Featured Article

Hypertension and obesity moderate the relationship between β-amyloid and cognitive decline in midlife

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Abstract

Background: This study tested if central obesity, hypertension, or depressive symptoms moderated the relationship between β-amyloid (Aβ) and longitudinal cognitive performance in late middle-aged adults enriched for Alzheimer's disease (AD) risk.

Methods: Participants ($n = 207$; ages = 40–70 years; 73% parental AD) in the Wisconsin Registry for Alzheimer's Prevention study completed 3+ neuropsychological evaluations and a [11C]PiB positron emission tomography scan or lumbar puncture. Linear mixed-effects regression models tested interactions of risk factor × Aβ × visit age on longitudinal Verbal Learning & Memory and Speed & Flexibility factor scores.

Results: The relationship between Aβ and Verbal Learning & Memory decline was moderated by hypertension ($\chi^2_{(1)} = 3.85$, $P = .04$) and obesity ($\chi^2_{(1)} = 6.12$, $P = .01$); those with both elevated Aβ and the risk factor declined at faster rates than those with only elevated Aβ or elevated risk factors.

Conclusion: In this cohort, hypertension and obesity moderated the relationship between Aβ and cognitive decline.

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Keywords: Preclinical Alzheimer's disease; β-amyloid; Hypertension; Obesity; Depression; Neuropsychology

1. Introduction

Although available treatments for Alzheimer's disease (AD) may provide some short-term benefits, they have limited efficacy in terms of modifying the course of the disease [1,2]. The lack of an effective disease-modifying therapy has led to increased efforts targeted at both early detection of AD and modifiable risk factors that may influence disease progression. Two commonly used antemortem biomarkers allowing for early detection of AD-related pathology are [11C]PiB positron emission tomography (PET), which allows for imaging of β-amyloid (Aβ) plaques in vivo [3], and cerebrospinal fluid (CSF) levels of Aβ 1–42 (Aβ$_{42}$), which are correlated with the formation of Aβ plaques in the brain [4,5]. Prior investigations indicate that cognitively unimpaired adults with higher mean cortical [11C]PiB binding potential and/or lower CSF Aβ$_{42}$ are at increased risk of developing dementia [6–9]. Furthermore, cognitively healthy adults with elevated Aβ deposition are more likely to exhibit cognitive decline than adults with lower Aβ levels [10–14]; however, up to 30%

of older adults with elevated Aβ remain cognitively unimpaired in late life [15]. This finding suggests that not all adults with elevated Aβ accumulation will progress to dementia and that other factors may moderate the relationship between Aβ and cognitive decline.

Supporting this hypothesis, epidemiological studies suggest that seven potentially modifiable risk factors for AD, including midlife hypertension, midlife obesity, smoking, depression, low educational attainment, physical inactivity, and diabetes may account for up to half of dementia cases in the United States [16]. Several studies report greater risk for dementia and/or longitudinal decline on neuropsychological measures in adults with depressive symptomatology [17–24], obesity [24–30], or hypertension [28,31–35]. Moreover, prior investigations revealed elevated Aβ deposition in nondemented older adults with depression [36] or hypertension [37,38]. Two recent studies also observed a relationship between midlife obesity and increased Aβ in later life [39,40]. Finally, one prior investigation demonstrated that adults with abnormal plasma Aβ levels and elevated blood pressure at midlife were at greatest risk of developing AD [41]; however, no study to date has examined if the relationships between these modifiable risk factors and Aβ deposition interact to affect longitudinal cognitive performance in cognitively unimpaired adults.

Therefore, the purpose of the present study was to determine if the presence of modifiable risk factors moderates the relationship between Aβ levels and longitudinal performance on neuropsychological measures in cognitively normal late middle-aged adults. This study focuses on three midlife modifiable risk factors that were well characterized in the Wisconsin Registry for Alzheimer's Prevention (WRAP) cohort: hypertension, obesity, and depression. We investigated the moderating effects of these risk factors on the relationship between Aβ deposition (as assessed via [11C]PiB PET imaging or CSF Aβ$_{42}$) and longitudinal neuropsychological performance. We hypothesized that each risk factor would moderate the relationship between Aβ burden and longitudinal cognitive performance (i.e., three-way interaction among visit age [time-varying] × risk factor group [time-invariant] × Aβ group [time-invariant] would account for a significant amount of variance in longitudinal neuropsychological performance).

2. Materials and methods

2.1. Participants

Data were from 207 participants enrolled in the WRAP study, which consists of a cohort of ∼1550 asymptomatic (at study entry) late middle-aged adults enriched for parental history of AD [42]. The ongoing parent study includes biennial evaluations (with the exception of a 4-year interval between visits 1 and 2) that involve a physical examination, laboratories, a neuropsychological evaluation, and optional linked studies for acquisition of neuroimaging and CSF biomarkers of AD pathophysiology. Inclusion criteria for this study were as follows: cognitive data for at least three longitudinal visits, no diagnosis of dementia as determined via consensus conference review using NIA-AA diagnostic criteria [43], and completion of either a [^{11}C]PiB PET scan or lumbar puncture. The inclusion of human subjects in this study was approved by the University of Wisconsin-Madison Institutional Review Board, and all participants provided informed consent.

