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

mL/min/1.73m^2 (no participants with higher than stage 3)).

Results: Cross-sectionally, GFAP was associated with all outcomes (*p*-values<0.005) and NfL was associated with memory and AD-signature region cortical thickness (*p*-values<0.05). In *predictor x eGFR* interaction models, GFAP and NfL interacted with eGFR on AD-signature cortical thickness, (*p*-values<0.004) and Ab42 interacted with eGFR on tau, p-tau, and memory (*p*-values<0.03). Tau did not interact with eGFR. Stratified models across predictors showed that associations were stronger in individuals with better renal functioning and no significant associations were found in individuals with stage 3 CKD. Longitudinally, higher GFAP and NfL were associated with memory decline (*p*-values<0.001). In *predictor x eGFR x time* interaction models, GFAP and NfL interacted with eGFR on p-tau (*p*-values<0.04). Other models were nonsignificant. Stratified models showed that associations were significant only in individuals with no CKD/stage 1 CKD and were not significant in participants with stage 2 or 3 CKD.

Conclusions: In this community-based sample of older adults free of dementia, plasma biomarkers of AD/neurodegeneration were associated with AD-related clinical outcomes both cross-sectionally and longitudinally; however, these associations were modified by renal functioning with no associations in individuals with stage 3 CKD. These results highlight the value of blood-based biomarkers in individuals with healthy renal functioning and suggest caution in interpreting these biomarkers in individuals with mild to moderate CKD.

Categories: Dementia (Alzheimer's Disease)
Keyword 1: dementia - Alzheimer's disease
Keyword 2: transdisciplinary research
Keyword 3: medical disorders/illness
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15 Different Languages, Different Linguistic Markers: Predicting Which Bilinguals will Develop Alzheimer's Disease with Spontaneous Spoken Language

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Objective: Spontaneous speech undergoes subtle but significant changes years before the onset of Alzheimer's dementia (AD). In monolinguals, these changes, or linguistic markers of AD, include the use of syntactically simpler structures, reduced lexical diversity, reduced semantic detail/specificity, and increased disfluencies (Ostrand & Gunstad, 2020; Slegers et al., 2018; Venneri et al., 2018). No studies have examined if bilinguals exhibit similar changes in their language output prior to diagnosis of AD though this question has important clinical relevance and can also shed light on which cognitive abilities decline first with AD pathology. Of particular interest, changes in semantic representations might affect both languages (because semantics are shared between the two), but changes in executive control might be more prominent in the nondominant language (because of interference from the dominant language).

Participants and Methods: Seventeen older Spanish-English bilinguals completed an interview in which they described a picture in each language and answered a series of questions beginning with "warm-up" questions and progressing to questions that elicited higher level language (e.g., defending an opinion). All participants were considered cognitively healthy at the time of testing, but 8 participants later developed Alzheimer's Disease (i.e., converters) on average after 4.1 (SD=2.5) years, while 9 matched controls remained cognitively healthy on average for 5.7 (SD=3.6) years (for as long as they were followed). Converters and controls were matched for age, education, language proficiency, and cognitive status at the time of testing. Language samples were transcribed word for word and analyzed using the Systematic Analysis of Language (Miller & Iglesias, 2012).

Results: Converters and controls were compared on measures of syntactic complexity, lexical diversity, abandoned utterances, errors, and disfluencies. In the dominant language, the number of different words (using a moving window average; a measure of lexical diversity), showed promise for classifying who would eventually convert (Area Under the Curve = 77), though the difference between converters and