Title: Modifiable risk factors moderate the relationship between amyloid and cognition in midlife

Authors: Lindsay R. Clark, PhD[abc], Rebecca L. Koscik, PhD[b], Samantha L. Allison, PhD[a], Sara E. Berman, BS[ad], Cynthia M. Carlsson, MD[abc], Derek Norton, MS[ae], Barbara B. Bendlin, PhD[a], Sanjay Asthana, MD[ac], Tobey Betthauser, BS[f], Bradley T. Christian, PhD[af], and Sterling C. Johnson, PhD[abc]

Affiliations:

[a]Alzheimer's Disease Research Center, University of Wisconsin School of Medicine and Public Health, Madison, WI 53792, USA.

[b]Wisconsin Alzheimer's Institute, University of Wisconsin School of Medicine and Public Health, Madison, WI 53792, USA.

[c]Geriatric Research Education and Clinical Center, William S. Middleton Memorial Veterans Hospital, Madison, WI 53705, USA.

[d]Medical Scientist and Neuroscience Training Programs, University of Wisconsin School of Medicine and Public Health, Madison, WI 53792, USA.

[e]Department of Biostatistics and Medical Informatics, University of Wisconsin, Madison, WI 53792, USA.

[f]Waisman Center and Department of Medical Physics, University of Wisconsin, Madison, WI 53792, USA.

Corresponding author: Lindsay R. Clark, PhD, University of Wisconsin Madison School of Medicine & Public Health, 600 Highland Avenue, J5/1 Mezzanine, Madison, WI, 53792, USA. Phone: 608-263-4405; Fax: 608-265-3091; Email: lrclark@medicine.wisc.edu.

ABSTRACT

Although evidence suggests a relationship between elevated beta-amyloid and cognitive decline, approximately 30% of older adults with positive markers of amyloid remain cognitively healthy. Our objective was to test if the presence of modifiable risk factors (i.e., central obesity, hypertension, and depressive symptoms) moderated the relationship between amyloid and longitudinal cognitive performance. Data were from 207 adults (140 females; age range=40-70) enriched for Alzheimer's disease risk (73% parental history of Alzheimer's disease) enrolled in the Wisconsin Registry for Alzheimer's Prevention study. Participants completed at least two neuropsychological evaluations and one biomarker visit ([C11]Pittsburgh Compound B PET scan or lumbar puncture). Participants were characterized as high or low on amyloid using cutoffs developed for [C11]Pittsburgh Compound B-PET distribution volume ratio or CSF amyloid beta 1-42 values. Participants were also coded as high or low risk on obesity, hypertension, and depressive symptoms. Linear mixed effects regression models examined three-way interactions between modifiable risk factor status x amyloid group x age at each study visit on longitudinal Verbal Learning & Memory and Speed & Flexibility factor scores. Results indicated that the relationship between beta-amyloid and Verbal Learning & Memory decline was associated with hypertension status (Likelihood ratio test for significance of hypertension status age x amyloid status x visit age interaction term; $\chi^2_{(1)} = 5.28$, $p = .02$). The relationship between beta-amyloid and Speed & Flexibility decline was associated with depression status (Likelihood ratio test for significance of amyloid status x depression status x visit age interaction term; $\chi^2_{(1)} = 7.10$, $p = .03$). The presence of obesity did not significantly moderate the relationship between beta-amyloid status and cognitive performance, although the direction of relationship was similar to above relationships (Likelihood ratio test for significance of obesity

status x amyloid status x visit age interaction term; $\chi^2_{(1)} = 1.52$, $p = .21$). In this at-risk for Alzheimer's disease cohort, the modifiable risk factors of hypertension and depression significantly moderated the relationship between beta-amyloid and cognitive decline. Identification and modification of these risk factors in late middle age may slow the effect of amyloid on the progression of cognitive symptoms.

Keywords: preclinical Alzheimer's disease, beta-amyloid, hypertension, obesity, depression

INTRODUCTION

Although available treatments for Alzheimer's disease may provide some short-term benefits, they have limited efficacy in terms of modifying the course of the disease (Klafki *et al.*, 2006; Salomone *et al.*, 2012). The lack of an effective disease-modifying medication has led to increased efforts targeted at both early detection of Alzheimer's disease and modifiable risk factors that may influence disease progression. Two commonly used ante-mortem biomarkers allowing for early detection of Alzheimer's disease-related pathology are the PET imaging tracer [C11]Pittsburgh Compound B, which allows for imaging of amyloid deposition in vivo (Ikonomovic *et al.*, 2008), and CSF levels of amyloid-beta 1-42, which are correlated with the formation of amyloid plaques in the brain (Strozyk *et al.*, 2003; Fagan *et al.*, 2006). Prior investigations indicate that cognitively normal adults with higher mean cortical binding potential values for the PET imaging tracer [C11]Pittsburgh Compound B and/or lower cerebrospinal levels of amyloid beta 1-42 are at increased risk of developing dementia (Morris *et al.*, 2009; Roe *et al.*, 2011; Soldan *et al.*, 2013; Chen *et al.*, 2014). Furthermore, adults with elevated amyloid deposition are more likely to exhibit cognitive decline over time prior to the development of clinical symptoms (Gustafson *et al.*, 2007; Lim *et al.*, 2014; Ossenkoppele *et al.*, 2014; Clark *et al.*, 2016; Petersen *et al.*, 2016). Although elevated amyloid deposition is associated with increased risk of both cognitive decline and dementia, up to 30% of older adults with elevated amyloid deposition remain cognitively normal in late life (Morris *et al.*, 2010). This finding suggests that not all adults with elevated amyloid deposition will progress to dementia, and that other factors may moderate the relationship between amyloid deposition and cognitive decline.

Supporting this hypothesis, epidemiological studies suggest that seven potentially modifiable risk factors for Alzheimer's disease, 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 (Barnes and Yaffe, 2011). Several studies report greater risk for dementia and/or longitudinal decline on neuropsychological measures in adults with depressive symptomatology (Berger *et al.*, 1999; Green *et al.*, 2003; Sachs-Ericsson *et al.*, 2005; Ownby *et al.*, 2006; Royall and Palmer, 2013; Verdelho *et al.*, 2013; Geda *et al.*, 2014; Xu *et al.*, 2015), obesity (Kivipelto *et al.*, 2005; Whitmer *et al.*, 2005a; Wolf *et al.*, 2007; Sabia *et al.*, 2009; Profenno *et al.*, 2010; Dahl *et al.*, 2013; Xu *et al.*, 2015), or hypertension (Whitmer *et al.*, 2005b; Wolf *et al.*, 2007; Gao *et al.*, 2009; Gottesman *et al.*, 2014; Haring *et al.*, 2015; Walker *et al.*, 2017). Moreover, prior investigations revealed elevated amyloid deposition in non-demented older adults with depression (Harrington *et al.*, 2015) or hypertension (Langbaum *et al.*, 2012; Nation *et al.*, 2013; Hughes *et al.*, 2014). Two recent studies also observed a relationship between midlife obesity and amyloid deposition in later life (Chuang *et al.*, 2016; Gottesman *et al.*, 2017). Finally, one prior investigation demonstrated that adults with abnormal plasma amyloid levels and elevated blood pressure at midlife were at greatest risk of developing Alzheimer's disease (Shah *et al.*, 2012); however, no study to date has examined whether cognitively healthy middle-aged adults with these risk factors and elevated amyloid deposition are more likely to decline than those with elevated amyloid but absence of these risk factors.

