotein E (APOE) ε allele was also determined with blood samples for each ADNI participant at their screening visit. Individuals with at least one ε allele were classified as ε carriers, while those without an allele ε were designated as non-carriers.

Statistical analyses

Baseline demographic and clinical characteristics by APOE ε4 status classification (i.e., absence or presence of at least one ε4 allele) were examined using analysis of variance (ANOVA) and chi-square tests to examine sex differences. Multiple linear regression, adjusting for covariates (i.e., age, education, sex, depressive symptoms, and antihypertensive medications), was used to examine the cross-sectional relationships between PP, APOE ε4 status, and FAQ scores at baseline. Multilevel modeling (MLM) was then used to examine whether vascular (i.e., elevated PP) and/or genetic risk (i.e., APOE ε4 status) altered rates of functional decline in our sample. This approach was specifically selected because it is considered the best practice for estimating longitudinal relationships in a sample with selective attrition [28], which is a common source of bias in longitudinal modeling. In order to determine the effects of time on functional decline over a four-year period, a visit variable consisting of six time points (i.e., baseline; months 6, 12, 24, 36, and 48) was included in the model as a continuous parameter. Participant FAQ scores from each of these time point were then examined as the response variable. Both linear and quadratic effects of visit were examined, although including a quadratic visit parameter did not improve model-fit based on –2 log likelihood (–2LL), Akaike information criterion (AIC), and Bayesian information criterion (BIC). Therefore, only the linear visit variable was included in the model. Data from all participants in the final analytic sample were included in the longitudinal analysis, as the multilevel modeling design does not require case-wise exclusion for missing data points [28].

Parameters of interest in the model included PP (continuous) and APOE ε4 status (dichotomous). Covariates that were adjusted for in the model included baseline variables for which there was a significant ($p < 0.05$) or trend-level ($p < 0.10$) difference by APOE ε4 status (i.e., age, education, and sex), as well as baseline variables with a known effect on PP (i.e., total number of antihypertensive medications) or functional difficulty (i.e., depressive symptoms [Geriatric Depression Scale; [29]). The model also included the random effect of intercept. The model was examined both in the raw-score metric and with normalized variables (resulting in normally distributed residuals). Normalized variables were ultimately used to reduce collinearity between parameters, and so the effect estimates were largely standardized. Model estimation was completed using the full information maximum likelihood method, which has been demonstrated to be less biased relative to other model estimation techniques (e.g., list-wise deletion of cases; [28]) due to its use of all available data in the generation of parameter estimates. Effect sizes were indexed by r-values. All analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 23 (SPSS IBM, New York, USA).

RESULTS

Participant characteristics

Baseline demographics and clinical characteristics of the sample are presented in Table 1. The mean age of the overall sample at baseline was 73.4 years (range: 55.2 to 90.2 years). Mean blood pressure (i.e., blood pressure [systolic, diastolic], PP) and clinical and functional scores were in the non-clinical range[3] both across the entire sample and within APOE ε4 status groups. Fifty percent of the sample

[3]Clinical cut points: hypertension, blood pressure >150/90 in older adults of 60+ years of age [30]; elevated pulse pressure, pulse pressure >60 [31, 32]; functional dependence, FAQ ≥6 [33]; presence of depressive symptoms, GDS >9 [29]; cognitive impairment, MMSE <24 [34].

Table 1
Baseline demographics and clinical characteristics by APOE ε4 status

	Overall Sample $N = 738$		APOE ε4- $n = 502$		APOE ε4+ $n = 236$			
	Mean	*SD*	Mean	*SD*	Mean	*SD*	F or χ^2	p-value
Age, y	73.43	6.86	74.03	6.68	72.16	7.06	12.05	**0.001**
Education, y	16.35	2.693	16.41	2.693	16.22	2.69	0.82	0.366
Gender (Female, %)	48.10%	—	49.40%	—	45.76%	—	0.76	0.383
Race (White, %)	93.8%	—	93.6%	—	94.1%	—	10.742	0.057
Ethnicity (Non-Hispanic %)	96.9%	—	97.2%	—	96.2%	—	0.821	0.663
GDS	1.19	1.34	1.16	1.33	1.25	1.36	0.70	0.402
FAQ Score	0.56	1.12	0.53	1.11	0.61	1.14	0.87	0.350
MMSE	28.74	1.43	28.79	1.33	28.62	1.61	2.02	0.156
Pulse Pressure, mmHg	59.94	14.67	59.76	14.06	60.33	15.93	0.24	0.622
Systolic BP, mmHg	134.72	16.39	134.37	15.59	135.46	17.99	0.71	0.398
Diastolic BP, mmHg	74.77	9.50	74.60	9.57	75.13	9.34	0.48	0.487
Antihypertensive medication use, %	50.30%	—	50.45%	—	50.00%	—	0.01	0.914
Number of antihypertensive medications	0.82	1.03	0.83	1.06	0.79	0.96	0.20	0.656

