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Research Report

Comparing Symmetric Dimethylarginine and Amyloid-β42 as Predictors of Alzheimer's Disease Development

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Abstract.
Background: Physicians may soon be able to diagnose Alzheimer's disease (AD) in its early stages using fluid biomarkers like amyloid. However, it is acknowledged that additional biomarkers need to be characterized which would facilitate earlier monitoring of AD pathogenesis.
Objective: To determine if a potential novel inflammation biomarker for AD, symmetric dimethylarginine, has utility as a baseline serum biomarker for discriminating prodromal AD from cognitively unimpaired controls in comparison to cerebrospinal fluid amyloid-β42 ($A\beta_{42}$).
Methods: Data including demographics, magnetic resonance imaging and fluorodeoxyglucose-positron emission tomography scans, Mini-Mental State Examination and Functional Activities Questionnaire scores, and biomarker concentrations were obtained from the Alzheimer's Disease Neuroimaging Initiative for a total of 146 prodromal AD participants and 108 cognitively unimpaired controls.
Results: $A\beta_{42}$ ($p = 0.65$) and symmetric dimethylarginine ($p = 0.45$) were unable to predict age-matched cognitively unimpaired controls and prodromal AD participants. $A\beta_{42}$ was negatively associated with regional brain atrophy and hypometabolism as well as cognitive and functional decline in cognitively unimpaired control participants ($p < 0.05$) that generally decreased in time. There were no significant associations between $A\beta_{42}$ and symmetric dimethylarginine with imaging or neurocognitive biomarkers in prodromal AD patients.
Conclusions: Correlations were smaller between $A\beta_{42}$ and neuropathological biomarkers over time and were absent in prodromal AD participants, suggesting a plateau effect dependent on age and disease stage. Evidence supporting symmetric dimethylarginine as a novel biomarker for AD as a single measurement was not found.

Keywords: Alzheimer's disease, amyloid, biomarker, methylarginines, SDMA, serum markers

[1]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (https://adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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INTRODUCTION

Alzheimer's disease (AD) dementia is an incurable neurodegenerative disease of the brain most often characterized by relentless memory loss, cognitive decline, and hypometabolism and neurodegeneration. A current challenge faced by health care providers is the early diagnosis of AD, particularly when individuals are in the mild cognitive impairment (MCI) stage or even earlier during the asymptomatic phase of the disease [1]. To that end, substantial efforts are centered on developing and identifying fluid biomarkers that are indicative of future cognitive decline. Given its importance in AD dementia and in particular, in the context of anti-amyloid therapies, several studies have centered on determining the utility of fluid biomarkers of amyloid, including biomarkers for amyloid-β42 ($A\beta_{42}$), with the closely related $A\beta_{40}$ first being sequenced in AD dementia and Down's syndrome participants approximately twenty years ago and was later discovered to be the primary component in AD plaques [2].

In recent years, cerebrospinal fluid (CSF) $A\beta_{42}$ or $A\beta_{42/40}$ have emerged as promising biomarkers for detection of AD dementia pathology for enrichment of clinical trials and potentially for clinical practice given that $A\beta_{42}$ is a surrogate marker for Aβ aggregation into senile plaques and that these CSF biomarkers have a relatively close association with amyloid pathology as measured with amyloid positron emission tomography (PET) [3, 4]. While some studies suggest that the $A\beta_{42/40}$ index does not improve diagnostic accuracy compared to $A\beta_{42}$ alone [5, 6], the ratio accounts for both production of amyloid as well as deposition, and the ratio is more closely associated with amyloid PET assessments [7]. Identifying the best biomarkers for clinical trial selection is critical, as improved treatments for AD dementia are expected in the coming years. The recently approved drug Aducanumab was found to reduce amyloid plaques in two international phase III randomized controlled trials known as ENGAGE and EMERGE, although ENGAGE found no cognitive improvement and the clinical improvement found in EMERGE was only modest at best [8]. While the United State Food and Drug Administration's (FDA) Peripheral and Central Nervous System Drugs Advisory Committee voted there was insufficient evidence of efficacy, the FDA accelerated its approval even as roughly 35% of participants suffered amyloid-related imaging abnormalities which include edema and brain hemorrhages [8]. More promise has been observed with recent monoclonal antibody treatments. Lecanemab, for example, has been shown to reduce markers of amyloid in early AD with patients having less cognitive and functional decline, though this treatment also suffered a high prevalence of adverse effects [9]. The FDA has at this time fully approved Lecanemab for the mild dementia stage of AD [10].

In addition to amyloid pathology, developments continue for additional biomarkers that relate to other aspects of AD pathophysiology and that could be used to improve early detection of AD dementia, as well as serve as outcomes in future clinical trials. Innate immune activation from genome-wide association studies have found associations between immune receptor genes and AD pathogenesis [11, 12]. Aging is also associated with decline in adaptive immunity and anti-inflammatory marker production, hence a potential reason why older age is a risk factor for AD [13]. Bacterial and viral infections, especially among periodontal infections and H. pylori, have been associated with AD due to the release of neuroinflammatory interleukins and inflammasomes [14], with $A\beta_{42}$ even having antimicrobial properties against periodontal bacteria [15]. Glial activation and associated neuroinflammation has long been recognized to play a role in AD. The activation of microglia and other immune cells has been implicated in the exacerbation of both amyloid and tau pathologies, while at the same time, a more systematic proinflammatory mechanism has been proposed as the common thread across risk factors of AD like diabetes mellitus, cardiovascular disease and atherosclerosis, among others [16]. In chronic kidney disease for example, worsening stages of the disease were associated with higher AD and vascular dementia risk [17]. Reasons proposed for an association between chronic kidney disease and AD include the kidneys being unable to excrete uremic toxins, which are inflammatory, as well as the kidney's involvement with blood pressure, erythropoietin and vitamin D production, two factors that are both neuroprotective and anti-inflammatory [18].

Given these observations, it is important to test novel biomarkers that act as predictors of non-amyloid processes linked to the natural history of AD; this would include, among others, neuroinflammation and neurodegeneration. One of such potentially useful biomarkers is symmetric dimethylarginine (SDMA), an enantiomer of asymmetric dimethylarginine (ADMA) which has been heavily studied in AD in addition to chronic kidney disease and car-

diovascular disease. SDMA is a biomarker for and a proinflammatory agent in chronic kidney disease but has also been correlated with neuropathological progression and cognitive decline in prodromal AD dementia participants [19–21]. It is significantly altered in participants with early and progressive stages of AD dementia when compared to controls [21, 22], and was also correlated with neurofilament light chain, a marker for neurodegeneration, in both Aβ– and Aβ+ groups [23]. SDMA was also increased in AD frontal cortex tissue samples [24]. As McEvoy et al. stated, SDMA may be associated with memory impairment through inflammation and an inflammatory state [25]. SDMA has also been linked to the proinflammatory state that takes place after an acute stroke [26]. It is our intention therefore to compare this novel blood constituent and its relationship to prodromal AD dementia against CSF $A\beta_{42}$. $A\beta_{42}$ is one of the core biochemical markers for the amyloidogenic process in AD as supported by the 2018 National Institute of Aging and Alzheimer's Association Research Framework [27]. Additionally, notwithstanding the probable limitations of CSF $A\beta_{42}$ as a lone measure in preclinical stages of AD dementia and MCI, we found it a suitable initial candidate to compare SDMA to, as it would allow us to revisit any lingering questions around the use of $A\beta_{42}$ use in the earliest stages of the disease. We hypothesized that SDMA would be more effective than $A\beta_{42}$ at discriminating between cognitively unimpaired controls and prodromal AD dementia and that either biomarker would be associated with brain hypometabolism and atrophy as well as cognition and function.