Therefore, the purpose of the current study was to determine if the presence of modifiable risk factors moderate the relationship between amyloid deposition and longitudinal performance on neuropsychological measures in cognitively normal late middle-aged adults. We decided to

focus this study on three risk factors that were objectively measured and well-characterized in the Wisconsin Registry for Alzheimer's Prevention cohort: hypertension, obesity, and depression. We investigated the moderating effects of these risk factors on the relationship between amyloid deposition (as assessed via the PET imaging tracer [C11]Pittsburgh Compound B or cerebrospinal levels of amyloid beta 1-42) and longitudinal neuropsychological performance (i.e., speed/flexibility and learning/memory). Similar to our prior work in this cohort, we hypothesized that elevated amyloid burden would be associated with greater cognitive decline. We further hypothesized that elevated amyloid burden and presence of each risk factor would be associated with greatest decline on cognitive measures.

MATERIALS AND METHODS

Participants

Data were from 207 participants enrolled in the Wisconsin Registry for Alzheimer's Prevention study, which consists of a cohort of ~1550 asymptomatic (at study entry) late middle-aged adults enriched for parental history of Alzheimer's disease (Sager *et al.*, 2005; Johnson *et al.*, 2018). The ongoing parent study includes biennial evaluations that involve a physical exam, labs, a neuropsychological evaluation, and optional linked studies for acquisition of neuroimaging and CSF biomarkers of Alzheimer's disease. The Wisconsin Registry for Alzheimer's Prevention protocol includes a baseline neuropsychological evaluation, a second visit four years after baseline, and subsequent visits every two years. Because a subset of modifiable risk factor data was not acquired until visit 2, the present study design included data collected at visits 2, 3, 4, and 5. Inclusion criteria for this study were as follows: completion of at least two study visits with relevant data completed, no diagnosis of dementia, and completion of either an amyloid 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.

Modifiable Risk Factor Assessment

Blood pressure and anthropometric measures were obtained at study visits 2 and on according to Atherosclerosis Risk in Communities Study protocol. Prior to 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 guidelines of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (i.e., systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥ 90 mm Hg (James *et al.*, 2014)). Use of antihypertensive medication was included as a covariate in primary analyses and examined further in post-hoc analyses. Waist circumferences were 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 (WHO, 2011). Depressive symptoms were assessed at all visits using the Center for Epidemiologic Studies of Depression scale, with total scores ≥ 16 coded as depressed (Lewinsohn *et al.*, 1997).

Cognitive Assessment

A comprehensive neuropsychological assessment was completed at each visit (Johnson *et al.*, 2018). 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 & Memory factor and that measures of speed and executive function (Trailmaking Test Parts A & B, Stroop Color-Word Interference condition) loaded onto a Speed & Flexibility factor (Dowling *et al.*, 2010). 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) (Koscik *et al.*, 2014).

Amyloid status determination

Positive or negative amyloid status was determined by mean distribution volume ratio obtained from the PET imaging tracer [C11]Pittsburgh Compound B on a Siemens EXACT HR+ scanner or by amyloid beta 1-42 or amyloid beta 1-42/amyloid beta 1-40 levels in CSF obtained from a lumbar puncture. If data from both modalities were available, positive status on either was indicated as positive in the amyloid group.

Detailed methods for [C-11]PiB radiochemical synthesis, [C11]Pittsburgh Compound B-PET sequence parameters, and distribution volume ratio map generation have been described previously (Johnson *et al.*, 2014). 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. Similar to prior studies in this cohort, a mean distribution volume ratio of 1.19 was used to define PET amyloid positivity (Racine *et al.*, 2016).

Twenty-two mL of CSF were removed from the L3-L4 or L4-L5 vertebral interspace via gentle extraction into polypropylene syringes. Samples were analyzed at the Clinical Neurochemistry Laboratory at the Sahlgrenska Academy of the University of Gothenburg, Sweden for amyloid beta 1-40 and amyloid beta 1-42 using commercially available enzyme-linked immunosorbent assay methods. An amyloid beta 1-42 (innotest) value < 471.54 or an amyloid beta 1-42/amyloid beta 1-40 < .09 was used to define CSF amyloid positivity, based on prior receiver operating characteristic analyses showing these values best discriminated cognitively healthy adults from individuals with dementia (Clark *et al.*, Under Review).

Experimental Design

Blinding and randomization were not performed for this study as this was a retrospective analysis of an observational cohort. Based on our sample size and

Statistical Analysis

To test the relationship between each modifiable risk factor and amyloid status, chi-square analyses of amyloid status (positive vs. negative) by risk factor status (1. hypertension vs no hypertension; 2. obesity vs no obesity; 3. depression vs no depression) were conducted in SPSS version 24. To test the hypothesis that longitudinal cognitive performance would vary by risk factor and amyloid status, linear mixed effects models were conducted in R version 3.3.1 using the lme4 package version 1.1-12. Outcome variables were Verbal Learning & Memory and a Speed & Flexibility factor scores (standardized using baseline mean (SD); z-scores). Fixed effects for model 1 included hypertension (yes/no), amyloid group (positive/negative), age at each visit (time-varying variable; centered on the sample mean), hypertension group x amyloid group, age at each visit x hypertension group, age at each visit x amyloid group, and age at each visit x hypertension group x amyloid group. Fixed effects for models 2 and 3 were identical to

model 1 with the exception of obesity (yes/no) and depression (yes/no) status instead of hypertension. Covariates included age at biomarker visit, sex, education, practice effects (number of prior exposures to cognitive test [total visits completed – 1]), and antihypertensive medication use (for model 1). Random effects included intercept and slope nested within-subject. 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 were performed using the Wald test. Statistical tests were two-tailed (except likelihood ratio test which was one-tailed) and an alpha-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.