SD, standard deviation; APOE ε4+, positive for at least one apolipoprotein E ε4 allele; FAQ, Functional Activities Questionnaire; GDS, Geriatric Depression Scale; MMSE, Mini-Mental State Exam; PP, pulse pressure; mmHg, millimeter of mercury; BP, blood pressure.

reported taking at least one antihypertensive medication at the time of baseline assessment. Among individuals who were on at least one antihypertensive medication, the average number of medications was 1.62 (range: 1–7 medications). The distribution of APOE genotypes was as follows in the study sample: ε2/ε2 = 1, ε2/ε3 = 84, ε3/ε3 = 417, ε3/ε4 = 204; ε4/ε4 = 32. The APOE ε4 carriers were significantly younger than non-carriers (mean age carrier = 72.16; mean age non-carrier = 74.03; $p = 0.001$). There were no significant group differences in terms of education, sex, physiological/psychometric clinical variables, or antihypertensive use.

Similar to results from the baseline assessment, mean scores for physiological and psychometric clinical variables were in the non-clinical range at the final follow-up visit (month 48). This was observed across the sample, as well as within both APOE ε4 status groups. However, the ε4 carriers did have significantly poorer everyday functioning (FAQ total score mean = 2.97, SD = 6.29) relative to ε4 non-carriers (mean = 1.38, SD = 3.42; $p = 0.002$). Similarly, APOE ε4 carriers demonstrated lower scores on a cognitive screening measure (MMSE total score mean = 28.12, SD = 2.54) relative to non-carriers (mean = 28.89, SD = 1.40, $p < 0.001$) at the 48-month follow-up visit. There were no group differences in age, education, sex, blood pressure (systolic, diastolic), cognitive status, or psychiatric symptoms.

In order to assess potential selective attrition, between-subjects ANOVA and chi-square analyses were used to examine whether demographic or clinical characteristic differed between participants in the analytic sample who completed the month 48 visit ($n = 357$) and those who were missing data at month 48 ($n = 381$). Participants who completed the visit did not significantly differ (all ps > 0.375) from those with missing FAQ data at 48 months on age, education, sex, APOE ε4 status, number of antihypertensive medications, clinical measures (i.e., GDS and MMSE total scores), or physiological variables (i.e., blood pressure, PP). Potential differences with respect to conversion to MCI or AD during follow-up were also assessed. Diagnostic conversion significantly differed between individuals with and without complete 48-month data (χ^2, such that a lower proportion of individuals with incomplete 48-month data converted to MCI (53.2%) relative to completers (63.2%). Comparatively, a greater number of individuals with incomplete data converted to AD ($n = 6$) relative to those with complete data ($n = 1$).

Cross-sectional effects of PP and APOE ε4 genotype on functional status

Multiple linear regression, adjusted for age, education, sex, and depressive symptoms was used to examine the cross-sectional relationship between APOE ε4 status, baseline PP, and baseline FAQ scores. There was no significant main effect of APOE ε4 status [$t(738) = 0.637$, $p = 0.524$] or baseline PP [$t(738) = 0.067$, $p = 0.947$] on baseline FAQ scores. Additionally, the APOE ε4 status by baseline PP interaction effect on baseline FAQ scores was non-significant [$t(738) = –0.230$, $p = 0.818$]. This pattern of findings was not altered in a subsequent model that included the total number of antihypertensive medications as a covariate.