MATERIALS AND METHODS

Data source

Data for this study was obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI). ADNI is an ongoing, longitudinal study launched in 2003 as a public–private partnership, led by principal investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test the extent to which serial magnetic resonance imaging (MRI), PET, other biological markers, and clinical and neuropsychological assessments provide utility for measuring the progression of MCI and early AD dementia, and to validate brain imaging, blood tests, and other diagnostics, as well as share data with the scientific community. For up-to-date information, see https://adni.loni.usc.edu/. Details on study design, participant recruitment, study approval, and informed consent procedures have been published previously [28]. The study was approved by the institutional review boards of all of the participating institutions/study sites. Informed written consent was obtained from all participants at each site. Metabolomics data for ADNI samples were generated by the Alzheimer Disease Metabolomics Consortium (ADMC) and deposited to the Laboratory of Neuroimaging (LONI). The mission of the ADMC is to create a comprehensive metabolomics database for AD. ADNI data used in the preparation of this article were also obtained from the ADNI-1 database (https://adni.loni.usc.edu) and included baseline blood serum metabolite concentrations (with concurrent structural MRI data) on 767 participants and concurrent CSF AD biomarker data on 403 participants. All ADNI studies are conducted according to the Good Clinical Practice guidelines, the Declaration of Helsinki, and U.S. 21 CFR Part 50 (Protection of Human Subjects), and Part 56 (Institutional Review Boards). Written informed consent was obtained from all participants before protocol-specific procedures were performed. ADNI was enriched with participants with MCI, who represent "prodromal AD". In this study, participants with MCI at baseline who subsequently converted back to normal cognition were excluded.

Participant cohort and assessments

The primary objective of this retrospective study is to determine if early baseline serum SDMA and CSF $A\beta_{42}$ levels could be used as reliable predictors for future AD dementia development. The reason for not conducting serum to serum comparisons is that the sample size of participants in ADNI that have both serum constituents is low and would have drastically reduced the power of our analysis. Additionally, CSF $A\beta_{42}$ remains highlighted as one of the most signature diagnostic markers according to the National Institute of Aging - Alzheimer's Association [27]. To obtain this data, research staff collected baseline subject level demographic information including age, sex, apolipoprotein E (*APOE*) genotype, and participant education level. Baseline biomarker levels of SDMA were analyzed using a Biocrates Absolute*IDQ* p180 kit and $A\beta_{42}$ was measured using the 2D-UPLC tandem mass spectrometry method described in the literature [29]. Baseline cognitive assessments including Functional Activities Ques-

tionnaire (FAQ) scores and Mini-Mental State Exam (MMSE) scores were taken by each participant at baseline and again at 24 months. *Post-hoc* analysis included scores at 48 and 72 months. FAQ is a measure of instrumental activities of daily living and has a score range from 0 to 30, with 0 being no impairment and 30 being severely impaired [30]. MMSE is a 30-point questionnaire used in research and clinical practice to measure cognitive impairment, with lower results indicating more pronounced cognitive impairment [31]. Image modalities included were MRI and fluorodeoxyglucose (FDG)-PET taken at baseline and 24 months with the aim of exploring potential associations between these measures and SDMA and $A\beta_{42}$ levels. *Post-hoc* analysis included imaging at 48 and 72 months. MRI region of interests (ROI) included the left and right mesio-temporal lobes and left and right hippocampus as these sites demonstrate the earliest structural changes in AD [32, 33]. FDG ROIs included the bilateral posterior cingulum and left and right temporal lobes based on reports that these areas demonstrate decreased metabolism in early AD dementia at ages 50–80 years [34, 35]. At the time of baseline data collection, none of the participants in the included cohort had AD dementia, though some would later develop AD dementia. Out of over 750 participants from the ADNI-1 database, there were 359 prodromal AD participants with both baseline SDMA and $A\beta_{42}$. 213 participants would be excluded because they did not complete either an MMSE, FAQ, MRI, or FDG-PET by 24 months. Therefore, there were a total of 108 participants without AD dementia and 146 participants with prodromal AD dementia who met our demographic, biomarker, and imaging criteria and were included.

Statistical analysis

Descriptive statistics were used to report baseline subject characteristics, and chi-square or student *t*-tests were used to report differences between cognitively unimpaired control and prodromal participants. Univariable and multivariable logistic regression analyses were used to examine the ability of baseline $A\beta_{42}$ and SDMA to predict prodromal AD dementia or cognitively unimpaired control. Multivariable analysis was applied to account for effect modification. Harrell's rule of thumb was applied to determine the maximum number of determinants in the final multivariable model (one determinant per 10 participants in the smallest cohort). Predictors that showed collinearity were not included in the regression model. All variables with $p < 0.3$ in the univariate models were included in the multivariable models using a backward elimination procedure using stepAIC() function in R (version 4.02.2). Interactions with either $A\beta_{42}$ or SDMA were included in the multivariable models as well. In total, there were three multivariate logistic regression models: one that included $A\beta_{42}$, one that included SDMA, and one that included $A\beta 42 \times$ SDMA. A *post-hoc* analysis incorporated longitudinal data collected over a span of 72 months following the baseline assessment. Specifically, there was a notable 72% attrition in neuropsychological assessments by the 48-month mark, with a subsequent reduction to 22% at the 72-month point. Similarly, FDG-PET scans were unavailable at the 48-month juncture, and only 11% of participants underwent FDG-PET imaging by the 72-month mark. Moreover, the study encountered a 46% attrition rate in MRI scans at 48 months, which increased substantially to 98% by the 72-month time point. Using this data, a mixed-effect logistic regression model with multiple imputations was performed using variables from the previous multivariable logistic regression models. Data analysis was performed using R (version 4.02.2).

To study adjusted associations in neurocognitive function *within* prodromal AD dementia and cognitively unimpaired control cohorts, partial correlations were conducted while adjusting for age and education. Because MMSE and FAQ are ordinal, these partial correlations are graphed as partial residual plots in order to showcase linearity. Separate partial correlations between prodromal AD dementia and cognitively unimpaired control cohorts were also created to examine the association of $A\beta_{42}$ and SDMA to MRI brain regional volume and brain regional metabolic activity using FDG-PET while adjusting for age and education. Because brain volume, whether by MRI or by FDG-PET, are continuous, these partial correlations are graphed as scatterplots. Data analysis was done using SPSS 26.

For partial correlations, tests which showed statistical significance with Bonferroni correction for multiple comparisons of FDG, MRI, and cognition (3 FDG regions $\times$ 2 visits, 4 MRI regions $\times$ 2 visits, 2 cognitive scores $\times$ 2 visits) were defined as $p < 0.0083$, $p < 0.00625$, and $p < 0.0125$ respectively. Otherwise, statistical significance was given as $p < 0.05$ such as for the multivariable logistic regression and mixed-effect models.

RESULTS

Subject characteristics are outlined in Table 1. Of the following demographic predictors—age, sex, subject education level, and *APOE* status—the only statistical difference between prodromal and cognitively unimpaired control participants was age as prodromal AD dementia participants were younger (median age 71 versus 73 years old, $p < 0.001$). Additionally, both biomarkers of interest, SDMA ($p = 0.156$) and $A\beta_{42}$ ($p = 0.242$), did not show a significant difference between cognitively unimpaired control and prodromal AD dementia participants (SDMA: mean/sd: 0.613 [0.146] μM and 0.589 [0.112] μM; $A\beta_{42}$: 1,279 [633] pg/mL and 1,180 [545] pg/mL). Finally, there was no correlation between $A\beta_{42}$ and SDMA within both prodromal AD dementia ($r = 0.0721$, $p = 0.374$) and cognitively unimpaired control ($r = 0.110$, $p = 0.257$) cohorts (Figs. 1 and 2). To summarize our comparison analyses (Table 1), there were no significant differences in functional and cognitive scores (FAQ and MMSE respectively) between cognitively unimpaired control and prodromal AD dementia participants at either baseline or 24 months. Additionally, there were no significant differences between the two groups regarding metabolic activity within the posterior cingulate or the temporal lobes, as well as no significant structural brain volume differences in the temporal lobe and the hippocampus when controlling for age (data not shown).

