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RESEARCH ARTICLE

Association of plasma biomarkers with cognitive function in persons with dementia and cognitively healthy in the Democratic Republic of Congo

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Abstract

Introduction: This study investigates whether plasma biomarkers (A β 42/40 and p-tau 181), APS, as well as apolipoprotein E (APOE) proteotype predict cognitive deficits in elderly adults from the Democratic Republic of Congo.

Methods: Forty-four with possible AD (pAD) and 41 healthy control (HC) subjects were screened using CSID and AQ, underwent cognitive assessment with the African Neuropsychology Battery (ANB), and provided blood samples for plasma A β 42, A β 40, A β 42/40, and APOE proteotype. Linear and logistic regression were used to evaluate the associations of plasma biomarkers with ANB tests and the ability of biomarkers to predict cognitive status.

Results: Patients with pAD had significantly lower plasma A β 42/40 levels, higher APS, and higher prevalence of APOE E4 allele compared to HC. Groups did not differ in levels of A β 40, A β 42, or P-tau 181. Results showed that A β 42/40 ratio and APS were

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significantly associated with African Naming Test (ANT), African List Memory Test (ALMT), and African Visuospatial Memory Test (AVMT) scores, while the presence of APOE E4 allele was associated with ANT, ALMT, AVMT, and APT scores. P-tau 181 did not show any significant associations while adjusting for age, education, and gender. APS showed the highest area under the curve (AUC) value (AUC = 0.78, 95% confidence interval [CI]: 0.68–0.88) followed by A β 42/40 (AUC = 0.75, 95% CI: 0.66–0.86) and APOE E4 (AUC = 0.69 (CI 0.57–0.81) in discriminating pAD from HC.

Discussion: These results demonstrate associations between select plasma biomarker of AD pathology (A β 42/40), APS, and APOE E4 allele) and ANB test scores and the ability of these biomarkers to differentiate pAD from cognitively normal SSA individuals, consistent with findings reported in other settings.

1 | INTRODUCTION

Recent technological breakthroughs have made it possible to soon move from invasive biomarkers, such as cerebrospinal fluid (CSF) analysis or PET, to blood tests to support the research and clinical practice of dementia related to Alzheimer's disease (AD) and other dementias in the high-income world.¹ AD biomarkers are becoming a crucial tool to provide objective in vivo measures of AD neuropathology. To date, biofluid research has focused mostly on CSF biomarkers, including amyloid-beta (A β ; A β 42/40 ratio),¹ and phosphorylated tau (p-tau),² which are considered a reflection of the neuropathological hallmarks of AD. Recent enhancements to the sensitivity of immunoassay and mass spectrometry analytical platforms make it possible to quantify plasma amyloid and tau variant concentrations, and these biomarkers accurately detect cerebral amyloid pathology (A β 42/40 ratio, p-tau, and APS).^{3–7} For example, an algorithm that includes plasma A β 42/40, APOE proteotype, and age generates the Amyloid Probability Score (APS) (APS; Hu et al.), which has validated diagnostic utility for estimating the likelihood of amyloid PET positivity vs negativity.

So far, these methods have primarily been utilized in Western countries and little is known of their performance in sub-Saharan countries which have different geographies, life-style factors, and different ethnicities. There are an estimated 2.1 million individuals currently living with dementia in Sub-Saharan Africa (SSA), and that number is projected to triple by the year 2040,⁹ due in part to a growing proportion of older adults, with a projected 161 million by 2050.¹⁰ Therefore, there is an urgent need to explore plasma AD biomarkers in less economically developed countries to determine their potential clinical use and relation with cognitive decline. The extant literature supports the need for additional research into the impact of ethnoracial factors on AD biomarkers (e.g., plasma AD biomarkers present differential associations by race/ethnicity with African Americans, having lower levels of p-tau in CSF compared to White Americans),^{7,11–15} although few studies have quantified plasma and genetic AD biomarkers in SSA cohorts.¹⁸

Presence of the APOE ϵ 4 allele is a well-known risk factor for AD,¹⁶ having been associated with a 50% increase in the risk of developing AD and with accelerated cognitive deficits in MCI and AD.¹⁷ AD risk associated with APOE ϵ 4, however, has been found to be smaller in persons of African versus European ancestry.¹⁵ Genetic analyses comparing cohorts of African Americans and Africans (Nigeria, Yoruba) demonstrated that the prevalence of the ϵ 4 allele was high but showed a weaker association with AD in Yoruba compared to African Americans.¹¹