Table 2
Estimates for the full longitudinal model of the effect of genetic and vascular risk on functional decline

	Estimate	S.E.	df	F-statistic	*p*-value	*r*-value
Level 2 (Between Subjects Effects)						
Age	0.020	0.009	300.65	2.32	**0.021**	0.132
Education	–0.035	0.022	301.22	–1.60	0.110	0.092
Gender	–0.476	0.118	300.48	–4.04	**<0.001**	0.227
GDS total score	–0.002	0.005	283.60	–0.31	0.756	0.018
Number of antihypertensive medications	–0.027	0.056	302.15	–0.48	0.635	0.028
APOE ε4 status	0.175	0.516	283.88	0.34	0.735	0.020
Pulse Pressure	0.313	0.043	299.19	7.26	**<0.001**	0.386
Pulse Pressure × APOE ε4	–0.002	0.008	284.11	–0.27	0.788	0.016
Intercept	–0.359	0.792	297.55	–0.45	0.651	0.026
Level 1 (Within Subjects Effects)						
Visit	–0.023	0.015	1668.95	–1.61	0.108	0.039
Pulse Pressure × Visit	0.001	0.000	1670.87	2.96	**0.003**	0.072
APOE ε4 × Visit	0.087	0.024	1678.11	3.64	**<0.001**	0.088
Pulse Pressure × APOE ε4 × Visit	–0.001	0.000	1683.53	–2.16	**0.031**	0.053

GDS, Geriatric Depression Scale; APOE ε4 status, presence of the ε4 allele; S.E., standard error of the estimate.

Longitudinal effects of PP and APOE ε4 genotype on functional decline over four-year follow-up

A MLM, adjusted for age, education, sex, depressive symptoms, and total number of antihypertensive medications was used to determine whether APOE ε4 status and baseline PP predicted change in FAQ scores across the 4-year follow-up period. Table 2 includes the MLM fixed and random effects. Of the baseline covariates that were included in the model to control for confounding effects on FAQ, age and sex were significant ($p < 0.05$). Specifically, women ($r = 0.227$) and participants who were older at baseline ($r = 0.132$) had higher FAQ scores (indicating worse performance) across all visits (*p*-values <0.05).

Fixed effects

There was a significant main effect of baseline PP ($p < 0.001$), such that higher baseline PP was associated with higher FAQ scores (more functional difficulty) across all time points and participants. There were no significant main effects of APOE ε4 status or visit. The two-way PP × APOE ε4 status interaction was also not significant ($ps > 0.05$). However, the two-way visit × PP interaction was significant ($p = 0.003$), such that elevated baseline PP was associated with greater decline in everyday functioning, as indexed by increasing FAQ scores, across follow-up visits. A significant two-way visit × APOE ε4 status interaction was also observed ($p < 0.001$), such that ε4 carriers had greater increases in FAQ scores (more functional difficulty) across follow-up visits relative to non-carriers.

The significant two-way interactions are qualified by the significant three-way PP x APOE ε4 status × visit interaction, such that the effect of baseline PP on FAQ score trajectories over time differed between APOE ε4 groups ($p = 0.031$). Figure 2 shows the FAQ score trajectories of ε4 carriers and non-carriers by baseline PP (High versus Low). Findings suggest that, while ε4 carriers had the greatest increase in FAQ scores across the 4-year follow-up period, FAQ scores trajectories did not differ depending on baseline PP level. Conversely, while non-carriers were observed to have less decline in functional ability, the rate of decline was greater for non-carriers with elevated baseline PP.

Random effects

The model examined between-subject variability in FAQ score (random intercept). The intercept accounted for significant random variance ($p < 0.001$), suggesting that there was inter-individual variability in the initial FAQ score that was not accounted for in the model.

DISCUSSION

We examined the independent and interactive effects of brachial PP and APOE genotype on decline in everyday functioning over time in a sample of well-characterized, healthy, initially cognitively normal older adults. Results showed that elevated PP predicted greater functional difficulty trajectories across all participants, such that individuals with higher baseline PP showed greater declines in everyday functioning (as indexed by increasing FAQ scores) across four years of follow-up relative to