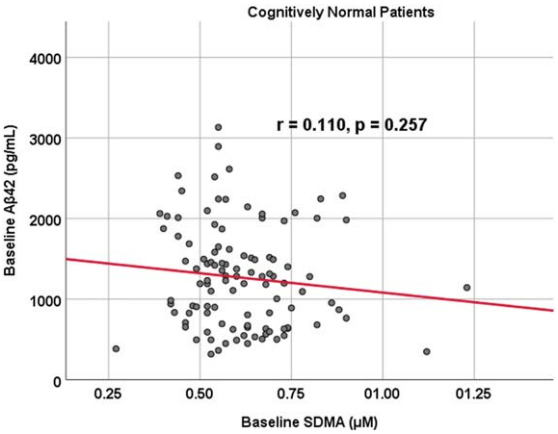

Fig. 1. Associations between baseline $A\beta_{42}$ and SDMA in cognitively unimpaired control participants. Scatterplots above are uncorrected for age, sex, education, and *APOE* ($r = 0.110$, $p = 0.257$).

Because AD dementia is an age-dependent disease, we analyzed the relationship between age and biomarker levels in cognitively unimpaired control and prodromal AD dementia subject cohorts (Figs. 3 and 4). We observed a positive correlation between age and SDMA levels in both cognitively unimpaired control ($r = 0.400$, $p < 0.00001$) and prodromal AD dementia participants ($r = 0.387$, $p < 0.00001$), and a negative correlation between age and $A\beta_{42}$ levels in both cognitively unimpaired control ($r = –0.155$, $p = 0.0549$) and prodromal AD dementia participants ($r = –0.214$, $p = 0.0262$).

Table 1
Group characteristics

Characteristics	Cognitively unimpaired control ($n = 108$) No. (%)	Prodromal ($n = 146$) No. %	p
Age (y) ** Q1, Median, Q3 (range)	**69, 73, 79 (56–91)	**64, 71, 76 (55–91)	<0.001
Subject Education (y) Q1, Median, Q3 (range)	16, 16, 19 (12–20)	14, 16, 18 (12–20)	0.107
Male Sex	61 (56.4)	79 (54.1)	0.804
APOE Q1, Median, Q3 (range)	**3/3, 3/3, 3/4 (3/2–4/4)	**3/3, 3/3, 3/4 (3/2–4/4)	0.790
2/3	15 (13.9)	18 (12.3)	
3/3	60 (55.6)	76 (52.0)	
3/4	27 (25.0)	46 (31.5)	
4/4	8 (7.4)	10 (6.84)	
SDMA Baseline Level (μM)	0.613 (0.146)	0.589 (0.112)	0.1556
$A\beta_{42}$ Baseline Level (pg/mL)	1,279 (633)	1,180 (545)	0.2423
FAQ Baseline	1.96(5.10)	1.78(2.88)	0.7188
FAQ 24 Months	3.42(7.79)	2.47(3.71)	0.4917350
MMSE Baseline	28.07(2.76)	28.33(1.66)	0.722915
MMSE 24 Months	27.27(4.43)	27.75(3.04)	0.5426080

APOE, apolipoprotein genotype; SDMA, symmetric dimethylarginine; FAQ, Functional Activities Questionnaire; MMSE, Mini-Mental State Examination. The table shows the subject characteristics of the two cohorts, cognitively unimpaired control and prodromal. Based on the p-values, age ($p < 0.001$) is the only known confounding variable in our analysis.

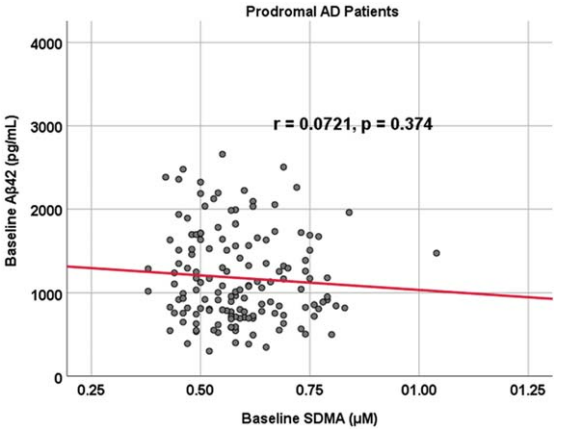

Fig. 2. Associations between baseline $A\beta_{42}$ and SDMA in prodromal AD dementia participants. Scatterplots above are uncorrected for age, sex, education, and *APOE* ($r = 0.0721$, $p = 0.374$).

To understand if SDMA or $A\beta_{42}$ as well as its interactions are associated with prodromal subject status, three multivariable logistic analyses were conducted adjusting for age: one looking at SDMA levels, another at $A\beta_{42}$ levels, and one at both together (Tables 3–5). Of note is that univariable analysis found baseline FAQ score to be able to significantly predict prodromal AD dementia participants and healthy controls ($p = 0.0264$; OR = 1.1201, 95% CI = 1.0212–1.2506). Ultimately, both univariable and multivariable models for SDMA ($p = 0.45$) and $A\beta_{42}$ ($p = 0.6518$) each showed no statistical difference in being able to predict prodromal AD dementia participants and normal controls (Tables 3 and 4). Although our multivariable model that included SDMA and $A\beta_{42}$ together was significant ($p = 0.00296$), they were not associated with predicting prodromal subject status ($p = 0.14490$), although baseline FAQ ($p = 0.02158$) and age ($p = 0.03481$) were. *Post-hoc* mixed-effects model in Table 6 was also significant ($p = 0.00157$) and revealed no significant predictive property of prodromal subject status with the addition of more longitudinal data from either baseline SDMA ($p = 0.26353$) or $A\beta_{42}$ ($p = 0.15073$), but age ($p = 0.0000084$) and education ($p = 0.00309$) were predictive.

To analyze for relationships between biomarker levels and cognitive function, scatterplots and associations were computed (Figs. 5–7). Note that a lower MMSE score indicates cognitive impairment, whereas a higher FAQ score may indicate cognitive impairment. A positive relationship was found in cognitively unimpaired participants between baseline $A\beta_{42}$ and baseline MMSE ($r = 0.386$, $p = 4.4 \times 10^{-5}$) and a negative relationship between baseline $A\beta_{42}$ and baseline FAQ ($r = -0.272$, $p = 0.0005$). A positive relationship, albeit smaller, was found between baseline $A\beta_{42}$ and MMSE at 24 months ($r = 0.277$, $p = 0.004$). Finally, a negative relationship was found between baseline $A\beta_{42}$ and MMSE decline over 24 months ($r = -0.251$, $p = 0.0109$), suggesting that lower baseline $A\beta_{42}$ was associated with worsening MMSE over 24 months. A positive relationship was found between baseline $A\beta_{42}$ and FAQ decline ($r = 0.246$, $p = 0.0111$), suggesting that lower $A\beta_{42}$ was associated with worsening FAQ scores over

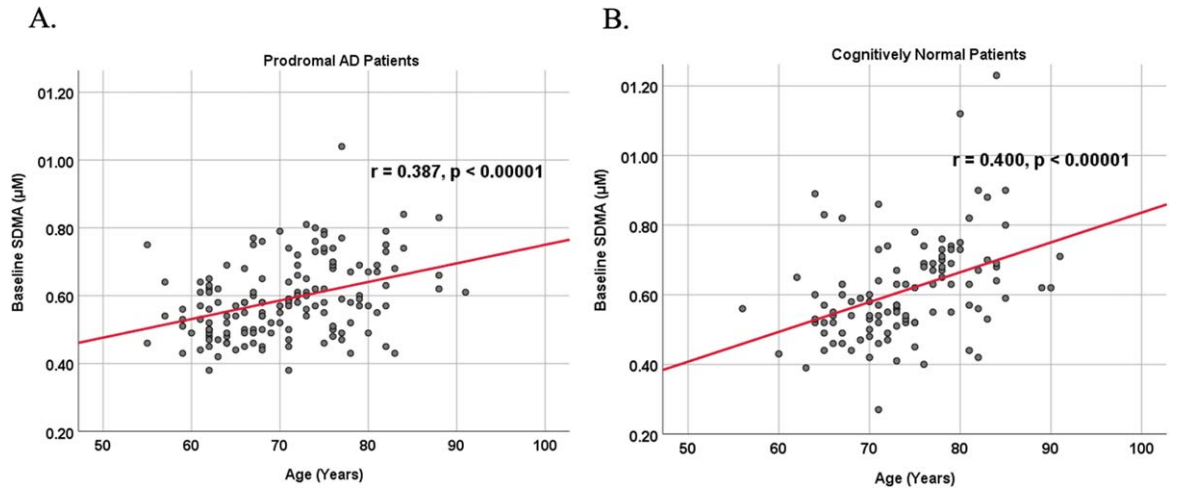

Fig. 3. Associations between baseline SDMA and age in cognitively unimpaired control and prodromal participants. Scatterplots above are uncorrected for sex, education, and APOE. A) SDMA versus Age in prodromal AD dementia participants ($r = 0.387$, $p < 0.00001$). B) SDMA versus Age in cognitively unimpaired control participants ($r = 0.400$, $p < 0.00001$).