2.2. Aβ status determination

The biomarker data were collected as part of linked study protocols and did not occur at the same study visit for all participants (see Fig. 1). Biomarker data were collected at visit 2 for $n = 61$ participants, at visit 3 for $n = 111$ participants, and at visit 4 for $n = 35$ participants. Elevated or nonelevated Aβ status was determined by mean [^{11}C]PiB distribution volume ratio or by CSF Aβ$_{42}$ or Aβ$_{42}$/Aβ$_{40}$ levels.

Detailed methods for [^{11}C]PiB radiochemical synthesis, PET imaging parameters, and parametric distribution volume ratio map generation were implemented as described previously [44]. Eight bilateral regions of interest (angular gyrus, anterior cingulate gyrus, posterior cingulate gyrus, frontal medial orbital gyrus, precuneus, supramarginal gyrus, middle temporal gyrus, and superior temporal gyrus) were selected from the automated anatomic labeling atlas, standardized, and reverse warped to native space. The mean distribution volume ratio across these eight regions of interest was calculated for determination of Aβ status (elevated or nonelevated) using a cutoff of 1.19 as previously reported for the WRAP cohort [45].
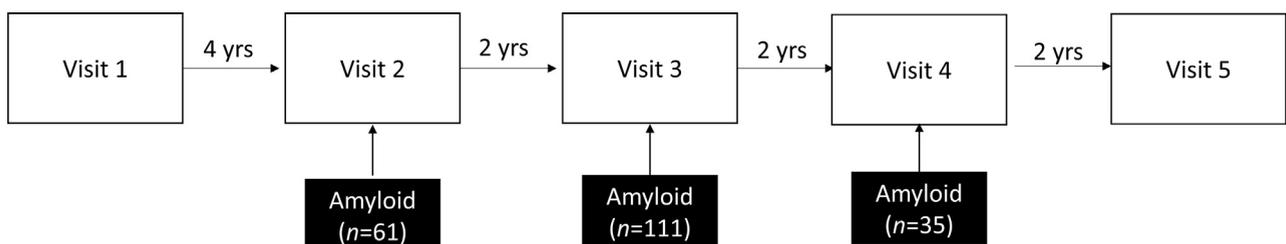

Fig. 1. Flow diagram of study visits. Neuropsychological evaluations are conducted at each visit. β-amyloid data were acquired as part of linked studies near visits 2, 3, or 4. Modifiable risk factor data were examined at the study visit closest to the biomarker acquisition visit.

CSF was collected in the morning after a minimum 12-hour fast. A Sprotte spinal needle was used to extract 22 mL of CSF from the L3-L4 or L4-L5 vertebral interspace via gentle extraction into polypropylene syringes. Within 30 minutes of collection, the CSF was combined, gently mixed, centrifuged to remove red blood cells or other debris, aliquoted into 0.5-mL polypropylene tubes, and stored at -80°C. Samples were analyzed at the Clinical Neurochemistry Laboratory at the Sahlgrenska Academy of the University of Gothenburg, Sweden, for Aβ 1–40 and Aβ 1–42 using commercially available enzyme-linked immunosorbent assay methods (INNOTEST assays; Fujirebio, Ghent, Belgium; Triplex assays, MSD Human Aβ peptide ultra-sensitive kit; Meso Scale Discovery, Gaithersburg, MD). An Aβ_{42} (INNOTEST) value of <471.54 pg/mL or an Aβ_{42}/Aβ_{40} (triplex) ratio of <.09 was used to define elevated Aβ, based on prior receiver operating characteristic analyses showing these values best discriminated cognitively healthy adults from individuals with dementia [46].

2.3. Modifiable risk factor assessment

The modifiable risk factors included in this study were hypertension, obesity, and depression, which were chosen because they were midlife modifiable risk factors included in the epidemiological study previously described [16] and were present in >10% of the entire WRAP cohort (diabetes was present in only 5% of the cohort, and current tobacco use was present in only 9% of the cohort). The data included in this study were collected at the closest point in time to the biomarker visit (mean time between risk factor data and biomarker data = 0.65 years, range = 0–2 years). Blood pressure and anthropometric measures were obtained according to the Atherosclerosis Risk in Communities Study protocol. Before cognitive test administration, participants were instructed to sit for 10 minutes and then have blood pressure readings obtained. Blood pressure was measured up to three times within an examination visit to obtain a stable measure, with the participant seated using a random-zero sphygmomanometer. Cuff size was chosen appropriate to the participant's arm circumference. Hypertension was defined according to the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure 8 guidelines [47] (i.e., systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg). Use of antihypertensive medication was included as a covariate in primary analyses and examined further in post hoc analyses. Waist circumference was measured with an anthropometric tape to the nearest centimeter with the participant standing. The waist circumference was taken at the level of the natural waist (narrowest part). Waist measurements were taken twice by trained staff, and the smallest measurement was used. Waist circumference measurements greater than 88 cm for women and 102 cm for men were coded as obese based on standard guidelines [48]. Depressive symptoms were assessed using the Center for Epidemiologic Studies of Depression scale

(CES-D), with total scores ≥ 16 coded as depressed [49]. Risk factor variables were dichotomized using clinically defined cutpoints to improve interpretability, generalizability, and clinical relevance.