Primary models included the risk factor information from the first visit included in this study (wave 2). Secondary models included cumulative risk factor information from all visits (e.g., yes = risk factor present at any visit; no = risk factor absent at all visits). Additional analyses were conducted to examine the effect of antihypertensive medication use. For these analyses, a group variable with four levels was created (non-hypertensive/non-medicated, non-hypertensive/medicated, hypertensive/non-medicated, hypertensive/medicated) and the same models as above were conducted using this variable as the risk factor group.

RESULTS

Sample characteristics

The sample was on average 59 years of age at visit 2, 68% female, highly educated (mean 16 years of education), and enriched for AD-risk (73% parents with AD; 38% *APOE* ε4 genotype carriers; see Table 1). A majority of participants (88% of sample) had neuropsychological data from at least three study visits (e.g., at least six years follow-up).

Approximately 30% of the sample was beta-amyloid positive. At the first visit included in this study, 17% of the sample was hypertensive, 39% was obese, and 7% was depressed.

Relationship between modifiable risk factors and amyloid status

Results of the chi-square analysis indicated that the risk factor groups did not differ by amyloid status (see Table 2). Specifically, there were no differences in proportion of participants classified as amyloid positive between the hypertensive groups ($\chi^2_{(1)}$ = .04, p = .83), obesity groups ($\chi^2_{(1)}$ = 1.03, p = .31), or depression groups ($\chi^2_{(1)}$ = .24, p = .63).

Relationships among modifiable risk factors, beta-amyloid, and cognition

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

Hypertension

Likelihood ratio tests comparing the full model and nested linear mixed-effects models indicated that the three-way interaction of hypertension group x amyloid group x visit age accounted for a statistically significant amount of variance in Verbal Learning & Memory performance ($\chi^2_{(1)}$ = 5.28, p = .02; see Table 3). This result indicates that the relationship between amyloid and rate of decline in list-learning with age was associated with hypertension status (see Figure 1A). Statistical comparison of model coefficients indicated that those with amyloid positivity and hypertension exhibited greater decline than those with amyloid positivity without hypertension (β = -0.07 (SE=.04), p = .06). The association between the interaction of hypertension group x amyloid group x visit age and Speed & Flexibility performance was non-

significant ($\chi^2_{(1)}$ = .25, p = .62; see Table 4). Additionally, when the three-way interaction term was removed from the model, none of the two-way interaction or main effect terms were significantly associated with Speed & Flexibility performance, although there was a trend for amyloid group x visit age; β = -0.02 (SE=.01), p = .15.

Secondary analyses on the same models, which included cumulative hypertension data (e.g., yes if hypertensive at any visit and no if not hypertensive at all visits), revealed similar results in that the three-way interaction of hypertension group x amyloid group x visit age was significantly associated with Verbal Learning & Memory performance ($\chi^2_{(1)}$ = 4.11, p = .04), but not with Speed & Flexibility performance ($\chi^2_{(1)}$ = .44, p = .51); see Supplemental Tables 1 and 2.

Additional analyses were conducted to examine the effect of antihypertensive medication use on these results. Nineteen percent (n=40) were treated with an antihypertensive medication. Of the sample of n=207, n=143 were non-hypertensive/non-treated (e.g., no hypertension), n=29 were non-hypertensive/treated (e.g., controlled hypertension), n=24 were hypertensive/non-treated (e.g., elevated BP but not on antihypertensive medications), and n=11 were hypertensive/treated (e.g., uncontrolled hypertension). Likelihood ratio tests comparing the full model and nested linear mixed-effects models indicated that the three-way interaction among hypertension/treatment group x amyloid group x visit age accounted for a statistically significant amount of variance in Verbal Learning & Memory performance ($\chi^2_{(3)}$ = 9.08, p = .03). Specifically, the hypertensive/non-treated group with amyloid positivity exhibited significantly greater decline with age compared to the reference group (non-hypertensive/non-treated) (β = -0.2, t = -2.82, p = .005), whereas the hypertensive/medicated group and non-hypertensive/medicated group did not differ from the non-hypertensive/non-treated group (see

Table 5). Similar results were not observed on Speed & Flexibility performance ($\chi^2_{(3)}$ = 2.48, p = .48).

Obesity

Likelihood ratio tests comparing the full model and nested linear mixed-effects models indicated that the three-way interaction obesity group x amyloid group x visit age was not statistically significant for the Verbal Learning & Memory factor ($\chi^2_{(1)}$ = 1.52, p = .21; Table 3) or the Speed & Flexibility factor ($\chi^2_{(1)}$ = .15, p = .69; Table 4). Additionally, when the three-way interaction term was removed from the model, none of the two-way interaction or main effect terms were significantly associated with cognitive performance, although there was a trend for amyloid group x visit age; β = -0.02 (SE=.01), p = .14. Secondary analyses on the same models, which included cumulative obesity data (e.g., yes if obese at any visit and no if not obese at all visits), revealed similar non-significant results (see Supplemental Tables 1 and 2).

Depression

Likelihood ratio tests comparing the full model and nested linear mixed-effects models indicated that the three-way interaction of depression group x amyloid group x visit age was not significantly associated with Verbal Learning & Memory performance ($\chi^2_{(1)}$ = 0.24, p = .62; see Table 3). However, the three-way interaction of depression group x amyloid group x visit age accounted for a statistically significant amount of variance in Speed & Flexibility performance ($\chi^2_{(1)}$ = 7.10, p = .03; see Table 4), indicating that the relationship between amyloid and rate of decline with age was associated with depression status (see Figure 1C). Statistical comparison of model coefficients indicated that those with amyloid positivity and depressive symptoms exhibited greater decline than those with amyloid positivity without depressive symptoms (β = -0.07 (SE=.04), p = .07). Additionally, when the three-way interaction term was removed from

the model, none of the two-way interaction or main effect terms were significantly associated with verbal learning and memory performance although there was a trend for amyloid group x visit age; β = -0.02 (SE=.01), p = .11.

Secondary analyses on the same models including cumulative depressive symptom data (e.g., yes if depressed at any visit and no if non-depressed at all visits) differed somewhat from baseline findings. Similar to the baseline findings, the three-way interaction among depression group x amyloid group x visit age was not associated with Verbal Learning & Memory performance ($\chi^2_{(1)}$ = 0.37, p = .54); however, the two-way interaction between depression and amyloid status was significantly associated with Verbal Learning & Memory performance ($\chi^2_{(1)}$ = 8.54, p = .003; see Supplemental Table 1). This finding indicates that the association between amyloid status and cognitive performance overall (but not age-related decline) was associated with depressive symptoms. In contrast to the baseline findings, the three-way interaction among depression group x amyloid group x visit age was not associated with Speed & Flexibility performance ($\chi^2_{(1)}$ = 0.15, p = .70; see Supplemental Table 2).