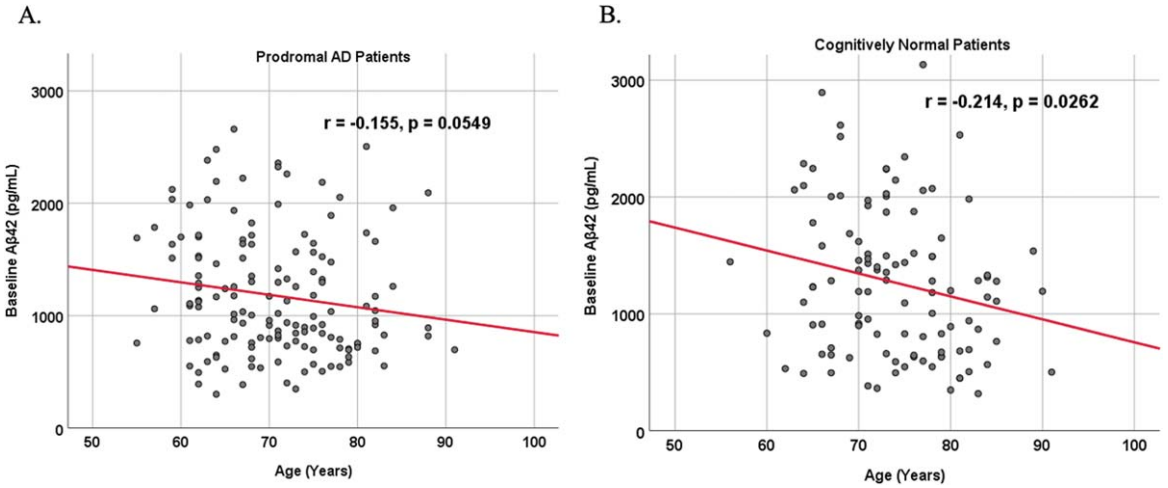

Fig. 4. Associations between baseline $A\beta_{42}$ and age in cognitively unimpaired control and prodromal participants. Scatterplots above are uncorrected for sex, education, and APOE. A) $A\beta_{42}$ versus Age in prodromal AD dementia participants ($r = -0.155$, $p = 0.0549$). B) $A\beta_{42}$ versus Age in cognitively unimpaired control participants ($r = -0.214$, $p = 0.0262$).

Table 2
Univariable logistic regression

Variable	β Estimate	Standard Error	OR (95% CI)	*p*
FAQ BL	0.11343	0.05109	1.1201(1.0212,1.2506)	0.0264
Age	–0.037	0.01931	0.9637(0.9273, 1.0005)	0.0553
Right Mesio-Temporal 24M% Decline	–4.9433	2.6003	0.0071(0.0001,1.0319)	0.0573
Left Mesio-Temporal 24M% Decline	–3.9927	2.2064	0.0184(0.0002,1.2984)	0.070357
Left Mesio-Temporal BL	0.0001469	0.00009555	1.0001(0.9999, 1.0003)	0.124
$A\beta_{42}$ BL	–0.0003298	0.0002238	0.997(0.9992,1.0001)	0.14066
Left Temporal 24M% Decline	–2.2242	1.8093	0.1082(0.0028,3.5480)	0.218936
FAQ 24M% Decline	0.001976	0.001686	1.0020(0.9986,1.0055)	0.241
Education	–0.05709	0.05117	0.9445(0.8534,1.0435)	0.265
Posterior Cingulum BL	0.8017	0.7668	2.2293(0.4978,10.1865)	0.296
MMSE 24M% Decline	–0.01321	0.01361	0.9869(0.9595,1.0135)	0.331794
Right Mesio-Temporal BL	0.00007593	0.00008631	1.0001(0.9999, 1.0002)	0.379
Right Hippocampus 24M% Decline	1.3737	1.5686	3.9500(0.1957,115.2847)	0.38117
Right Hippocampus BL	0.0001673	0.0002238	1.0002(0.9997,1.0006)	0.455
MMSE BL	–0.03882	0.06323	0.9893(0.8807,1.1079)	0.539
APOE	0.1013	0.1783	1.1066(0.7813,1.5761)	0.57
Left Hippocampus 24M% Decline	–0.3558	1.27	0.7006(0.0433,8.2812)	0.77935
Right Temporal 24M% Decline	–0.4655	1.9347	0.6278(0.0133,27.9509)	0.809871
Left Hippocampus BL	0.00005174	0.0002256	1.0001(0.9996,1.0005)	0.819
Right Temporal BL	–0.2322	1.0784	0.7928(0.0936,6.5742)	0.83
Sex	–0.0495	0.2649	0.9517(0.5661,1.6015)	0.852
SDMA BL	–0.2359	1.1123	0.7899(0.0891,7.1498)	0.832
Posterior Cingulum 24M% Decline	0.1851	1.17731	1.2033(0.0349,38.9213)	0.91686
Left Temporal BL	–0.09299	0.96987	0.9112(0.1338,6.1061)	0.924

FAQ, Functional Activities Questionnaire; BL, Baseline Level; 24M, 24 months; MMSE, Mini-Mental State Examination; *APOE*, apolipoprotein genotype; SDMA, symmetric dimethylarginine.

24 months. No significant correlation was found between $A\beta_{42}$ and cognitive scores in prodromal AD dementia participants. Additionally, no significant correlation was found between SDMA and neurocognitive scores for either cognitively unimpaired participants or prodromal AD dementia participants.

To analyze for relationships between biomarker levels and regional neuroimaging assessments, scatterplots and associations were computed (Figs. 8–12). See Supplementary Figures for scatterplots and associations across all participants. Positive relationships were found in cognitively unimpaired participants between baseline $A\beta_{42}$ and posterior

Table 3
Multivariable logistic regression including SDMA

Variable	β Estimate	Standard Error	*p*
Intercept	2.42	3.23	0.45
SDMA BL	3.19	2.82	0.25685
MRI Left Mesio-Temporal 24M% Decline	–17.33	6.69	0.00963
MRI Left Mesio-Temporal BL	0.000421	0.0002035	0.0386
FDG Left Temporal 24M% Decline	–5.57	3.73	0.13564
FAQ 24M% Decline	–0.001961	0.002396	0.41306
FDG Posterior Cingulum BL	–1.38	1.66	0.40481
Age	–0.0618	0.04197	0.14093

SDMA, symmetric dimethylarginine; BL, Baseline Level; 24M, 24 months.

Table 4
Multivariable logistic regression including $A\beta_{42}$

Variable	β Estimate	Standard Error	*p*
Intercept	1.66	3.67	0.6518
$A\beta_{42}$ BL	–0.0007975	0.0005634	0.1569
MRI Right Mesio-Temporal 24M% Decline	–8.56	5.7	0.1329
MRI Left Mesio-Temporal 24M% Decline	–16.43	6.83	0.0161
MRI Left Mesio-Temporal BL	0.0003284	0.0001981	0.0973
FDG Left Temporal 24M% Decline	–4.1	3.85	0.287
FAQ 24M% Decline	–0.001319	0.002387	0.5807
Age	–0.0282	0.03821	0.4604

BL, Baseline Level; 24M, 24 months.