2.4. Cognitive assessment

A comprehensive neuropsychological assessment was completed at each visit [42]. A prior factor analysis indicated that learning trials 3–5 and the delayed recall trial (trial 7) on the Rey Auditory Verbal Learning Test loaded onto a Verbal Learning and Memory factor and that measures of speed and executive function (Trail making Test Parts A & B, Stroop Color-Word Interference condition) loaded onto a Speed & Flexibility factor [50]. Each factor was calculated as a weighted composite of the contributing tests and then standardized around the baseline mean and standard deviation of the composite (i.e., each factor is a z-score) [51]. These factors were selected for analyses because they represent cognitive domains that have been shown to exhibit early decline, are associated with Aβ in preclinical AD based on prior meta-analyses [52–54], and include measures that were given at all study visits.

2.5. Statistical analysis

To test for the presence of relationships between Aβ status and modifiable risk factors, χ^2 analyses were conducted for the dichotomous risk factor variables and ANOVAs were conducted for the continuous risk factor variables in SPSS, version 24. To test the hypothesis that longitudinal cognitive performance would vary by risk factor and Aβ status, linear mixed-effects regression analysis was conducted in R, version 3.3.1, using the lme4 package, version 1.1-12 [55]. Linear mixed-effects models were used due to their ability to handle unbalanced and missing data as well as a continuous variable for time [56]. Outcome variables were Verbal Learning & Memory and Speed & Flexibility factor scores. Random effects included intercept and slope nested within subjects. Fixed effects for model 1 included main effects of hypertension status, Aβ status, and age at each visit (time-varying variable; centered on the sample mean) and interaction terms of hypertension status × Aβ status, age at each visit × hypertension status, age at each visit × Aβ status, and age at each visit × hypertension status × Aβ status. Fixed effects for models 2 and 3 were identical to model 1 except for obesity status and depression status instead of hypertension. Covariates included age at biomarker visit, sex, education, practice effects (time-varying variable; number of prior exposures to cognitive test [total visits completed − 1]), and treatment status (e.g., antihypertensive medication use [yes vs. no] for model 1 or antidepressant medication use [yes vs. no] for model 3). The overall significance of the three-way interaction term was assessed by likelihood ratio tests comparing the full model and a nested model that did not include the three-

way interaction term. Statistical comparison of model coefficients to determine direction of group differences was performed using the Wald test. Statistical tests were two-tailed, and an α-level of $P < .05$ was used to determine statistical significance. Model fit was evaluated by visual inspection of the residuals and a Pearson goodness-of-fit test.

3. Results

3.1. Sample characteristics

The sample was on average 55 years of age at study enrollment and 61 years of age at biomarker visit. The sample was 68% females, highly educated (mean 16 years of education), and enriched for AD risk (73% had at least one parent with AD; 38% apolipoprotein [*APOE*] ε4 genotype carriers; see Table 1). All 207 participants completed at least three neuropsychological evaluations. Twenty-five participants (12%) completed three study visits (6-year follow-up), 82 (40%) completed four study visits (8-year follow-up), and 100 (48%) completed five study visits (10-year follow-up). There was a mean of 6 months between the neuropsychological evaluation and biomarker visit (range = 0–2 years), and this did not differ between Aβ groups [$t(205) = 0.43$, $P = .67$]. Sixty-two participants

(30%) exhibited elevated levels of Aβ. At the study visit closest to the biomarker assessment, $n = 40$ (19%) were hypertensive, $n = 89$ (43%) were obese, and $n = 13$ (6%) were depressed. Results of χ^2 analyses indicated no significant association between hypertension and obesity status ($\chi^2_{(1)} = 0.99$, $P = .32$), hypertension and depression status ($\chi^2_{(1)} = 0.14$, $P = .71$), or obesity and depression status ($\chi^2_{(1)} = 1.95$, $P = .16$).

3.2. Relationship between modifiable risk factors and Aβ status

Results of χ^2 analyses indicated that risk factor status did not differ by Aβ status (see Table 2). Specifically, there were no differences in proportion of participants with elevated Aβ by hypertension status ($\chi^2_{(1)} = .15$, $P = .70$), obesity status ($\chi^2_{(1)} = 2.04$, $P = .15$), or depression status ($\chi^2_{(1)} = .004$, $P = .95$). Similarly, there were no differences between Aβ groups in systolic blood pressure ($F = 0.06$, $P = .80$; estimated marginal means: Aβ− = 125.6 [95% confidence interval {CI}: 123.0–128.2], Aβ+ = 126.2 [95% CI: 122.2–130.1]), diastolic blood pressure ($F = 0.04$, $P = .84$; estimated marginal means: Aβ− = 74.4 [95% CI: 72.8–76.0], Aβ+ = 74.7 [95% CI: 72.2–77.1]), waist circumference ($F = 1.62$, $P = .21$; estimated marginal means:

Table 1
Sample characteristics [mean (SD) or N (%)]