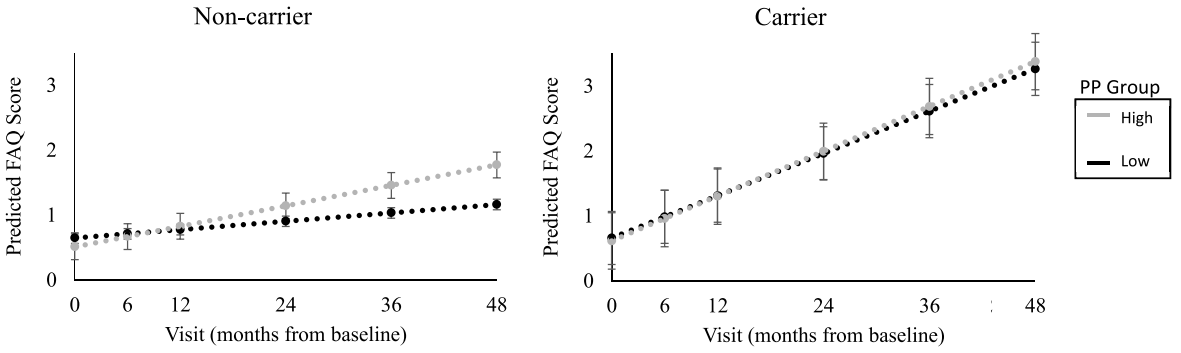

Fig. 2. APOE ε4 status modifies the effect of pulse pressure on everyday functioning over time. FAQ, Functional Activities Questionnaire; PP, pulse pressure. The model predicted values, controlling for age, education, sex, and depressive symptoms, are shown. Pulse pressure levels were determined by a median split of the values in the analytic sample (Low = PP ≤58; High = PP >58). Higher FAQ scores indicate greater functional difficulty. Error bars represent the standard error of the mean.

individuals with lower baseline PP levels. Additionally, APOE ε4 status also significantly predicted functional difficulty trajectories, such that APOE ε4 carriers demonstrated the greatest increases in FAQ scores over the follow-up period (relative to non-carriers). Interestingly, although non-carriers showed less dramatic declines in functional ability across time relative to ε4 carriers, the rate of decline was increased for non-carriers with higher baseline PP values. Such findings suggest that, while APOE ε4 status is the most prominent predictor of functional difficulty for APOE ε4 carriers, the relatively smaller effect of arterial stiffening on functional difficulty is still observed in non-carriers. Additionally, results suggest that APOE ε4 status and PP do not have an additive effect on risk of functional difficulty in relatively healthy older adults. Such results add to the growing literature attempting to disentangle the factors that contribute to the development and progression of prevalent degenerative brain aging conditions that result in functional decline, such as AD and vascular cognitive impairment.

The present study converges with a burgeoning body of research that confirms the deleterious role of APOE ε4 in aging. APOE ε4 remains the greatest known genetic risk factor for AD [35, 36], and has been repeatedly linked to AD neuropathology [37, 38], cerebrovascular disease [39], as well as cognitive impairment [15, 16]. There are several possible mechanisms through which the presence of an APOE ε4 allele may exert its effect of increasing risk for AD, such as altering the amyloid-β (Aβ) clearance and deposition in vulnerable brain regions, exacerbating tau-mediated neurodegeneration in AD [40], as well as influencing the extent of cognitive reserve available to compensate for accumulating neuropathology [41–43]. Alternatively, it may be that the presence of the APOE ε4 allele exacerbates Aβ accumulation in the brain *secondary* to an initial vascular damage to the brain (e.g., hypoxia, perfusion stress, blood-brain-barrier disruption; see [44] for a review). The exact mechanism, however, by which APOE exerts its effect on specific neurodegenerative processes remains unclear. Moreover, while the robust effects of the APOE ε4 genotype on pathological brain aging makes it a prime candidate for the early detection of individuals at risk for functional decline, there is a lack of effective risk-modifying treatments based on genetic susceptibility. Thus, a focus on targeting modifiable risk factors—such as elevated PP—to prevent or slow functional decline and pathological brain aging may prove to be more fruitful. Indeed, the present study confirms the importance of considering vascular factors, even in asymptomatic older adults, when determining risk for future functional decline.