Table 5
Multivariable logistic regression including SDMA × $A\beta_{42}$

Variable	β Estimate	Standard Error	*p*
Intercept	5.5052849	1.8527855	0.00296
SDMA BL × $A\beta_{42}$ BL	–0.0005728	0.0003929	0.14490
MRI Right Mesio-Temporal 24M% Decline	–4.3946445	2.9739123	0.13948
MRI Left Mesio-Temporal 24M% Decline	–3.8302686	2.6132666	0.14273
Education	–0.0908523	0.0539301	0.09206
FAQ BL	0.1222798	0.0532205	0.02158
Age	–0.0433383	0.0205335	0.03481

FAQ, Functional Activities Questionnaire; BL, Baseline Level; 24M, 24 months.

Table 6
Post-hoc Mixed-effect logistic regression with multiple imputations

Variable	β Estimate	Standard Error	*p*
Intercept	2.70716	0.85642	0.00157
Time	0.3101	0.48986	0.52671
SDMA BL	0.68454	0.61223	0.26353
$A\beta_{42}$ BL	–0.97543	0.67882	0.15073
FAQ	0.02464	0.52501	0.96256
FDG Left Temporal	0.05765	0.5224	0.91213
MRI Left Mesio-Temporal	1.35702	0.74324	0.06788
MRI Right Mesio-Temporal	–0.17772	0.75693	0.81437
Education	–2.04067	0.68972	0.00309
FDG Posterior Cingulum	0.33892	0.60528	0.57552
Age	–3.25965	0.73173	0.0000084

SDMA, symmetric dimethylarginine; BL, Baseline Level; FAQ, Functional Activities Questionnaire.

cingulum metabolism ($r = 0.270$, $p = 0.005$), left temporal metabolism ($r = 0.477$, $p = 2.324 \times 10^{-7}$), and right temporal metabolism ($r = 0.358$, $p = 0.000161$) at baseline. In cognitively unimpaired participants, there were also positive associations between baseline $A\beta_{42}$ and baseline right ($r = 0.301$, $p = 0.00173$) and left ($r = 0.328$, $p = 0.000587$) hippocampal volume. At 24 months, the association slightly decreased

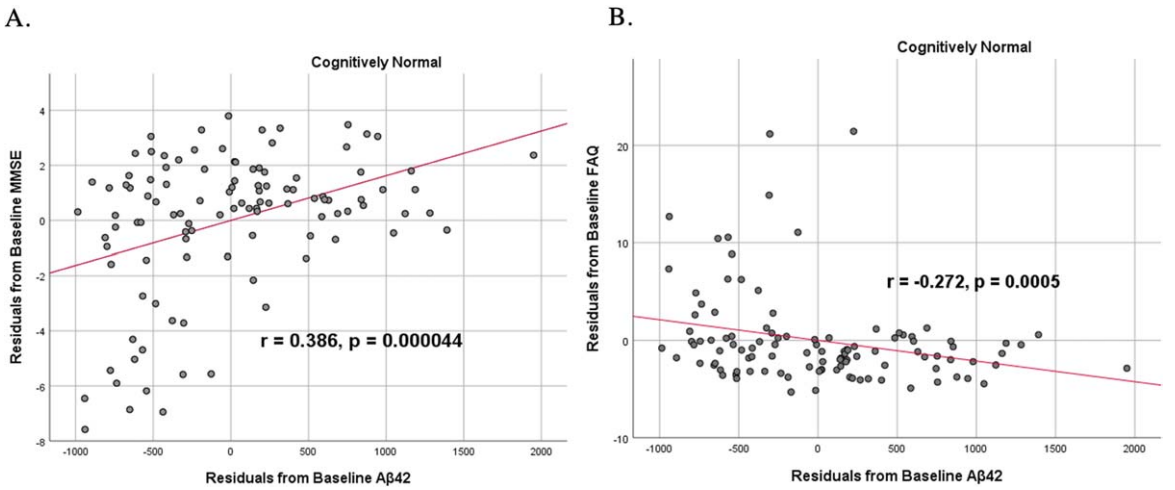

Fig. 5. Partial correlations between baseline $A\beta_{42}$ concentration and baseline neurocognitive function in normal controls, corrected for age and education. Scatterplots above are corrected for age and education. A) $A\beta_{42}$ versus MMSE ($r = 0.386$, $p = 4.4 \times 10^{-5}$). B) $A\beta_{42}$ versus FAQ ($r = -0.272$, $p = 0.0005$).

between baseline $A\beta_{42}$ and left temporal metabolism ($r = 0.446$, $p = 2.0 \times 10^{-6}$), though the metabolic association increased for the right temporal lobe ($r = 0.380$, $p = 0.000059$). The association between baseline $A\beta_{42}$ and right hippocampal volume at 24 months also slightly decreased ($r = 0.286$, $p = 0.003$) and for the right increased ($r = 0.347$, $p = 0.000263$). Finally, negative associations were found regarding baseline $A\beta_{42}$ and right mesio-temporal volume change ($r = -0.382$, $p = 0.000052$) and left mesio-temporal volume change ($r = -0.316$, $p = 0.000953$) and are weakly negative. No significant correlation was found between $A\beta_{42}$ and brain regions in prodromal AD dementia participants. Additionally, no significant correlation was found between SDMA and regional neuroimaging measures for either cognitively unimpaired participants or prodromal AD dementia participants.

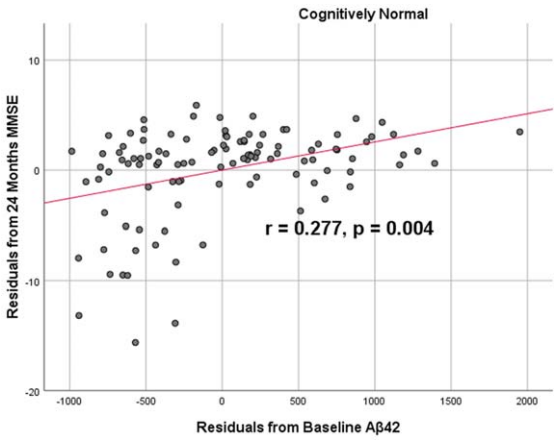

Fig. 6. Partial correlations between baseline $A\beta_{42}$ concentration and 24 months neurocognitive function in normal controls, corrected for age and education. Scatterplots above are corrected for age and education. Aβ42 versus MMSE ($r = 0.277$, $p = 0.004$).

DISCUSSION

The main goal of this study was to evaluate a novel blood constituent, SDMA, against $A\beta_{42}$ as a biomarker for AD dementia while reevaluating past inconsistent results of $A\beta_{42}$ as a potential predictor of AD dementia progression, in addition to understanding the relationship between SDMA and $A\beta_{42}$ with brain hypometabolism and atrophy as well as cognition and function. SDMA is an enantiomer of ADMA which is an inhibitor of nitric oxide synthase and a mediator of vascular endothelial function [36]. As a vascular risk factor, ADMA has been thought to contribute to the development of AD dementia; one study found ADMA plasma concentration level significantly increased and nitric oxide decreased in AD dementia patients [37]. Serum ADMA was increased in chronic kidney disease in parallel with increase of fecal tryptamine [38], which was shown to induce neurodegeneration in cells and animals [39, 40]. Additionally, in a prospective cohort study, serum ADMA concentration predicted worsening cognition in patients and was suggested to be a potential early detection marker for dementia and AD [41].