Characteristics	Total sample	Aβ+	Aβ−
Total participants	207	62	145
Baseline age, years	54.6 (6.3)	56.7 (5.4)	53.7 (6.5)
Biomarker (PET or CSF) age	60.7 (6.4)	63.0 (5.0)	59.8 (6.7)
Biomarker visit to WRAP visit interval (years)	0.6 (0.5)	0.6 (0.5)	0.7 (0.5)
Sex (female)	140 (68%)	43 (69%)	97 (67%)
Education (years)	16.1 (2.4)	16.5 (2.4)	15.9 (2.3)
APOE (ε4 carrier)	78 (38%)	35 (57%)	43 (30%)
Parental history of AD (positive)	151 (73%)	48 (77%)	103 (71%)
Baseline Verbal Learning & Memory (z-score)	0.08 (1.0)	0.17 (0.9)	0.04 (1.0)
Baseline Speed & Flexibility (z-score)	−0.003 (0.9)	−0.19 (0.9)	0.07 (1.0)
Aβ modality	CSF: 26 (13%)	CSF: 5 (8%)	CSF: 21 (15%)
	PiB: 75 (36%)	PiB: 19 (31%)	PiB: 56 (39%)
	Both: 106 (51%)*	Both: 38 (61%)	Both: 68 (47%)
Hypertension[†]	40 (19%)	13 (21%)	27 (19%)
Obesity[‡]	89 (43%)	22 (36%)	67 (46%)
Depression[§]	13 (6%)	4 (7%)	9 (6%)
Diabetes	4 (2%)	0 (0%)	4 (3%)
Tobacco use (current smoker)	8 (4%)	2 (3%)	6 (4%)
Systolic blood pressure	125.8 (15.7	126.2 (16.1)	125.6 (15.6)
Diastolic blood pressure	74.4 (9.7)	74.7 (9.9)	74.4 (9.6)
Waist circumference (cm)	92.3 (14.9)	90.3 (15.1)	93.2 (14.8)
Center for Epidemiologic Studies of Depression scale	5.9 (5.9)	5.6 (5.1)	6.0 (6.2)
Antihypertensive medication use	45 (22%)	18 (29%)	27 (19%)

Abbreviations: Aβ, β-amyloid; CSF, cerebrospinal fluid; PET, positron emission tomography; SD, standard deviation; WRAP, Wisconsin Registry for Alzheimer's Prevention.

*Of these 106, $n = 85$ (80%) were congruent across modalities and $n = 21$ (20%) were incongruent ($n = 9$ were classified as Aβ elevated by PiB, but non-elevated by CSF, and $n = 12$ were classified as Aβ elevated by CSF, but non-elevated by PiB). Elevated status using either modality resulted in classification in the Aβ-elevated group.

[†]Systolic blood pressure > 139 mm Hg or diastolic blood pressure > 89 mm Hg.

[‡]Waist circumference > 102 cm for males or > 88 cm for females.

[§]Center for Epidemiologic Studies of Depression scale ≥ 16.

Table 2
Aβ status by risk factor status [n (%)]

| Aβ status | Hypertension | | Obesity | | Depression | | Total |
	Normal	Elevated*	Normal	Elevated†	Normal	Elevated‡	
Nonelevated	118 (81)	27 (19)	78 (54)	67 (46)	136 (94)	9 (6)	145
Elevated	49 (79)	13 (21)	40 (65)	22 (35)	58 (94)	4 (6)	62
Total	167 (81)	40 (19)	118 (57)	89 (43)	194 (94)	13 (6)	207
$\chi^2_{(1)}$, p	.15	.70	2.04	.15	.004	.95	

Abbreviation: Aβ, β-amyloid.
Note: $n = 20$ participants are in both elevated hypertension and elevated obesity groups, $n = 8$ participants are in both elevated obesity and elevated depression groups, $n = 2$ participants are in both elevated hypertension and elevated depression groups, and $n = 1$ participant was elevated on all 3 risk factors.
*Systolic blood pressure > 139 mm Hg or diastolic blood pressure > 89 mm Hg.
†Waist circumference > 102 cm for males or > 88 cm for females.
‡Center for Epidemiologic Studies of Depression scale ≥ 16.

Aβ− = 93.2 [95% CI: 90.8–95.6], Aβ+ = 90.32 [95% CI: 86.6–94.1]), and CES-D depressive symptoms (F = 0.14, P = .71; estimated marginal means: Aβ− = 5.96 [95% CI: 5.0–6.9], Aβ+ = 5.6 [95% CI: 4.2–7.1]).

3.3. Relationships among modifiable risk factors, Aβ, and cognition

Regression diagnostics were performed and indicated that all models met the necessary assumptions. Specifically, model residuals appeared normally distributed, did not exhibit heteroscedasticity, and Pearson goodness-of-fit tests were nonsignificant. Random effects (e.g., intercept and slope) were not correlated with residuals, and the random effect residuals were normally distributed.

3.3.1. Hypertension

Likelihood ratio tests comparing full and nested linear mixed-effects models indicated that the three-way interaction of hypertension status × Aβ status × visit age accounted for a statistically significant amount of variance in Verbal Learning & Memory performance ($\chi^2_{(1)} = 3.85$, P = .04; see Table 3). This result indicates that the relationship between Aβ and age-related decline in verbal learning and memory was a function of hypertension status (see Fig. 2 [left]). Rates of cognitive change for each group were calculated from model coefficients (Table 4) and demonstrate greater rates of decline in the elevated Aβ group with hypertension compared with other groups. Statistical comparison of the model coefficients using the Wald test indicated that those with elevated Aβ and hypertension exhibited significantly greater decline than those with elevated Aβ without hypertension ($\beta = -0.05$ (SE = .02), P = .046) and those with low Aβ with hypertension ($\beta = -0.06$ [SE = .03], P = .02). The interaction of hypertension status × Aβ status × visit age did not account for a significant amount of variability in Speed & Flexibility performance ($\chi^2_{(1)} = .04$, P = .83; see Table 5).