DISCUSSION

In a sample of 207 late middle-aged adults enriched for Alzheimer's disease risk, the presence of both amyloid (on PET scan or in CSF) and hypertension was associated with significantly greater longitudinal decline on learning and memory performance, and the presence of both amyloid and depression was associated with significantly greater rates of decline on speed and flexibility performance. Although the direction of relationships were similar for central obesity as those described above, the results were non-significant. These findings suggest that cognitively normal adults with both positive markers of amyloid deposition and hypertension or depression are at greatest risk for cognitive decline. Although hypertension and

depression interacted with amyloid to increase cognitive decline, there were no associations between these two risk factors and elevated amyloid. These findings suggest that there may be an additive effect of amyloid pathology and these modifiable risk factors to accelerate cognitive decline. Further longitudinal follow-up is ongoing and needed to confirm if these individuals exhibiting greatest decline do go on to develop clinical symptoms of dementia.

Within the sample with hypertension, we found some variability showing that those with hypertension who were untreated exhibited the strongest relationship between elevated amyloid and cognitive decline. In contrast, participants who had hypertension, but were on antihypertensive medications exhibited similar relationships between amyloid and cognition as those who were non-hypertensive. This is consistent with prior reports showing that those with hypertension who are not medicated exhibit greater decline and are at increased risk of dementia when compared to those with hypertension who are medicated (Gelber *et al.*, 2013; Gottesman *et al.*, 2014). The current findings add to the literature by showing that untreated hypertension seems to exacerbate the negative relationship between amyloid burden and longitudinal cognitive performance. These findings suggest that by treating hypertension during midlife, it may be possible to attenuate the effect of amyloid burden on cognitive decline. However, this hypothesis needs further study through randomized-controlled trials. Interestingly, in contrast to some prior reports, we did not find that hypertension was associated with elevated amyloid deposition. This may be because our sample was younger than some prior reports (e.g., mean age of ~60 in our study compared to mean ages of 69.4 (Nation *et al.*, 2013) and 86.9 (Hughes *et al.*, 2013)) or due to different analysis methods (e.g., Langbaum *et al.* (2012) demonstrated that systolic BP and pulse pressure positively correlated with PiB distribution in frontal, temporal, and parietal

regions, whereas we categorized participants in groups based on BP and composite amyloid cutoffs).

Moreover, we observed that adults with depression at baseline and amyloid positivity exhibited greater decline primarily on speed and executive functioning measures. However, if depression was measured cumulatively across the study, we observed that those with both depressive symptoms endorsed at any study visit and positive amyloid exhibited lower memory scores overall, but without significant decline with age. Many studies on depression show that those with depression exhibit poorer cognitive performances, perhaps due to amotivation, fatigue, and concentration difficulties inherent in depression (Gotlib and Joormann, 2010). However, other studies also show that older adults with depression are more likely to decline over time as well (Thomas and O'Brien, 2008). It has been debated as to whether this latter finding might be because depressive symptoms are a part of the prodromal symptoms of dementia. Our findings are somewhat mixed in that they suggest that those who already have Alzheimer's disease pathology may decline if depressive symptoms are present early (e.g., at our first visit included in these analyses), but may exhibit stable lower scores if depressive symptoms are present at later study visits. These findings warrant further study on whether specific depressive symptoms endorsed (e.g., somatic, emotional, cognitive) or the onset period (e.g., chronically depressed vs new onset depression in mid or late life) are more likely to moderate relationships between amyloid deposition and cognitive decline.

Obesity has been less studied with regard to amyloid deposition and cognition compared to hypertension and depression. Our study did not find that obesity was associated with elevated amyloid, or that obesity moderated the relationship between amyloid burden and cognitive decline. A couple of recent studies have found that higher body mass index (Chuang *et al.*,

2016; Gottesman *et al.*, 2017) in midlife was associated with greater amyloid deposition in late life; however, our findings suggest that obesity (as measured via waist circumference) was not associated with elevated amyloid burden measured during midlife. Although mid-life obesity is a clear risk factor for late-life decline, more specific mechanisms that are associated with obesity, such as insulin resistance or diabetes, may need to be evaluated to see this relationship more clearly.

The current study adds to the literature by demonstrating that hypertension and depression may moderate the relationship between amyloid and cognitive decline in middle-age. However, this study has several limitations that need to be considered when interpreting these results. First, these findings may not generalize to populations that are dissimilar to the current study cohort who are generally at higher risk for Alzheimer's disease, well-educated, Caucasian adults. Participants in this study have at most mild cognitive impairments and it is not certain that all participants who exhibit greater decline on neuropsychological measures will progress to a diagnosis of dementia; continued follow up of these participants is needed. Although these results are promising in that they suggest potential preventative strategies to mitigate effects of amyloid on cognition, future studies are needed to determine if treating these risk factors prevent or delay the onset of clinical symptoms of dementia.

ACKNOWLEDGMENTS

We gratefully acknowledge the assistance of researchers and staff at the Wisconsin Registry for Alzheimer's Prevention and Wisconsin Alzheimer's Disease Research Center for assistance in recruitment and data collection. Most importantly, we thank the dedicated Wisconsin Registry for Alzheimer's Prevention participants for their continued support and participation in this research.

FUNDING

The project described was supported by the Clinical Translational Science Award program through the National Institutes of Health (NIH) National Center for Advancing Translational Sciences, and grant UL1TR00427. This study was supported in part by a core grant to the Waisman Center from the National Institute of Child Health and Human Development (P30 HD03352). Additional funding support was provided by NIH grants R01 AG021155 (SCJ), R01 AG027161 (SCJ), ADRC P50 AG033514 (SA), R01AG037639 (BBB), F30 AG054115 (SEB), T32 GM007507 (SEB), and T32 GM008692 (SEB).