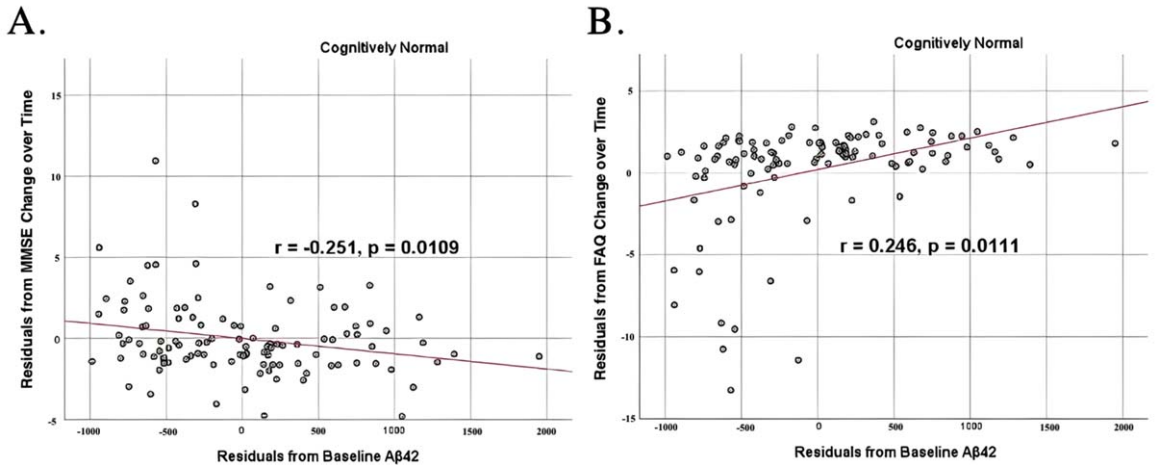

Fig. 7. Partial correlations between baseline $A\beta_{42}$ concentration and neurocognitive function decline in normal controls, corrected for age and education. Scatterplots above are corrected for age and education. A) $A\beta_{42}$ versus MMSE ($r = -0.251$, $p = 0.0109$). B) $A\beta_{42}$ versus FAQ ($r = 0.246$, $p = 0.0111$).

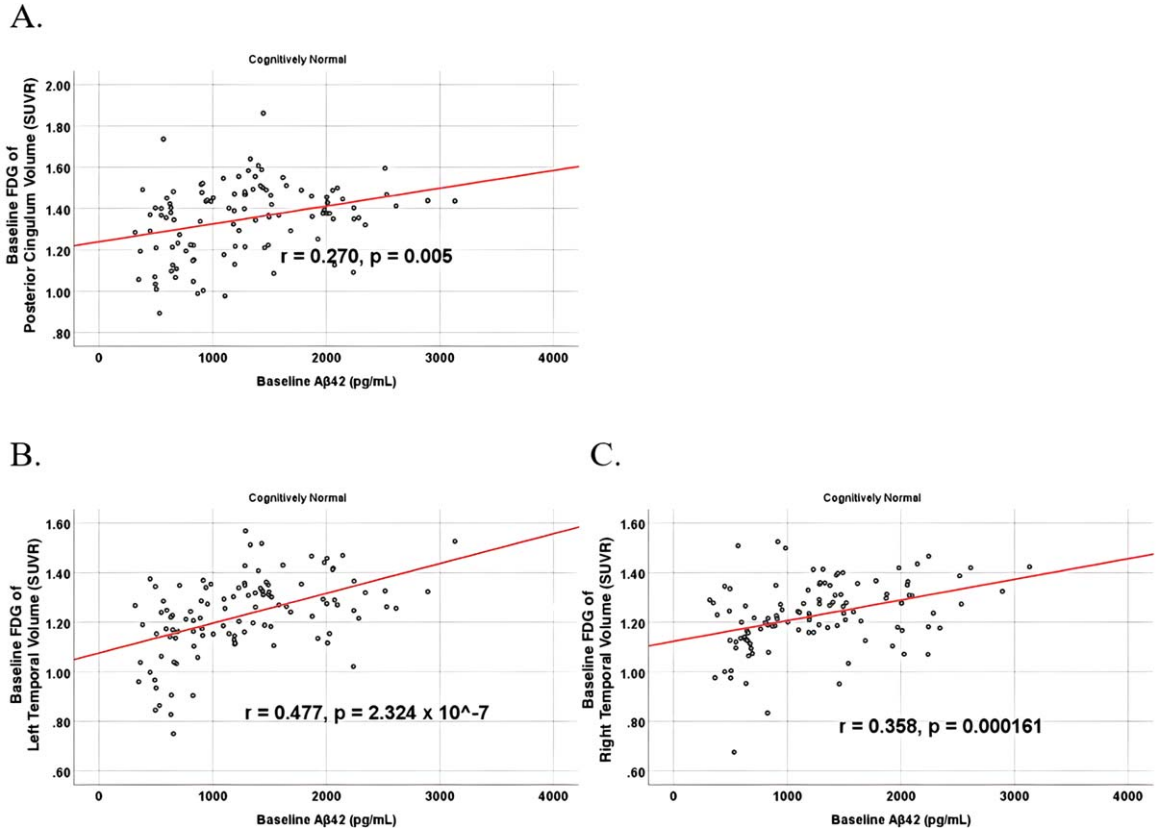

Fig. 8. Partial correlations between baseline $A\beta_{42}$ and baseline FDG brain volume regions in cognitively unimpaired control participants, corrected for age and education. Scatterplots above are corrected for age and education. A) $A\beta_{42}$ versus Posterior Cingulum ($r = 0.270$, $p = 0.005$). B) $A\beta_{42}$ versus Left Temporal ($r = 0.477$, $p = 2.324 \times 10^{-7}$). C) $A\beta_{42}$ versus Right Temporal ($r = 0.358$, $p = 0.000161$).

Based on our data analysis, we do not have sufficient evidence to conclude that either SDMA or $A\beta_{42}$ as measured with 2D-UPLC tandem mass spectrometry is a reliable predictor of future cognitive status. For SDMA, our study is the first to our knowledge to look at SDMA as a single biomarker measurement

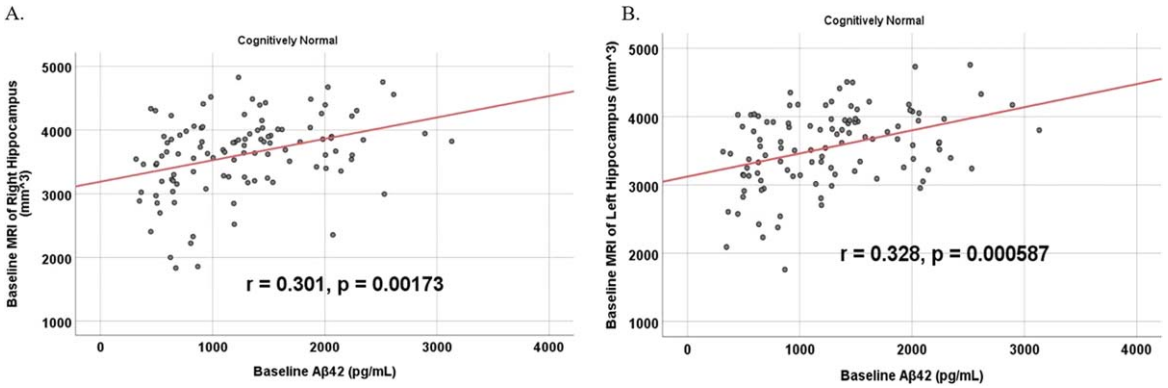

Fig. 9. Partial correlations between baseline $A\beta_{42}$ and baseline MRI brain volume regions in cognitively unimpaired control participants, corrected for age and education. Scatterplots above are corrected for age and education. A) $A\beta_{42}$ versus Right Hippocampus ($r = 0.301$, $p = 0.00173$). B) $A\beta_{42}$ versus Left Hippocampus ($r = 0.328$, $p = 0.000587$).