Post hoc analyses were conducted to examine the effect of antihypertensive medication use on these results. Twenty-two percent ($n = 45$) were treated with an antihyper-

tensive medication. Of the sample of $n = 207$, $n = 132$ were normotensive/nontreated, $n = 35$ were normotensive/treated (e.g., blood pressure in normal range and taking an antihypertensive medication), $n = 30$ were hypertensive/nontreated, and $n = 10$ were hypertensive/treated (e.g., elevated blood pressure despite antihypertensive medication use). The overall three-way interaction among blood pressure status/treatment status (4-level variable) × Aβ status × visit age did not account for a statistically significant amount of variance in Verbal Learning & Memory performance ($\chi^2_{(3)} = 5.82$, P = .12; see Supplementary Table 1).

3.3.2. Obesity

Likelihood ratio tests comparing the full and nested linear mixed-effects models indicated that the three-way interaction of obesity status × Aβ status × visit age was statistically significant for the Verbal Learning & Memory factor ($\chi^2_{(1)} = 6.12$, P = .01; Table 3), indicating that the relationship between Aβ status and rate of age-related decline in verbal learning and memory was dependent on obesity status (see Fig. 2 [middle]). Rates of change in Table 5 show greater decline in those with elevated Aβ and obesity. Statistical comparison of model coefficients indicated that obese participants with elevated Aβ exhibited greater decline than nonobese participants with elevated Aβ ($\beta = -0.04$ [SE = .02], P = .02) and obese participants with low Aβ ($\beta = -0.05$ [SE = .02], P = .006). Similar to analyses with hypertension, the three-way interaction of obesity status × Aβ status × visit age was not associated with performance on the Speed & Flexibility factor ($\chi^2_{(1)} = .004$, P = .95; Table 4).

3.3.3. Depression

Likelihood ratio tests comparing the full and nested linear mixed-effects models indicated that the three-way interaction of depression status × Aβ status × visit age was not significantly associated with Verbal Learning & Memory ($\chi^2_{(1)} = 2.01$, P = .16; see Table 3) or Speed & Flexibility ($\chi^2_{(1)} = 0.07$, P = .80; see Table 4) performances (see Fig. 2 [right]).

Table 3
Model parameter estimates for association between presence of modifiable risk factors and Verbal Learning & Memory outcome

Predictor	Risk factor		
	Hypertension	Obesity	Depression
	β (SE); [95% CI]	β (SE); [95% CI]	β (SE); [95% CI]
Intercept	−2.3 (1.6); [−5.3, 0.7]	−2.2 (1.6); [−5.2, 0.9]	−2.3 (1.6); [−5.4, 0.7]
Risk factor group	−0.2 (0.2); [−0.5, 0.1]	−0.1 (0.1); [−0.4, 0.1]	−0.1 (0.3); [−0.7, 0.4]
Aβ group	0.04 (0.1); [−0.2, 0.3]	−0.001 (0.2); [−0.3, 0.3]	0.2 (0.1); [−0.1, 0.4]
Centered visit age (slope)	−0.04 (0.02); [−0.1, 0.01]	−0.04 (0.02); [−0.1, 0.002]	−0.04 (0.02); [−0.1, 0.01]
Biomarker age	0.01 (0.02); [−0.04, 0.1]	0.01 (0.02); [−0.04, 0.1]	0.01 (0.02); [−0.04, 0.1]
Sex	0.8*** (0.1); [0.6, 1.1]	0.8*** (0.1); [0.6, 1.1]	0.8*** (0.1); [0.6, 1.1]
Education	0.1** (0.02); [0.03, 0.1]	0.1** (0.02); [0.02, 0.1]	0.1** (0.02); [0.02, 0.1]
Practice effect	0.1 (0.1); [−0.03, 0.2]	0.1 (0.1); [−0.02, 0.2]	0.1 (0.1); [−0.02, 0.2]
Treatment status	0.1 (0.1); [−0.2, 0.3]	–	−0.1 (0.1); [−0.3, 0.1]
Risk factor group × Aβ group	0.4 (0.3); [−0.2, 1.0]	0.3 (0.2); [−0.1, 0.8]	−0.7 (0.5); [−1.6, 0.3]
Centered visit age × risk factor group	0.01 (0.01); [−0.02, 0.03]	0.01 (0.01); [−0.01, 0.03]	−0.03 (0.02); [−0.1, 0.02]
Centered visit age × Aβ group	−0.01 (0.01); [−0.03, 0.02]	0.01 (0.01); [−0.02, 0.03]	−0.02 (0.01); [−0.04, 0.004]
Centered visit age × Aβ group × risk factor group	−0.1* (0.03); [−0.1, −0.001]	−0.1 (0.02)**; [−0.1, −0.01]	0.1 (0.04); [−0.02, 0.1]

Abbreviations: Aβ, β-amyloid; CI, confidence interval.
***$P \leq .001$; **$P \leq .01$; *$P \leq .05$; P values for fixed effect coefficients were calculated using asymptotic properties of the estimates.