REFERENCES

Barnes DE, Yaffe K. The projected effect of risk factor reduction on Alzheimer's disease prevalence. The Lancet Neurology 2011; 10(9): 819-28.
Berger A-K, Fratiglioni L, Forsell Y, Winblad B, Bäckman L. The occurrence of depressive symptoms in the preclinical phase of AD A population-based study. Neurology 1999; 53(9): 1998-.
Chen X, Li M, Wang S, Zhu H, Xiong Y, Liu X. Pittsburgh compound B retention and progression of cognitive status–a meta-analysis. European journal of neurology 2014; 21(8): 1060-7.
Chuang Y, An Y, Bilgel M, Wong D, Troncoso J, O'brien R*, et al.* Midlife adiposity predicts earlier onset of Alzheimer's dementia, neuropathology and presymptomatic cerebral amyloid accumulation. Molecular psychiatry 2016; 21(7): 910-5.
Clark LR, Berman SE, Norton D, Koscik RL, Jonaitis EM, Blennow K*, et al.* Age-accelerated cognitive decline in asymptomatic adults with CSF β-amyloid. Under Review.
Clark LR, Racine AM, Koscik RL, Okonkwo OC, Engelman CD, Carlsson CM*, et al.* Beta-amyloid and cognitive decline in late middle age: Findings from the Wisconsin Registry for Alzheimer's Prevention study. Alzheimer's & Dementia 2016; 12(7): 805-14.
Dahl AK, Hassing LB, Fransson EI, Gatz M, Reynolds CA, Pedersen NL. Body mass index across midlife and cognitive change in late life. International journal of obesity 2013; 37(2): 296-302.
Dowling NM, Hermann B, La Rue A, Sager MA. Latent Structure and Factorial Invariance of a Neuropsychological Test Battery for the Study of Preclinical Alzheimer's Disease. Neuropsychology 2010; 24(6): 742-56.
Fagan AM, Mintun MA, Mach RH, Lee SY, Dence CS, Shah AR*, et al.* Inverse relation between in vivo amyloid imaging load and cerebrospinal fluid Aβ42 in humans. Annals of neurology 2006; 59(3): 512-9.
Gao S, Jin Y, Unverzagt FW, Liang C, Hall KS, Ma F*, et al.* Hypertension and cognitive decline in rural elderly Chinese. Journal of the American Geriatrics Society 2009; 57(6): 1051-7.
Geda YE, Roberts RO, Mielke MM, Knopman DS, Christianson TJ, Pankratz VS*, et al.* Baseline neuropsychiatric symptoms and the risk of incident mild cognitive impairment: a population-based study. American Journal of Psychiatry 2014; 171(5): 572-81.
Gelber RP, Ross GW, Petrovitch H, Masaki KH, Launer LJ, White LR. Antihypertensive medication use and risk of cognitive impairment: the Honolulu-Asia Aging Study. Neurology 2013; 81(10): 888-95.
Gotlib IH, Joormann J. Cognition and Depression: Current Status and Future Directions. Annual review of clinical psychology 2010; 6: 285-312.
Gottesman RF, Schneider AL, Albert M, Alonso A, Bandeen-Roche K, Coker L*, et al.* Midlife hypertension and 20-year cognitive change: the atherosclerosis risk in communities neurocognitive study. JAMA neurology 2014; 71(10): 1218-27.
Gottesman RF, Schneider AL, Zhou Y, Coresh J, Green E, Gupta N*, et al.* Association between midlife vascular risk factors and estimated brain amyloid deposition. Jama 2017; 317(14): 1443-50.
Green RC, Cupples LA, Kurz A, Auerbach S, Go R, Sadovnick D*, et al.* Depression as a risk factor for Alzheimer disease: the MIRAGE Study. Archives of neurology 2003; 60(5): 753-9.
Gustafson DR, Skoog I, Rosengren L, Zetterberg H, Blennow K. Cerebrospinal fluid β-amyloid 1–42 concentration may predict cognitive decline in older women. Journal of Neurology, Neurosurgery & Psychiatry 2007; 78(5): 461-4.
Haring B, Wu C, Coker LH, Seth A, Snetselaar L, Manson JE*, et al.* Hypertension, dietary sodium, and cognitive decline: results from the women's health initiative memory study. American journal of hypertension 2015; 29(2): 202-16.
Hughes TM, Kuller LH, Barinas-Mitchell EJ, McDade EM, Klunk WE, Cohen AD*, et al.* Arterial stiffness and β-amyloid progression in nondemented elderly adults. JAMA neurology 2014; 71(5): 562-8.

Ikonomovic MD, Klunk WE, Abrahamson EE, Mathis CA, Price JC, Tsopelas ND*, et al.* Post-mortem correlates of in vivo PiB-PET amyloid imaging in a typical case of Alzheimer's disease. Brain 2008; 131(6): 1630-45.
James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: Report from the panel members appointed to the eighth joint national committee (jnc 8). JAMA 2014; 311(5): 507-20.
Johnson SC, Christian BT, Okonkwo OC, Oh JM, Harding S, Xu G*, et al.* Amyloid burden and neural function in people at risk for Alzheimer's Disease. Neurobiology of Aging 2014; 35(3): 576-84.
Johnson SC, Koscik RL, Jonaitis EM, Clark LR, Mueller KD, Berman SE*, et al.* The Wisconsin Registry for Alzheimer's Prevention: A review of findings and current directions. Alzheimer's & Dementia: Diagnois, Assessment, & Disease Monitoring 2018; In press.
Kivipelto M, Ngandu T, Fratiglioni L, Viitanen M, Kåreholt I, Winblad B*, et al.* Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease. Archives of neurology 2005; 62(10): 1556-60.
Klafki H-W, Staufenbiel M, Kornhuber J, Wiltfang J. Therapeutic approaches to Alzheimer's disease. Brain 2006; 129(11): 2840-55.
Koscik RL, La Rue A, Jonaitis EM, Okonkwo OC, Johnson SC, Bendlin BB*, et al.* Emergence of mild cognitive impairment in late middle-aged adults in the wisconsin registry for Alzheimer's prevention. Dementia and geriatric cognitive disorders 2014; 38(1-2): 16-30.
Langbaum JB, Chen K, Launer LJ, Fleisher AS, Lee W, Liu X*, et al.* Blood pressure is associated with higher brain amyloid burden and lower glucose metabolism in healthy late middle-age persons. Neurobiology of aging 2012; 33(4): 827. e11-. e19.
Lewinsohn PM, Seeley JR, Roberts RE, Allen NB. Center for Epidemiologic Studies Depression Scale (CES-D) as a screening instrument for depression among community-residing older adults. Psychology and aging 1997; 12(2): 277-87.
Lim YY, Maruff P, Pietrzak RH, Ames D, Ellis KA, Harrington K*, et al.* Effect of amyloid on memory and non-memory decline from preclinical to clinical Alzheimer's disease. Brain 2014; 137(1): 221-31.
Morris JC, Roe CM, Grant EA, Head D, Storandt M, Goate AM*, et al.* Pittsburgh compound B imaging and prediction of progression from cognitive normality to symptomatic Alzheimer disease. Archives of neurology 2009; 66(12): 1469-75.
Morris JC, Roe CM, Xiong C, Fagan AM, Goate AM, Holtzman DM*, et al.* APOE predicts amyloid-beta but not tau Alzheimer pathology in cognitively normal aging. Annals of neurology 2010; 67(1): 122-31.
Nation DA, Edland SD, Bondi MW, Salmon DP, Delano-Wood L, Peskind ER*, et al.* Pulse pressure is associated with Alzheimer biomarkers in cognitively normal older adults. Neurology 2013; 81(23): 2024-7.
Ossenkoppele R, van der Flier WM, Verfaillie SC, Vrenken H, Versteeg A, van Schijndel RA*, et al.* Long-term effects of amyloid, hypometabolism, and atrophy on neuropsychological functions. Neurology 2014; 82(20): 1768-75.
Ownby RL, Crocco E, Acevedo A, John V, Loewenstein D. Depression and risk for Alzheimer disease: systematic review, meta-analysis, and metaregression analysis. Archives of general psychiatry 2006; 63(5): 530-8.
Petersen RC, Wiste HJ, Weigand SD, Rocca WA, Roberts RO, Mielke MM*, et al.* Association of elevated amyloid levels with cognition and biomarkers in cognitively normal people from the community. JAMA neurology 2016; 73(1): 85-92.
Profenno LA, Porsteinsson AP, Faraone SV. Meta-analysis of Alzheimer's disease risk with obesity, diabetes, and related disorders. Biological psychiatry 2010; 67(6): 505-12.
Racine AM, Clark LR, Berman SE, Koscik RL, Mueller KD, Norton D*, et al.* Associations between Performance on an Abbreviated CogState Battery, Other Measures of Cognitive Function, and