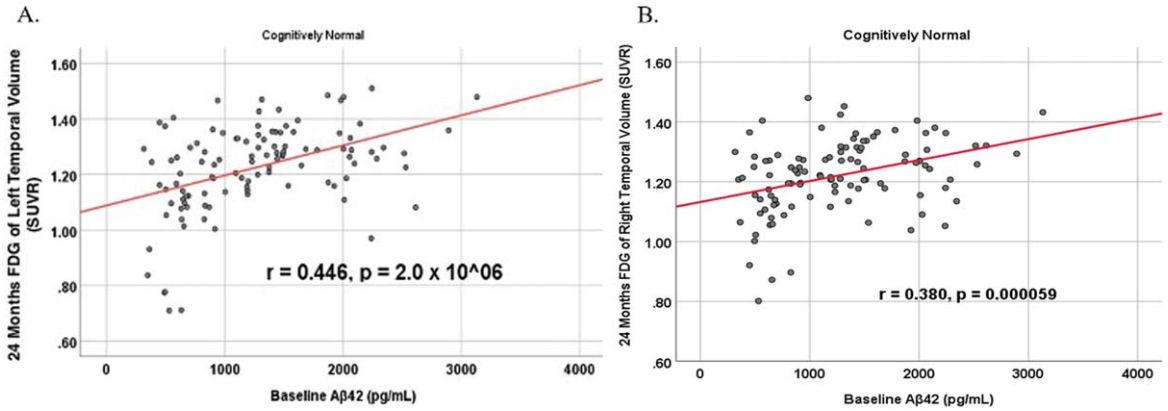

Fig. 10. Partial correlations between baseline $A\beta_{42}$ and 24 Month FDG brain volume regions in cognitively unimpaired control participants, corrected for age and education. Scatterplots above are corrected for age and education. A) $A\beta_{42}$ versus Left Temporal ($r = 0.446$, $p = 2.0 \times 10^{-6}$). B) $A\beta_{42}$ versus Right Temporal ($r = 0.380$, $p = 0.000059$).

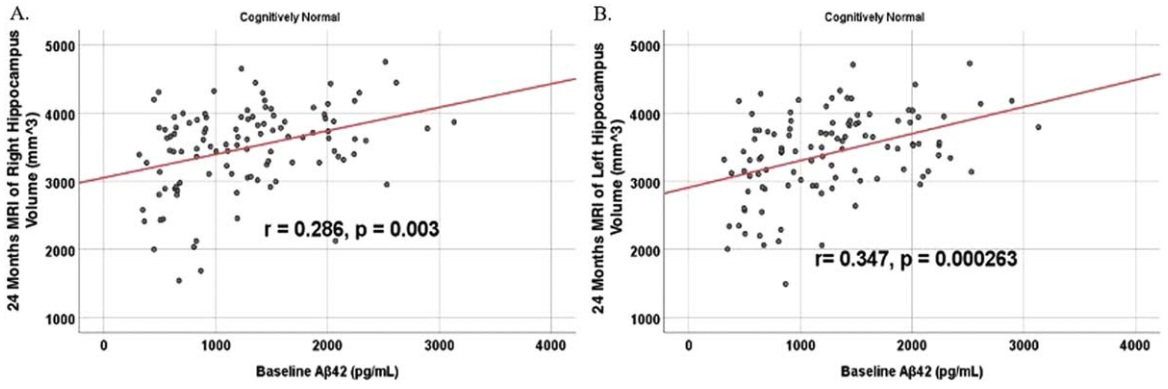

Fig. 11. Partial correlations between baseline $A\beta_{42}$ and 24 Month MRI brain volume regions in cognitively unimpaired control participants, corrected for age and education. Scatterplots above are corrected for age and education. A) $A\beta_{42}$ versus Right Hippocampus ($r = 0.286$, $p = 0.003$). B) $A\beta_{42}$ versus Left Hippocampus ($r = 0.347$, $p = 0.000263$).

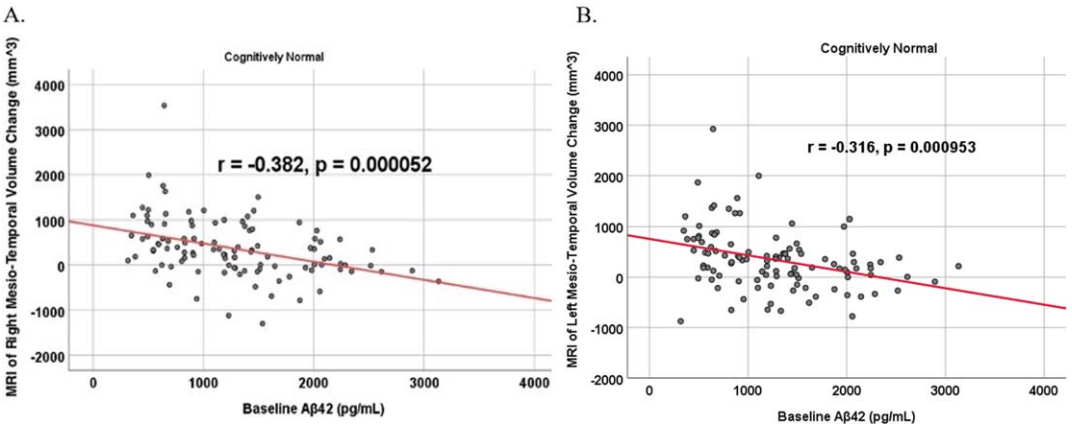

Fig. 12. Partial correlations between baseline $A\beta_{42}$ and MRI brain regional volume change in cognitively unimpaired control participants, corrected for age and education. Scatterplots above are corrected for age and education. A) $A\beta_{42}$ versus Right Mesio-Temporal ($r = –0.382$, $p = 0.000052$). B) $A\beta_{42}$ versus Left Mesio-Temporal ($r = –0.316$, $p = 0.000953$).

for predicting diagnosis of prodromal AD dementia. Previous studies with SDMA included it with other renal biomarkers and have shown promising results discriminating between MCI and AD dementia participants [21, 42], but our study differs in its conclusion. Of note, one of the studies had a much smaller sample size and compared normal controls to MCI and AD dementia patients at the time of their illness; but did not examine baseline SDMA or $A\beta_{42}$ to predict a future diagnosis [42]. Additionally, the other study found SDMA to be positively associated with AD dementia cognitive status and global AD brain pathology burden; however, SDMA was not analyzed via serum like this investigation but by concentrations in the brain from autopsy donors, and the study also had a smaller sample size [21]. The patients in that study were also significantly older at an average of 90 years compared to both groups in this study. To investigate the prognostic value of SDMA and $A\beta_{42}$ further, we looked at the relationship between these biomarker levels and cognitive decline and neuroimaging outcome variable within prodromal AD dementia and cognitively unimpaired control subject cohorts. A previous study found higher SDMA, in contrast to our results, was associated with objective and subjective cognitive impairment [25]. However, the SDMA concentrations they found to be associated were much higher than the average SDMA concentration of either this investigation's control group and prodromal AD dementia group. Nevertheless, we found no correlation between SDMA and MRI, FDG-PET, and neurocognitive scores in either the prodromal AD dementia group or the cognitively unimpaired controls.

While all the results were negative for SDMA, some results did point to an association between lower CSF levels of $A\beta_{42}$ and cognitive and functional decline. For $A\beta_{42}$, our results are in support of a review conducted of 26 previous studies that also found insufficient evidence in using plasma and CSF $A\beta_{42}$ in the diagnosis or even risk assessment of AD dementia as a single measurement [43]. This review and other recent studies are in support of measuring $A\beta_{42}$ and $A\beta_{40}$ together for better prediction of amyloid pathology in prodromal AD dementia [7, 44]. In contrast, our results did find levels of CSF $A\beta_{42}$, and not SDMA, positively correlate with temporal and hippocampal brain volume, brain metabolic activity, and neurocognitive scores in cognitively unimpaired controls but not in prodromal AD dementia participants, which is in line with previous research [45, 46]. In the prodromal AD dementia participants, the absence of a correlation between $A\beta_{42}$ and the anatomical and functional changes that often typify AD may suggest that these pathologies are independent of one another, or alternatively, that CSF $A\beta_{42}$ levels might behave differently across the lifespan [47]. For example, a study found higher and lower CSF $A\beta_{42}$ in patients <75 years was indicative of future MCI/AD dementia, but over the age of 75 years, $A\beta_{42}$ could not predict MCI/AD dementia [48]. In our investigation, correlations were smaller between $A\beta_{42}$ and MMSE at 24 months and absent in prodromal AD dementia participants, suggesting a possible plateau effect, perhaps stemming from a more advanced age and/or disease-stage. The association of $A\beta_{42}$ with markers of neurodegeneration (i.e., MRI and FGD-PET) might also be the result of a

plateau effect that is dependent not only upon age but also the disease stage. Although not exactly the same, a similar effect has been reported in the literature in which $A\beta_{42}$ plateaus as a patient progresses into MCI and then decrease in concentration as they advance into AD dementia [49]. In normal controls, however, there are varying reports on the behavior of $A\beta_{42}$ with age, with some reports that $A\beta_{42}$ increases with age consistently and another that it decreases in early life, increases in midlife, and then becomes unassociated with age at later years [50]. For both the normal controls and prodromal AD dementia patient groups, $A\beta_{42}$ was inversely associated with age.