3.3.4. Post hoc sensitivity analysis

Owing to lack of three-way interaction effects for any of the risk factors on the Speed & Flexibility outcome, post hoc analyses were conducted to test if the risk factors were associated with Speed & Flexibility performance in the absence of an interaction with Aβ. To test this hypothesis, the three-way interaction term (risk factor status × Aβ status × visit age) was removed from each model and the effect of each two-way interaction (risk factor x age, Aβ status x age, risk factor status x Aβ) was examined—results indicated that the two-way interaction effects were not significantly related to Speed & Flexibility performance. To further test this hypothesis, the Aβ terms were removed from the models and the effect of the two-way interactions (risk factor × age) and main effects of the risk factors were examined. These results indicated nonsignificant interactions and main effects for hypertension and obesity factors, but a near-significant interaction effect of depression × age ($P = .08$) and a significant main effect of depression ($P = .04$) on Speed & Flexibility performance.

4. Discussion

In a sample of 207 late middle-aged adults enriched for AD risk, presence of hypertension or obesity moderated the relationship between Aβ (on PET scan or in CSF) and longitudinal Verbal learning & Memory, but not Speed & Flexibility, performance. These findings suggest that the presence of hypertension or obesity in midlife may exacerbate subtle cognitive decline associated with Aβ deposition. These results have potentially important implications for asymptomatic adults with elevated Aβ, which included 30% of the current sample, similar to prior reports of prevalence of elevated Aβ in cognitively unimpaired adults [57,58]. The results suggest that the increased risk for cognitive decline in those with elevated Aβ [13,14,59] may be driven by those with both elevated Aβ and vascular risk factors. Specifically, in this sample, the annual estimated rate of memory decline was doubled in those with elevated Aβ and hypertension or obesity compared with those with elevated Aβ without hypertension or obesity. Based on this estimate, adults in the high-risk groups (Aβ+ and hypertensive or obese) would be expected to exhibit a one standard deviation decline on the memory composite within 10 years, thus potentially crossing the threshold into the clinically impaired range

Table 4
Estimated annual rates of cognitive change (z-score units) across groups

β-amyloid / Risk factor groups	Verbal learning & memory	Speed & flexibility
	β [95% CI]	β [95% CI]
Hypertension		
Aβ−/HTN−	−0.039 [−0.083, 0.005]	0.002 [−0.037, 0.041]
Aβ+/HTN−	−0.043 [−0.089, 0.002]	−0.011 [−0.051, 0.029]
Aβ−/HTN+	−0.033 [−0.083, 0.017]	−0.001 [−0.044, 0.042]
Aβ+/HTN+	−0.091 [−0.150, −0.032]	−0.020 [−0.073, 0.032]
Obesity		
Aβ−/OB−	−0.043 [−0.089, 0.002]	0.005 [−0.035, 0.045]
Aβ+/OB−	−0.038 [−0.084, 0.009]	−0.010 [−0.051, 0.030]
Aβ−/OB+	−0.032 [−0.077, 0.013]	0.001 [−0.039, 0.040]
Aβ+/OB+	−0.082 [−0.134, −0.030]	−0.014 [−0.059, 0.031]
Depression		
Aβ−/DEP−	−0.038 [−0.082, 0.007]	−0.0001 [−0.039, 0.038]
Aβ+/DEP−	−0.056 [−0.102, −0.011]	−0.014 [−0.053, 0.026]
Aβ−/DEP+	−0.067 [−0.127, −0.006]	−0.030 [−0.085, 0.025]
Aβ+/DEP+	−0.028 [−0.102, 0.046]	−0.035 [−0.095, 0.025]

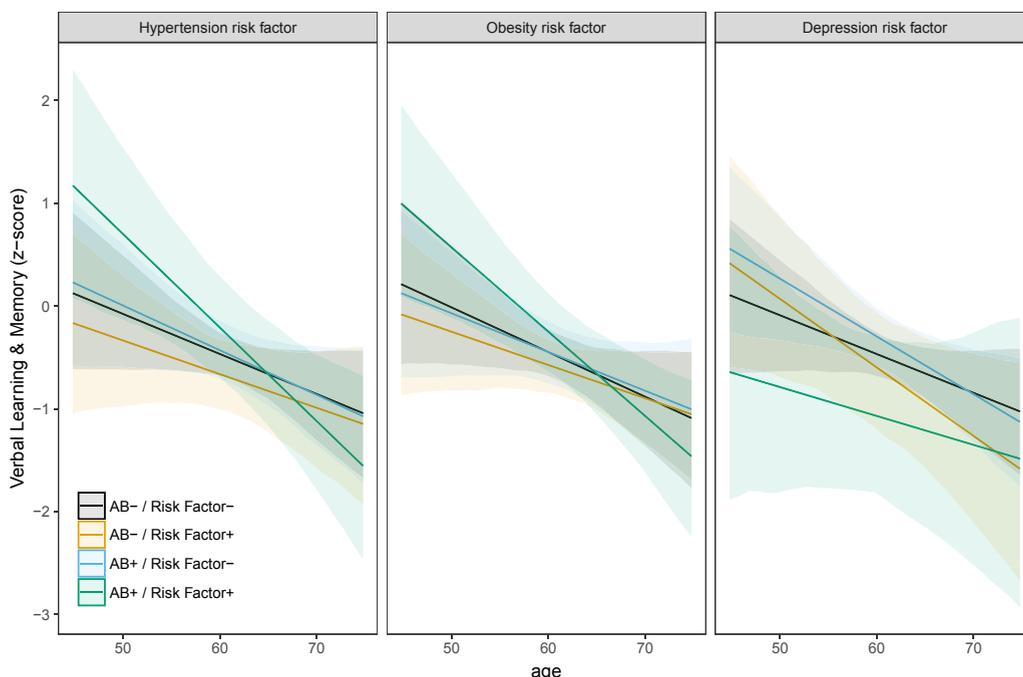Abbreviations: Aβ, β-amyloid; HTN, hypertension; OB, obesity; DEP, depression.