Biomarkers in People at Risk for Alzheimer's Disease. Journal of Alzheimer's disease : JAD 2016; 54(4): 1395-408.
Roe C, Fagan A, Williams M, Ghoshal N, Aeschleman M, Grant E*, et al.* Improving CSF biomarker accuracy in predicting prevalent and incident Alzheimer disease. Neurology 2011; 76(6): 501-10.
Royall DR, Palmer RF. Alzheimer's disease pathology does not mediate the association between depressive symptoms and subsequent cognitive decline. Alzheimer's & Dementia 2013; 9(3): 318-25.
Sabia S, Kivimaki M, Shipley MJ, Marmot MG, Singh-Manoux A. Body mass index over the adult life course and cognition in late midlife: the Whitehall II Cohort Study. The American journal of clinical nutrition 2009; 89(2): 601-7.
Sachs-Ericsson N, Joiner T, Plant EA, Blazer DG. The influence of depression on cognitive decline in community-dwelling elderly persons. The American journal of geriatric psychiatry 2005; 13(5): 402-8.
Sager MA, Hermann B, La Rue A. Middle-Aged Children of Persons With Alzheimer's Disease: APOE Genotypes and Cognitive Function in the Wisconsin Registry for Alzheimer's Prevention. Journal of Geriatric Psychiatry and Neurology 2005; 18(4): 245-9.
Salomone S, Caraci F, Leggio GM, Fedotova J, Drago F. New pharmacological strategies for treatment of Alzheimer's disease: focus on disease modifying drugs. British journal of clinical pharmacology 2012; 73(4): 504-17.
Shah NS, Vidal J-S, Masaki K, Petrovitch H, Ross GW, Tilley C*, et al.* Midlife Blood Pressure, Plasma β-Amyloid, and the Risk for Alzheimer Disease. Hypertension 2012: HYPERTENSIONAHA. 111.178962.
Soldan A, Pettigrew C, Li S, Wang M-C, Moghekar A, Selnes OA*, et al.* Relationship of cognitive reserve and cerebrospinal fluid biomarkers to the emergence of clinical symptoms in preclinical Alzheimer's disease. Neurobiology of aging 2013; 34(12): 2827-34.
Strozyk D, Blennow K, White L, Launer L. CSF Aβ 42 levels correlate with amyloid-neuropathology in a population-based autopsy study. Neurology 2003; 60(4): 652-6.
Thomas AJ, O'Brien JT. Depression and cognition in older adults. Current opinion in psychiatry 2008; 21(1): 8-13.
Verdelho A, Madureira S, Moleiro C, Ferro JM, T O'Brien J, Poggesi A*, et al.* Depressive symptoms predict cognitive decline and dementia in older people independently of cerebral white matter changes: the LADIS study. J Neurol Neurosurg Psychiatry 2013; 84(11): 1250-4.
Walker KA, Power MC, Gottesman RF. Defining the relationship between hypertension, cognitive decline, and dementia: a review. Current hypertension reports 2017; 19(3): 24.
Whitmer RA, Gunderson EP, Barrett-Connor E, Quesenberry CP, Yaffe K. Obesity in middle age and future risk of dementia: a 27 year longitudinal population based study. Bmj 2005a; 330(7504): 1360.
Whitmer RA, Sidney S, Selby J, Johnston SC, Yaffe K. Midlife cardiovascular risk factors and risk of dementia in late life. Neurology 2005b; 64(2): 277-81.
WHO. Waist Circumference and Waist-Hip Ratio: Report of a WHO Expert Consultation. 2011.
Wolf PA, Beiser A, Elias MF, Au R, Vasan RS, Seshadri S. Relation of obesity to cognitive function: importance of central obesity and synergistic influence of concomitant hypertension. The Framingham Heart Study. Current Alzheimer Research 2007; 4(2): 111-6.
Xu W, Tan L, Wang H-F, Jiang T, Tan M-S, Tan L*, et al.* Meta-analysis of modifiable risk factors for Alzheimer's disease. J Neurol Neurosurg Psychiatry 2015: jnnp-2015-310548.

Table 1. Sample characteristics

Characteristics	**Mean (SD) or N (%)**
Age at wave 2	58.5 (6.3)
Biomarker (PET or CSF) age	60.7 (6.4)
Sex (Female)	140 (68%)
Education (years)	16.1 (2.4)
APOE (ε4 carrier)	78 (38%)
Parental history of Alzheimer's disease (positive)	151 (73%)
Number study visits included in this study	3.4 (0.7)
Verbal Learning & Memory composite score at wave 2	.02 (1.0)
Speed & Flexibility composite score at wave 2	.12 (0.9)
Beta-amyloid positive	62 (30%)
Beta-amyloid modality acquired	CSF: 38 (18%) PiB: 84 (41%) Both CSF and PiB: 85 (41%)
Systolic blood pressure (wave 2)	124.5 (15.3)
Diastolic blood pressure (wave 2)	74.4 (9.5)
Waist circumference (wave 2)	91.6 (15.4)
Center for Epidemiologic Studies of Depression scale total score (wave 2)	6.2 (5.9)
Anti-hypertensive medication use (wave 2)	40 (19%)
Anti-hypertensive medication use at least one visit (cumulative)	66 (32%)