While $A\beta_{42}$ may be a poor biomarker as a standalone measure, performance is improved when combined with $A\beta_{40}$ as a ratio, as $A\beta_{42}/A\beta_{40}$ has proven to be a more precise and reproducible marker for amyloid-positivity [51]. For example, replacing $A\beta_{42}$ for $A\beta_{42/40}$ improved the concordance with amyloid PET by 15% in patients with MCI [52]. Apart from amyloid-positivity, studies have also found better diagnostic performance of AD dementia utilizing $A\beta_{42/40}$ compared to Aβ42 alone [53, 54]. Altogether, based on prior reports pointing to the usefulness of $A\beta_{42}$ as a standalone measure and its even more promising role as part of the $A\beta_{42/40}$ index, our results suggest consideration of this ratio in future studies, as well as alternative explanations of our otherwise negative findings [3, 4]. For this reason, we explore the role of a multiplicity of potentially limiting and confounding factors.

Sample size

Another potential limitation to our study is the sample size. Although several studies of anti-amyloid therapies comprise smaller sample sizes [55], it is worth mentioning that positive findings have been published in studies with sample sizes larger than ours in regards to $A\beta_{42}$ [53, 56–59]. However, this study is currently believed to be the largest in regards to assessing SDMA as a predictor of AD dementia, though there are very few select investigations of its utility in dementia. Future investigations of larger sample sizes are therefore encouraged in order to support the generalization of these results for both SDMA and $A\beta_{42}$.

Comorbidities

Hepatic, renal, and neurodegenerative diseases can influence biomarker measurements in the older adult population. Biomarkers, such as phosphorylated tau (p-tau), neurofilament light chain, and total tau, can elevate by 2 to 4 folds in individuals with cirrhosis and show correlations with creatinine levels [60]. The liver makes albumin and filters proteins from blood, so cirrhosis may alter biomarker binding, especially sticky Aβ, and reduce protein elimination, whereas glomerular diseases of the kidneys may result in proteinuria that alters the level of blood protein [61]. Severe liver and kidney diseases, and peripheral neuropathy, such as diabetic neuropathy, can increase the concentration of neurodegenerative biomarkers [62, 63]. Our study has been able to rule out renal and hepatic diseases, with mean lab values within normal limits and no significant differences between the normal control and prodromal AD dementia cohorts. In the normal control cohort, the mean liver enzyme values are ALT 23.33, AST 26.18, and alkaline phosphatase 73.38. Renally, the mean creatinine is 0.88 and urea nitrogen is 19.82. In the prodromal AD dementia cohort, the mean liver enzyme values are ALT 22.63, AST 24.97, and alkaline phosphatase 68.97. Renally, the mean creatinine is 0.85 and urea nitrogen is 18.56. The prevalence of diabetes in the United States in 2019 is 11.3% of the population (37.3 million individuals), and among seniors, 29.2% of those aged 65 and older have diabetes (15.9 million individuals) [64]. One study has demonstrated that in patients with AD dementia, the prevalence of diabetes is higher (35% compared to 18% in control participants) and glucose tolerance is more impaired (46% compared to 24% in control participants) [65]. Although studies often exclude comorbid conditions, investigation of these factors can be valuable in understanding the clinical interpretation of biomarkers.

Race and ethnicity

Our study uses ADNI data, which includes around 10% of African American and Hispanic participants, specifically our data includes 91.67% White participants in the cognitively unimpaired cohort, and 91.78% White participants in the prodromal AD dementia cohort which is a limitation of the data set. Although one ADNI study that controlled covariates did not find differences between racial groups, ADNI itself is not population-based and unable to represent the general population [66]. Future studies should examine a larger and more diverse cohort of participants in a longitudinal study. It is important to ensure that studies are representative of the population in terms of racial and ethnic diversity, as well as

social factors that are associated with dementia and pathology outcomes.

Age

Another explanation for why neither biomarker showed a significant difference between cognitively unimpaired control and prodromal AD dementia is the confounding variable age. Age has been documented to be the main predictor of CSF and plasma $A\beta_{42}$ before, with mixed results in other studies for SDMA [67–69]. Although we adjusted for this variable in our multivariable analysis, we believe further prospective investigations are needed into these biomarkers that control for age using restriction or matching as part of the initial study design. An important limitation in our analysis is that we only collected baseline $A\beta_{42}$ and SDMA levels. We found that these early baseline values were not significantly capable of predicting AD dementia from cognitively unimpaired controls, though we did not perform longitudinal analyses of constituent changes in relation to changes in brain volume, metabolic activity, and cognitive decline. Additionally, our study's time frame of 24 months may be too narrow of a window for indicators to develop. Individuals with MCI have a 10 to 15% incidence of developing dementia each year [64]. One-third of individuals with MCI develop dementia due to AD within five years [65]. A timeframe of 24 months may not have been robust enough to see significant distinctions in imaging and biomarkers between cognitively unimpaired controls and prodromal AD dementia participants.

Further studies should be conducted that collect $A\beta_{42}$ and SDMA levels over time to determine if there is a critical window during which these biomarkers have predictive capability of AD pathogenesis and progression. This approach has been fruitful in the past, with at least one prospective cohort study showing that repeated testing of serum $A\beta_{42}$ may be useful in the detection of participants at risk for cognitive decline [70].

Socioeconomic

Social determinants of health (SDOH) are factors that can alter an individual's health and wellbeing, including chronic disease management and comorbidities related to dementia. Important SDOH factors should be examined are financial and housing stability, social support, discrimination, food deserts, education, access to care, and quality of care. Our study was limited by our methods and did not examine most of these relevant SDOH factors. We did not find any studies that examined the relationship between SDOH factors and fluid AD dementia biomarkers. One study noted that neurodegenerative diseases may correlate with homelessness in individuals with challenging socioeconomic and unsupportive environments [71]. ADNI is a multi-site study and enrolls mostly college-educated participants with over 16 years of education. Previous studies have shown an association between higher education and reduced cognitive decline [72]. High education levels can inflate MMSE scores, possibly due to structural and cognitive process differences in individuals with more education. Additionally, ADNI limits study locations by including less diverse zip codes, especially areas with greater disparities and disease burdens. Further, individuals with little or no practical access to care and lack of trust in healthcare providers might go to less preventative and follow-up visits. Many chronic health conditions, including dementia and other comorbidities, may not be diagnosed and treated early on, thereby worsening disease outcomes. Future studies should examine the impact of SDOH factors on AD dementia biomarkers through prospective studies and interviews.

Conclusion

Our results are in support of other investigations concluding that there is insufficient evidence in utilizing baseline CSF $A\beta_{42}$ in the diagnosis and risk assessment of AD dementia as a single measurement. Nevertheless, our results by no means preclude its use as part of a $A\beta_{42/40}$ ratio, a use strongly supported by the current literature [3, 4, 51]. We were also unable to find conclusive evidence to support the usage of SDMA as a novel biomarker capable of predicting AD pathogenesis. However, our results suggest that $A\beta_{42}$ may be associated with neurodegeneration in the earliest phases of the disease when a ceiling or plateau effect of the biomarker appears less likely. Future larger studies should be conducted that collect $A\beta_{42}$ and/or $A\beta_{42/40}$ as well as SDMA concentration levels over time to determine if there is a critical window during which these biomarkers may have predictive capability of AD pathogenesis and progression.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to report.

DATA AVAILABILITY

The data supporting the findings of this study are available on request from the corresponding author.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/ADR-230054.

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