associated with earlier Alzheimer's disease onset.
Participants and Methods: Participants included 9,585 individuals with autopsy confirmed Alzheimer's disease pathology, that had available ApoE genotype data, TBI data, and clinician determined age of cognitive decline, representing disease onset. A 2x3 factorial ANOVA was conducted to compare the main effects of ApoE-e4 status and TBI history and the interaction effect between the two on disease onset. The analyses used three ApoE-e4 groups and two TBI groups. The groups included: (1) no ApoE-e4 allele; (2) one ApoE-e4 allele; (3) two ApoE-e4 alleles; (4) no TBI history, (5) positive TBI history.
Results: Results indicated a significant interaction effect between ApoE-e4 status and TBI history. Secondary analyses determined the driving force behind the interaction was the effect of ApoE-e4, which had a significant impact on the age of onset in both TBI groups, while TBI history only significantly impacted onset in individuals without an ApoE-e4 allele.
Conclusions: Contrary to prior research, these findings did not indicate TBI was significant in determining earlier onset. However, it is important to consider the large variability within the TBI group from the lack of differentiation between mild, moderate, and severe TBIs. Overall, these findings underline the greater risk and stronger impact that ApoE-e4 poses for Alzheimer's disease onset compared to TBI. The results of this study emphasize the importance of evaluating ApoE-e4 status for determining risk of earlier onset AD. Clinicians can better determine risk by considering patients' ApoE-e4 status alongside TBI history.

Categories: Dementia (Alzheimer's Disease)
Keyword 1: dementia - Alzheimer's disease
Keyword 2: apolipoprotein E
Keyword 3: traumatic brain injury
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13 Regional White Matter Hyperintensities are Associated with Cognition in Prospective Alzheimer's Clinical Trial Participants

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Objective: Previous research established that white matter hyperintensities (WMH), a biomarker of small vessel cerebrovascular disease, are strong predictors of cognitive function in older adults and associated with clinical presentation of Alzheimer's disease (AD), particularly when distributed in posterior brain regions. Secondary prevention clinical trials, such as the Anti-Amyloid Treatment in Asymptomatic Alzheimer's (A4) study, target amyloid accumulation in asymptomatic amyloid positive individuals, but it is unclear the extent to which small vessel cerebrovascular disease accounts for performance on the primary cognitive outcomes in these trials. The purpose of this study was to examine the relationship between regional WMH volume and performance on the Preclinical Alzheimer Cognitive Composite (PACC) among participants screened for participation in the A4 trial. We also determined whether the association between WMH and cognition is moderated by amyloid positivity status.
Participants and Methods: We assessed demographic, amyloid PET status, cognitive screening, and raw MRI data for participants in the A4 trial and quantitated regional (by cerebral lobe) WMH volumes from T2-weighted FLAIR in amyloid positive and amyloid negative participants at screening. Cognition was assessed using PACC scores, a z-score sum of four cognitive tests: The Mini-Mental State Examination (MMSE), the Free and Cued Selective Reminding Test, Logical Memory Test, and Digit Symbol Substitution Test. We included 1329 amyloid positive and 329 amyloid negative individuals (981 women; mean age=71.79 years; mean education=16.58 years) at the time of the analysis. The sample included Latinx (n=50; 3%), non-Latinx (n=1590; 95.9%), or unspecified ethnicity (n=18; 1.1%) individuals who identified as American Indian/Alaskan Native (n=7; 0.4%), Asian (n=38; 2.3%), Black/African American (n=41; 2.5%), White (n=1551 ; 93.5%), or unspecified (n=21; 1.3%) race. We first

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examined the associations of total and regional WMH volume and amyloid positivity on PACC scores (the primary cognitive outcome measure for A4) using separate general linear models and then determined whether amyloid positivity status and regional WMH statistically interacted for those WMH regions that showed significant main effects.
Results: Both increased WMH, in the frontal and parietal lobes particularly, and amyloid positivity were independently associated with poorer performance on the PACC, with similar magnitude. In subsequent models, WMH volume did not interact with amyloid positivity status on PACC scores.
Conclusions: Regionally distributed WMH are independently associated with cognitive functioning in typical participants enrolled in a secondary prevention clinical trial for AD. These effects are of similar magnitude to the effects of amyloid positivity on cognition, highlighting the extent to which small vessel cerebrovascular disease potentially drives AD-related cognitive profiles. Measures of small vessel cerebrovascular disease should be considered explicitly when evaluating outcomes in trials, both as potential effect modifiers and as possible targets for intervention or prevention. The findings from this study cannot be generalized widely, as the participants are not representative of the overall population.

Categories: Dementia (Alzheimer's Disease)
Keyword 1: cerebrovascular disease
Keyword 2: dementia - Alzheimer's disease
Keyword 3: neuroimaging: structural
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14 Performance of Novel Blood Based Biomarkers of Alzheimer's Disease is Dependent on Renal Functioning

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Objective: Novel blood-based biomarkers for Alzheimer's disease (AD) could transform AD diagnosis in the community; however, their interpretation in individuals with medical comorbidities is not well understood. Specifically, kidney function has been shown to influence plasma levels of various brain proteins. This study sought to evaluate the effect of one common marker of kidney function (estimated glomerular filtration rate (eGFR)) on the association between various blood-based biomarkers of AD/neurodegeneration (glial fibrillary acidic protein (GFAP), neurofilament light (NfL), amyloid-b42 (Ab42), total tau) and established CSF biomarkers of AD (Ab42/40 ratio, tau, phosphorylated-tau (p-tau)), neuroimaging markers of AD (AD-signature region cortical thickness), and episodic memory performance.
Participants and Methods: Vanderbilt Memory and Aging Project participants (n=329, 73±7 years, 40% mild cognitive impairment, 41% female) completed fasting venous blood draw, fasting lumbar puncture, 3T brain MRI, and neuropsychological assessment at study entry and at 18-month, 3-year, and 5-year follow-up visits. Plasma GFAP, Ab42, total tau, and NfL were quantified on the Quanterix single molecule array platform. CSF biomarkers for Ab were quantified using Meso Scale Discovery immunoassays and tau and p-tau were quantified using INNOTEST immunoassays. AD-signature region atrophy was calculated by summing bilateral cortical thickness measurements captured on T1-weighted brain MRI from regions shown to distinguish individuals with AD from normal cognition. Episodic memory functioning was measured using a previously developed composite score. Linear mixed-effects regression models related predictors to each outcome adjusting for age, sex, education, race/ethnicity, *apolipoprotein E*-e4 status, and cognitive status. Models were repeated with a *blood-based biomarker x eGFR x time* interaction term with follow-up models stratified by chronic kidney disease (CKD) staging (stage 1/no CKD: eGFR>90 mL/min/1.73m^2, stage 2: eGFR=60-89 mL/min/1.73m^2; stage 3: eGFR=44-59

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