Table 2. Proportion of sample classified as amyloid negative and positive within each risk factor group

Amyloid status	***Hypertension***		***Obesity***		***Depression***		***Total***
	Negative	*Positive*	*Negative*	*Positive*	*Negative*	*Positive*	
Negative	121 (83%)	24 (17%)	85 (59%)	60 (41%)	136 (94%)	9 (6%)	145
Positive	51 (82%)	11 (18%)	41 (66%)	21 (34%)	57 (92%)	5 (8%)	62
Total	172 (83%)	35 (17%)	126 (61%)	81 (39%)	193 (93%)	14 (7%)	207

[a](systolic blood pressure < 139 or diastolic blood pressure > 89)

[b](waist circumference > 102 cm for males or 88 cm for females)

[c](Center for Epidemiologic Studies of Depression scale ≥ 16)

Table 3. LME model parameters for wave 2 risk factor and Verbal Learning & Memory outcome

	Risk Factor		
	Hypertension	Obesity	Depression
	β (SE)	β (SE)	β (SE)
Intercept	-1.9 (2.1)	-1.5 (2.1)	-1.6 (2.1)
Risk factor group	-0.2 (0.2)	-0.2 (0.1)	0.2 (0.3)
Amyloid group	-0.02 (0.1)	-0.0 (0.2)	0.2 (0.1)
Centered visit age (slope)	-0.03 (0.0)	-0.0 (0.0)	-0.0 (0.0)
Biomarker Age	-0.0 (0.0)	-0.0 (0.0)	-0.0 (0.0)
Sex	0.9*** (0.1)	0.9*** (0.1)	0.8*** (0.1)
Education	0.1** (0.0)	0.1** (0.0)	0.1** (0.0)
Practice Effect	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)
Medication	0.04 (0.2)	--	--
Risk factor group x Amyloid group	0.8* (0.3)	0.4 (0.3)	-0.8 (0.5)
Centered visit age x Risk factor group	0.03 (0.0)	0.0 (0.0)	0.0 (0.0)
Centered visit age x Amyloid group	-0.002 (0.0)	-0.0 (0.0)	-0.0 (0.0)
Centered visit age x Amyloid group x Risk factor group	-0.1* (0.0)	-0.0 (0.0)	-0.0 (0.1)

***p≤.001; **p≤.01; *p<.05; p-values for fixed effect coefficients were calculated using asymptomatic properties of the estimates

Table 4. LME model parameters for wave 2 risk factor and Speed & Flexibility outcome

	Risk Factor		
	Hypertension	Obesity	Depression
	β (SE)	β (SE)	β (SE)
Intercept	2.6(1.9)	2.6(1.9)	2.3(1.8)
Risk factor group	0.0(0.2)	0.0(0.1)	-0.3(0.2)
Amyloid group	-0.1(0.1)	-0.0(0.1)	-0.1(0.1)
Age at each visit (centered)	-0.0(0.0)	-0.0(0.0)	-0.0(0.0)
Biomarker Age	-0.0(0.0)	-0.0(0.0)	-0.0(0.0)
Sex	-0.1(0.1)	-0.0(0.1)	-0.0(0.1)
Education	-0.0(0.0)	-0.0(0.0)	-0.0(0.0)
Practice Effect	0.1(0.1)	0.1(0.1)	0.1(0.1)
Medication use	-0.1(0.1)	--	--
Risk factor group x Amyloid group	-0.1(0.3)	-0.2(0.2)	-0.5(0.4)
Age at each visit (centered) x Risk factor group	0.0(0.0)	-0.0(0.0)	0.0(0.0)
Age at each visit (centered) x Amyloid group	-0.0(0.0)	-0.0(0.0)	-0.0(0.0)
Age at each visit (centered) x Amyloid group x Risk factor group	0.0(0.0)	-0.0(0.0)	-0.1*(0.0)

***p≤.001; **p≤.01; *p<.05; p-values for fixed effect coefficients were calculated using asymptomatic properties of the estimates

Table 5. LME model parameters for wave 2 hypertension/treatment group and Verbal Learning & Memory performance

	β (SE)
Intercept	-2.1 (2.1)
Hypertension/treatment group	
Non-hypertensive/non-medicated group	--
Non-hypertensive/medicated	-0.34 (0.2)
Hypertensive/non-medicated	-0.38 (0.2)
Hypertensive/medicated	0.28 (0.4)
Amyloid group	-0.2 (0.1)
Age at each visit (centered)	-0.04 (0.0)
Biomarker Age	0.01 (0.0)
Sex	0.87 (0.1)***
Education	0.07 (0.0)**
Practice Effect	0.09 (0.1)
Age at each visit (centered) x Amyloid Group	-0.01 (0.0)
Amyloid Group x hypertension/treatment group	
Amyloid Group x non-hypertensive/non-medicated	--
Amyloid Group x non-hypertensive/medicated	0.7 (0.4)
Amyloid Group x hypertensive/non-medicated	1.0 (0.4)*
Amyloid Group x hypertensive/medicated	0.1 (0.7)
Age at each visit (centered) x hypertension/treatment group	
Age at each visit (centered) x non-hypertensive/non-medicated	--

Age at each visit (centered) x non-hypertensive/medicated	0.01 (0.0)
Age at each visit (centered) x hypertensive/non-medicated	0.03 (0.0)
Age at each visit (centered) x hypertensive/medicated	-0.01 (0.0)
Age at each visit (centered) x Amyloid Group x hypertension/treatment group	
Age at each visit (centered) x Amyloid Group x non-hypertensive/non-medicated	--
Age at each visit (centered) x Amyloid Group x non-hypertensive/medicated	0.01 (0.0)
Age at each visit (centered) x Amyloid Group x hypertensive/non-medicated	-0.16 (0.1)**
Age at each visit (centered) x Amyloid Group x hypertensive/medicated	0.02 (0.1)

***p≤.001; **p≤.01; *p<.05; p-values for fixed effect coefficients were calculated using asymptomatic properties of the estimates

Supplementary Tables

Supplementary Table 1. LME model parameters for cumulative risk factor and Verbal Learning & Memory outcome