Fig. 2. Graphs depict Verbal Learning & Memory z-scores on the y-axis, age at each visit on the x-axis, and estimated slopes for four β-amyloid (Aβ)/risk factor groups. For all plots, sex was male, mean biomarker age of 60.7 years, mean education of 16.1 years, mean practice effect of 2.5 prior test exposures, and negative for antihypertensive or antidepressant medication use (for hypertension and depression plots, respectively). Risk factor groups were determined based on status at study visit closest to biomarker assessment. The left figure depicts the estimated slope for nonelevated Aβ and nonhypertensive (black; $n = 118$), nonelevated Aβ and hypertensive (orange; $n = 27$), elevated Aβ and nonhypertensive (blue; $n = 49$), and elevated Aβ and hypertensive (green; $n = 13$). The middle figure depicts the estimated slope for nonelevated Aβ and nonobese (black; $n = 78$), nonelevated Aβ and obese (orange; $n = 67$), elevated Aβ and nonobese (blue; $n = 40$), and elevated Aβ and obese (green; $n = 22$). The right figure depicts the estimated slope for nonelevated Aβ and nondepressed (black; $n = 136$), nonelevated Aβ and depressed (orange; $n = 9$), elevated Aβ and nondepressed (blue; $n = 58$), and elevated Aβ and depressed (green; $n = 4$).

earlier than those in other groups. Although the estimated rate of change is subtle, the potential to identify and modify this expected trajectory by addressing and effectively treating modifiable risk factors of hypertension and obesity could

possibly result in delaying the onset of clinically significant cognitive impairment.

In contrast, the interaction among age $\times$ Aβ $\times$ depression was nonsignificant. A smaller proportion of the sample

Table 5
Model parameter estimates for association between presence of modifiable risk factors and Speed & Flexibility outcome

	Risk factor		
	Hypertension	Obesity	Depression
Predictor	β (SE); [95% CI]	β (SE); [95% CI]	β (SE); [95% CI]
Intercept	4.3** (1.4); [1.6, 7.0]	4.3** (1.4); [1.6, 7.0]	4.1** (1.4); [1.4, 6.8]
Risk factor group	0.1 (0.2); [−0.2, 0.4]	0.1 (0.1); [−0.1, 0.4]	−0.4 (0.3); [−0.8, 0.1]
Aβ group	−0.1 (0.1); [−0.3, 0.2]	0.02 (0.1); [−0.3, 0.3]	−0.1 (0.1); [−0.3, 0.2]
Age at each visit (centered)	0.002 (0.02); [−0.04, 0.04]	0.01 (0.02); [−0.03, 0.04]	−0.0001 (0.02); [−0.04, 0.04]
Biomarker age	−0.1*** (0.02); [−0.1, −0.03]	−0.1*** (0.02); [−0.1, −0.03]	−0.1*** (0.02); [−0.1, −0.03]
Sex	−0.02 (0.1); [−0.2, 0.2]	−0.04 (0.1); [−0.3, 0.2]	−0.01 (0.1); [−0.2, 0.2]
Education	−0.002 (0.02); [−0.04, 0.04]	−0.001 (0.02); [−0.04, 0.04]	0.001 (0.02); [−0.04, 0.04]
Practice effect	0.05 (0.1); [−0.1, 0.2]	0.04 (0.1); [−0.1, 0.1]	0.1 (0.1); [−0.1, 0.2]
Medication use	0.005 (0.1); [−0.2, 0.3]	—	−0.03 (0.1); [−0.2, 0.2]
Risk factor group $\times$ Aβ group	0.04 (0.3); [−0.5, 0.6]	−0.2 (0.2); [−0.7, 0.2]	−0.2 (0.4); [−1.1, 0.7]
Centered visit age $\times$ risk factor group	−0.003 (0.01); [−0.03, 0.02]	−0.005 (0.01); [−0.02, 0.01]	−0.03 (0.02); [−0.1, 0.01]
Centered visit age $\times$ Aβ group	−0.01 (0.01); [−0.03, 0.01]	−0.02 (0.01); [−0.04, 0.01]	−0.01 (0.01); [−0.03, 0.004]
Centered visit age $\times$ Aβ group $\times$ risk factor group	−0.01 (0.02); [−0.1, 0.04]	0.001 (0.02); [−0.04, 0.04]	0.01 (0.03); [−0.1, 0.1]

Abbreviations: Aβ, β-amyloid; CI, confidence interval.
***$P \leq .001$; **$P \leq .01$; *$P \leq .05$; P values for fixed effect coefficients were calculated using asymptotic properties of the estimates.

endorsed clinically significant depressive symptoms (6%) compared with those who met criteria for hypertension or obesity; it is possible that participants with depression in the larger WRAP cohort are less likely to participate in biomarker study procedures, and therefore these results may reflect a biased sample of depressed individuals. In addition, the small sample size may have reduced the power to detect a modifying effect. Further studies in larger sample sizes, as well as additional examination of types of depressive symptoms endorsed (e.g., somatic, emotional, cognitive) and the onset period of symptoms (e.g., chronically depressed vs. new onset depression in mid or late life), are needed to further evaluate this relationship.