There exists a large body of evidence implicating vascular risk factors (e.g., hypertension, atherosclerosis, hyperlipidemia, metabolic syndrome, diabetes mellitus) in pathological brain aging, as evidenced by the development and progression of cerebrovascular disease, AD brain pathology, cognitive impairment, and functional decline [45]. Recent studies have revealed a particularly robust association between arterial stiffness with various aspects of brain disease in old age, including gray and white matter degradations, accumulation of AD neuropathology, and cognitive decline [7, 46]. As previously stated, arterial stiffness leads to a deleterious hypertensive state that can cause further damage to vulnerable microvasculature and associated tissue [46, 47]. The brain is especially vulnerable to these effects due to the high density and low impedance of its

microvasculature, allowing for increased pulsatile loads to deeply penetrate the delicate microvascular beds [10]. Hypertension resulting from increased arterial stiffness is thus thought to cause chronic hypoperfusion and ischemia of brain tissue [11], ultimately resulting in the development of tissue damage [7, 48]. Such deleterious effects of arterial stiffening on brain structure and function have been demonstrated as early as young and mid-adulthood [13, 49, 50], highlighting the chronic, insidious contribution of vascular disease to cognitive aging. The findings of the present study extend this literature by demonstrating that PP predicts 4-year functional decline in cognitively normal, asymptomatic older adults.

While APOE ε4 and PP both predicted functional difficulty, it should be noted that the sample was, on average, still functionally independent at the 48-month visit. Prior work has shown that a cutoff of $\geq$6 on the FAQ best discriminated MCI from AD [33]. While this suggests that the change in functional ability captured by the present study may reach the level of dependence on IADLs, previous studies have demonstrated that increased functional difficulty is a significant risk factor for future functional disability and cognitive decline [51–53]. Thus, the present findings have implications for the early identification of individuals that are increased risk for functional decline, and they add to a promising body of literature highlighting the utility of employing cardiovascular-based intervention strategies as a method for reducing the prevalence of functional decline due to cognitive impairment in the aging population (see [54] or [55] for a review).

An unexpected finding of the present study was the nature of the interaction between genetic and vascular risk factors on functional ability trajectories. We hypothesized that elevated vascular risk would modify the effect of APOE ε4 status on longitudinal FAQ scores, such that ε4 carriers with elevated baseline PP would have the greatest amount of observed functional decline in our sample. We predicted this, given the growing body of literature to suggest that the presence of one or more ε4 allele may exacerbate the effect of certain vascular risk factors on pathological brain aging [15, 16, 18, 56]. While we did observe that the presence of at least one ε4 allele was, indeed, associated with the greatest risk for declines in functional ability, the absence or presence of elevated PP at baseline *did not* significantly alter the functional decline trajectories of ε4 carriers. Conversely, while non-carriers were observed to generally have less dramatic declines in functional ability across time relative to their ε4 carrier counterparts, the rate of decline was increased for non-carriers with elevated PP at baseline. Differently stated, elevated PP only appeared to increase the risk of functional decline in individuals who were not genetically susceptible to developing AD.

There are several possible explanations for this pattern of observed findings. As previously noted, APOE ε4 carriers were observed to have much steeper rates of functional decline relative to non-carriers. Thus, it is possible that this relatively larger effect of APOE ε4 status may have subsumed the potentially smaller effect of arterial stiffening on FAQ trajectories in APOE ε4 carriers. The characteristics of the ADNI sample, combined with the method used to assess functional activity, may furthermore contribute to such potential masking effects of ε4 status. Specifically, the ADNI sample is more highly educated and exhibits fewer vascular health related issues than would be expected for the community-dwelling population. Thus, it is possible that FAQ was not sensitive enough to capture slight PP effects on functional decline in ε4 carriers with relatively low vascular illness at baseline, especially given their comparatively faster rate decline. Moreover, the effects of PP could have further been masked by compensation in this highly-educated group of participants. Alternatively, the present findings might also be attributable to differential age effects across the APOE ε4 groups. That is, APOE ε4 carriers were significantly younger than non-carriers in this sample. Thus, it is possible that pulse pressure did not predict functional decline in ε4 carriers because of their younger age (and potentially greater cerebral resilience against the deleterious effect of increased pulse pressure).