	Risk Factor		
	Hypertension	Obesity	Depression
	β (SE)	β (SE)	β (SE)
Risk factor group	-0.0(0.2)	-0.1(0.1)	0.2(0.2)
Amyloid group	-0.0(0.2)	0.1(0.2)	0.3(0.1)
Age at each visit (centered)	-0.0(0.0)	-0.0(0.0)	-0.0(0.0)
Biomarker Age	-0.0(0.0)	-0.0(0.0)	-0.0(0.0)
Sex	0.9***(0.1)	0.9***(0.1)	0.9***(0.1)
Education	0.1**(0.0)	0.1**(0.0)	0.1**(0.0)
Practice Effect	0.1(0.1)	0.1(0.1)	0.1(0.1)
Medication use at some visits	0.0(0.2)	--	--
Medication use at all visits	-0.0(0.2)	--	--
Risk factor group x Amyloid group	0.3 (0.3)	-0.1(0.3)	-0.9**(0.3)
Age at each visit (centered) x Risk factor group	0.0(0.0)	0.0(0.0)	-0.0(0.0)
Age at each visit (centered) x Amyloid group	0.0(0.0)	0.0(0.0)	-0.0(0.0)
Age at each visit (centered) x Amyloid group x Risk factor group	-0.1*(0.0)	-0.0(0.0)	0.0(0.0)

; ***p≤.001; **p≤.01; *p<.05; p-values for fixed effect coefficients were calculated using asymptomatic properties of the estimates

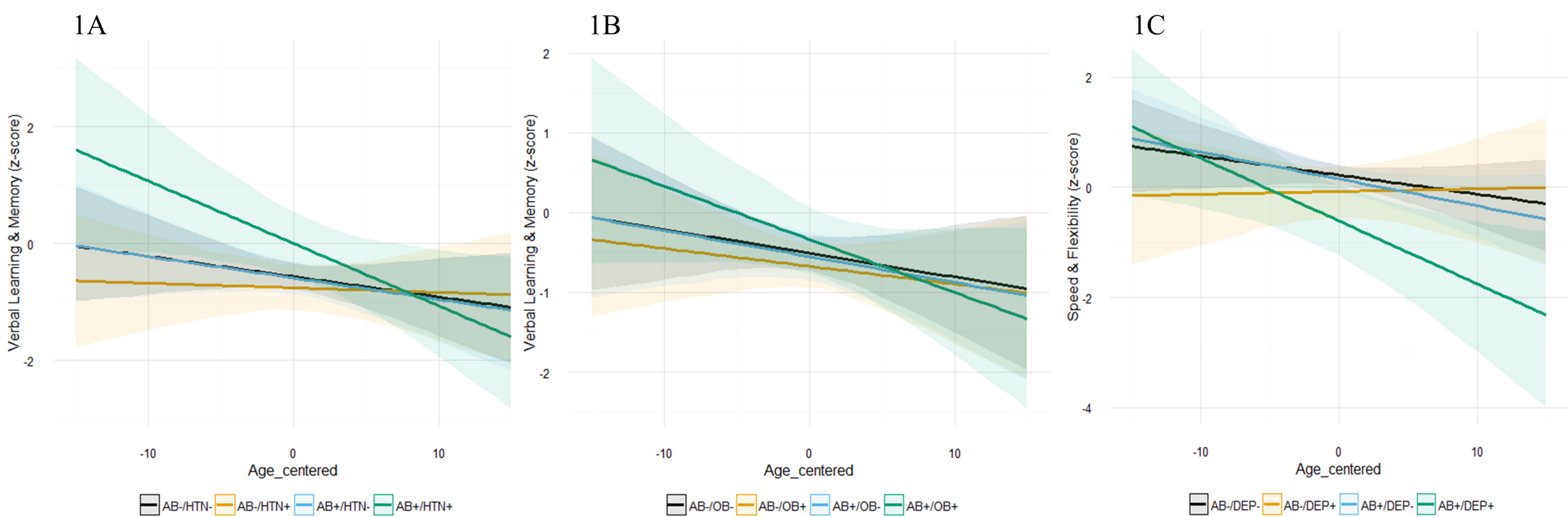
Supplementary Table 2. LME model parameters for cumulative risk factor and Speed & Flexibility outcome

	Risk Factor		
	Hypertension	Obesity	Depression
	β (SE)	β (SE)	β (SE)
Intercept	2.9(1.9)	2.8(1.8)	2.2(1.8)
Risk factor group	0.1(0.1)	-0.0(0.1)	-0.1(0.2)
Amyloid group	-0.2(0.1)	-0.0(0.2)	-0.0(0.1)
Age at each visit (centered)	-0.0(0.0)	-0.0(0.0)	-0.0(0.0)
Biomarker Age	-0.0(0.0)	-0.0(0.0)	-0.0(0.0)
Sex	-0.0(0.1)	-0.0(0.1)	-0.0(0.1)
Education	-0.0(0.0)	-0.0(0.0)	-0.0(0.0)
Practice Effect	0.1(0.1)	0.1(0.1)	0.1(0.1)
Medication use at some visits	-0.1(0.2)	---	---
Medication use at all visits	-0.2(0.1)	---	---
Risk factor group x Amyloid group	0.2(0.2)	-0.2(0.2)	-0.4(0.3)
Age at each visit (centered) x Risk factor group	0.0(0.0)	-0.0(0.0)	-0.0(0.0)
Age at each visit (centered) x Amyloid group	-0.0(0.0)	-0.0(0.0)	-0.0(0.0)
Age at each visit (centered) x Amyloid group x Risk factor group	-0.0(0.0)	-0.0(0.0)	0.0(0.0)

***p≤.001; **p≤.01; *p<.05; p-values for fixed effect coefficients were calculated using asymptomatic properties of the estimates

Figure 1 Legend.

Graphs depict neuropsychological performance on the y-axis and age at each visit (centered on mean age) on the x-axis. Each line depicts the estimated cognitive slope for four groups: Amyloid positive and risk factor negative (black), amyloid negative and risk factor positive (orange), amyloid positive and risk factor negative (blue), and amyloid positive and risk factor positive (green), adjusting for covariates of age at biomarker visit, sex, education, and practice effects. Figure 1A displays the three-way interaction of age at each visit x amyloid x hypertension on the Verbal Learning & Memory composite score, Figure 1B displays the three-way interaction of age at each visit x amyloid x obesity on the Verbal Learning & Memory composite score, and Figure 1C displays the three-way interaction of age at each visit x amyloid x depression on the Speed & Flexibility composite score.


1A
Verbal Learning & Memory (z-score)
2
0
-2
-10
0
10
Age_centered
AB-/HTN-
AB-/HTN+
AB+/HTN-
AB+/HTN+
1B
Verbal Learning & Memory (z-score)
2
1
0
-1
-2
-10
0
10
Age_centered
AB-/OB-
AB-/OB+
AB+/OB-
AB+/OB+
1C
Speed & Flexibility (z-score)
2
0
-2
-4
-10
0
10
Age_centered
AB-/DEP-
AB-/DEP+
AB+/DEP-
AB+/DEP+