Effects of antihypertensive medication use on cognitive decline were not observed in this sample; however, it is possible that the small sizes of each cell in these post hoc analyses may have limited statistical power to detect potential relationships. Examinations of model coefficients suggest that the hypertensive/untreated group exhibited greater rates of cognitive decline compared with the normotensive/treated group. This result should be interpreted with significant caution because the overall interaction term was nonsignificant; however, follow-up of this finding is warranted in a larger sample to confirm that there is no effect of antihypertensive medication use on cognitive decline in individuals with elevated levels of Aβ. In addition, if treatment of midlife hypertension in those with elevated Aβ is associated with slowed rates of decline, clinical trials are needed to test hypotheses generated from the results of this study. Ultimately, a multimodal intervention (i.e., similar to the FINGER study; [60]) that targets appropriate management of vascular risk factors along with physical, cognitive, and social activities may prove most effective in reducing risk for cognitive decline.

The exact cause of accelerated decline in adults with amyloid and hypertension or obesity is unknown and will require further investigation. One hypothesis is that hypertension and obesity lead to reduced cerebral blood flow and blood-brain barrier dysfunction, which may reduce Aβ clearance, increase Aβ production, and result in neuronal dysfunction and ultimately cognitive decline [61]. However, in this sample, there were no differences in the proportion of participants with elevated Aβ by hypertension, obesity, or depression status. These findings differ from some prior reports suggesting that vascular risk factors are associated with elevated Aβ [36–40]. These differences may be due to the use of different analytic methods (e.g., prior studies have found that higher blood pressure is associated with greater regional Aβ burden [37]), the timing of the assessments (e.g., a prior study found that multiple vascular risk factors in midlife was associated with greater Aβ accumulation in later life [40]), or sample age (e.g., mean age of ∼60 years in our study compared with mean age of 69.4 [38]). Another hypothesis is that hypertension or obesity is associated with cerebrovascular disease and that the additive effect of Aβ burden and cerebrovascular disease results in accelerated decline. Our future investigations will build on the present study by incorporating markers of cerebrovascular function (e.g., white matter lesion, cerebral blood flow) and neurodegeneration (e.g., atrophy) to further investigate the potential underlying mechanisms of the decline observed in this sample.

There are several limitations of the present study that require consideration. The Aβ data were not collected at the same study visit for all participants, which makes interpretation of the time course of biomarker positivity and vascular risk factor development on cognitive decline challenging; however, as Aβ is thought to accumulate gradually over the course of many years, this is less likely to threaten the validity of these results. The use of dichotomous rather than continuous variables for each vascular risk factor may reduce power to detect significant effects; however, use of clinically defined cutpoints may have stronger ecological validity. Significant associations were only observed on Verbal Learning & Memory and not Speed & Flexibility performances, with the exception of a main effect of depression; exploration of individual measures that comprise this construct and evaluation across participants at varying ages may be helpful to generate additional hypotheses to test in future investigations. The sample size was relatively small for testing three-way interactions with several covariates, and although the mean age was 61 years, there was a wide age gap across the sample (ages 40–70 years). Model diagnostics suggested that model assumptions were not violated and there were no influential data points; however, an initiative to increase biomarker participation in the WRAP cohort is ongoing, and we plan to replicate and extend these models as more data become available. Future studies are also needed to determine whether longitudinal changes in vascular risk factors (e.g., changes in blood pressure or waist circumference) modify the effect of Aβ on cognitive decline and whether comorbid conditions (e.g., hypertension and obesity) or other potential modifiable factors (e.g., physical activity) are associated with longitudinal cognitive trajectories. Finally, these studies were conducted on a sample at higher risk for AD than the general public and may not generalize to nonrisk populations.

Despite these limitations, the present study adds to the literature by demonstrating that hypertension and obesity moderate relationships between Aβ and memory decline in late middle-age. This study supports the hypothesis that modifiable risk factors and Aβ interact to affect cognition, suggesting that vascular interventions in late middle-age in persons with elevated Aβ aggregation may mitigate effects of Aβ on cognition. Future work determining if treating hypertension or obesity in late middle-age slows the rate of cognitive decline or delays the onset of clinical symptoms of dementia is needed.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jalz.2018.09.008.

RESEARCH IN CONTEXT

1 Systematic review: A literature review was conducted using PubMed and Web of Science databases. Although relationships among β-amyloid (Aβ) and modifiable risk factors including hypertension, obesity, and depression have been observed, the interaction among Aβ and modifiable risk factors on longitudinal cognitive performance in midlife was not well characterized.

2 Interpretation: In a sample of 207 late middle-aged adults enriched for Alzheimer's disease risk, presence of hypertension or obesity moderated the relationship between Aβ (on positron emission tomography scan or in cerebrospinal fluid) and longitudinal Verbal Learning & Memory, but not Speed & Flexibility, performance. These findings suggest that hypertension or obesity in midlife may exacerbate subtle cognitive decline associated with Aβ deposition.

3 Future directions: Future studies are needed to determine if treatment of hypertension or obesity during midlife reduces the rate of cognitive decline and delays the onset of clinical symptoms of dementia. Further examination of physical activity level, diet, and antihypertensive medication use would be beneficial.

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