A recent meta-analysis of studies assessing the association between arterial stiffness, cerebral small vessel disease, and cognitive impairment concluded that, while the literature supports an association between arterial stiffness and microvascular brain disease, the link with cognition is much weaker [57]. Similarly, there is evidence to suggest that the association between arterial stiffness and cognition is mediated by pathways that include cerebral microvascular remodeling and microvascular parenchymal damage [58]. Such findings suggest that the relationship between arterial stiffness and cognition is complex, and that it is critical to consider additional factors that may affect whether chronic vascular disease results in subsequent brain damage that gives rise to changes in cognitive performance. Given that cognitive impairment is largely thought to drive

functional decline in populations with AD or related dementias [5], we speculate that similarly complex relationships exist between PP, ε4 status, and functional decline. Future studies are warranted that attempt to model such multifarious relationships, with careful consideration of potential factors that may mediate or moderate the effects of arterial stiffening at at-risk populations, Furthermore, there is an increasing focus in the fields of aging and dementia on understanding the time-signatures of factors initiating or promoting brain pathology and clinical dementia syndromes [59]. Thus, consideration of potentially different timing-related effects of PP and APOE ε4 status on functional trajectories should be considered in future studies.

There are several strengths to the present study. Critically, the study employed a prospective study design to investigate risk factors for functional decline over time in older adults that were asymptomatic at baseline. The longitudinal clinical follow-up allowed for the investigation of the progression of functional ability, rather than only characterizing cross-sectional associations with everyday function. As demonstrated by the findings of our study, such an approach is imperative when exploring such associations in asymptomatic older adults. Indeed, we found that neither PP nor APOE ε4 status was associated with functional difficulty cross-sectionally; however, both interacted with time (visit) to predict future decline in functional ability. Additionally, the large sample size and multilevel modeling approach allowed the power to test for both independent and interactive associations between PP and APOE genotype on longitudinal FAQ scores, and afforded us the ability to statistically control for a variety of potential confounds. Finally, we identified cognitively normal older adults within the ADNI dataset using highly sensitive diagnostic criteria [25]. These criteria have been shown to be more reliable and stable than the conventional diagnostic criteria for MCI, and they yield far fewer (33%) false positives diagnostic errors [26, 60].

There are some important limitations to the present study that must also be considered. For example, there was a notable amount of attrition observed between baseline and the 48-month follow up visit. That is, while the modeling design employed in this study (i.e., mixed-effects design, full-information maximum likelihood, and the inclusion of attrition covariates) was selected because it is considered the best practice for estimating longitudinal relationships in a sample with selective attrition [28], bias due to attrition should still be considered as a potential limitation when interpreting the present findings. Additionally, while the present study did control for antihypertensive use at baseline, longitudinal antihypertensive use was not incorporated due to modeling constraints. Additionally, the ADNI exclusion and inclusion criteria yielded a sample with a relatively low frequency of health issues, including the presence of vascular disease, compared to the general population. Thus, the direction of the interaction between vascular and genetic risk on functional ability trajectories may apply only to populations with a relatively restricted range of vascular disease, thus limiting the generalizability of the present study findings. Moreover, there was limited information available for this sample regarding the presence of other risk factors to arterial stiffness and vascular disease (e.g., fasting blood glucose, A1c levels, dietary factors, and physical exercise). Thus, replication of these results in a more representative community sample that is well characterized with respect to vascular risk is recommended to further elucidate the role of arterial stiffness as a predictor of functional decline in late life. Indeed, future research that employs multivariate models to explore more complex associations between longitudinal PP measurements, vascular risk management (e.g., antihypertensive medication use and compliance, lifestyle modifications), and functional decline is needed.

Conclusion

Our results demonstrate that both elevated PP and the presence the APOE ε4 allele are associated with functional difficulty over time in older adults. Given that the sample consisted of asymptomatic, cognitively normal older adults at baseline, these findings have important implications for the early identification of individuals at risk for functional decline, as well as the development of treatment targets for continued independence and quality of life in at-risk older adults. The proportion of people over the age of 65 is rapidly increasing in our population, and with it the social, economic, and psychological burden of providing care for those who have lost their independence in late life due to functional decline. While we do not yet have therapies that can intervene with genetic risk factors for AD and functional decline, there are a variety of validated preventative approaches and interventions that can target vascular risk factors. Thus, identifying such high-risk individuals using potentially modifiable markers, such as

elevated PP (which is a relatively quick, cost effective, and non-invasive proximate measure of arterial stiffness), prior to the onset of functional decline may help to relieve this burden and promote independence in late adulthood. Future studies are warranted to clarify the etiology of the association between PP and different brain aging processes, in addition to further exploring its utility as an individual or combined marker of risk for functional decline due to AD and related dementias.

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SUPPLEMENTARY MATERIAL

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