The Diagnostic and Statistical Manual of Mental Disorders-5th Edition (DSM-5) considers neuropsychological testing as an important part of the diagnosis of AD and related dementias. Previous studies have found associations between plasma biomarkers A β 42/40 and p-tau with cognitive deficits in individuals on the AD continuum,¹⁸ specifically with deficits in attention, episodic memory, semantic fluency, and executive functioning suggestive of probable AD.^{19–21} However, most neuropsychological measures are heavily impacted by various cultural and linguistic factors,^{25–26} which limits diagnostic accuracy of cognitive impairment in culturally diverse individuals. Thus, the African Neuropsychology Battery (ANB) was created and validated against Western cognitive tests for SSA, Congolese individuals.²²

In the current study, we examined the relationships of plasma protein biomarker concentrations (A β 42/40 ratio, p-tau181), APS and APOE proteotype, with cognitive function (language, memory, and executive function) using the ANB.²² We hypothesized that lower plasma A β 42/40 ratio, high APS and plasma p-tau 181 levels, and the presence of 1 or 2 APOE ϵ 4 alleles would significantly predict lower ANB scores (language, memory, and executive functions), and that individuals with dementia would have: (a) low A β 42/40 levels, high p-tau 181 and APS levels, and higher prevalence of APOE ϵ 4 allele; and (b) lower ANB cognitive scores compared to HC. We expected A β 42/40 ratio, APS, p-tau 181 and APOE ϵ 4 alleles would discriminate between persons with dementia vs. HC using the receiver operating characteristic curves (ROC)-area under the curve (AUC).

RESEARCH IN CONTEXT

1. **Systematic review:** Cross-sectional and longitudinal measurements of plasma biomarkers of Alzheimer's disease (AD) in Western countries are being applied in clinical practice, whereas their associations with culturally validated cognitive tests in other settings remain unknown. Recent enhancements to the sensitivity of immunoassay and mass spectrometry analytical platforms make it possible to quantify plasma amyloid and tau isoform concentrations, and these biomarkers accurately detect cerebral amyloid pathology ($A\beta_{42/40}$ ratio, p-tau, and APS).³⁻⁷ For example, an algorithm that includes plasma $A\beta_{42/40}$, apolipoprotein E (APOE) proteotype, and age generates the Amyloid Probability Score (APS) (APS; Hu et al.), which has validated diagnostic utility for estimating the likelihood of amyloid positron emission tomography (PET) positivity versus negativity.

So far, these methods have primarily been utilized in Western countries and little is known of their performance in sub-Saharan countries, which have different geographies, life-style factors, and different ethnicities. There are an estimated 2.1 million individuals currently living with dementia in Sub-Saharan Africa (SSA), and that number is projected to triple by the year 2040,⁹ due in part to a growing proportion of older adults, with a projected 161 million by 2050.¹⁰ Therefore, there is an urgent need to explore plasma AD biomarkers in less economically developed countries to determine their potential clinical use and relation with cognitive decline. The extant literature supports the need for additional research into the impact of ethnoracial factors on AD biomarkers (e.g., plasma AD biomarkers present differential associations by race/ethnicity with African Americans, having lower levels of p-tau in cerebrospinal fluid (CSF) compared to White Americans),^{7,11-15} although few studies have quantified plasma and genetic AD biomarkers in SSA cohorts.¹⁸

2. **Interpretation:** The primary study outcomes were cognitive scores in the ANB [African Naming Test (ANT), African List Memory Test (ALMT), African Visuospatial Memory Test (AVMT), African Proverb Test (APT), and African Card Game Test (ACGT)] and cognitive status (dementia, HC). Individuals with dementia had significantly lower $A\beta_{42/40}$ levels, higher APS, and higher APOE $\epsilon 4$ prevalence compared to HC. Linear regressions showed significant associations between $A\beta_{42/40}$ and APS with ANT, ALMT, and AVMT scores, while APOE $\epsilon 4$ presence was associated with ANT, ALMT, AVMT, and APT scores. APS showed the highest AUC value (AUC = 0.78, 95% CI: 0.68–0.88) followed by $A\beta_{42/40}$ (AUC = 0.75, 95% CI: 0.66–0.86) and APOE $\epsilon 4$ (AUC = 0.69 (CI 0.57–0.81) in discriminating dementia from HC. These findings may have implications for the assessment of AD biomarkers in SSA.

3. **Future directions:** The following represent limitations to our current study. Our findings should be interpreted in light of several limitations, such as the cross-sectional nature, low power and lack of amyloid PET imaging confirming AD pathology. The degree to which the current associations between plasma biomarkers of AD pathology and cognitive scores reflect disease trajectory and progression should be further explored with longitudinal analyses. Second, the moderate sample size in both groups may have obscured significant associations among variables examined; thus, future studies should replicate these findings with larger sample sizes. Finally, this study analyzed only selected plasma AD biomarkers ($A\beta_{42/40}$, p-tau181, and APOE). Future studies should aim to replicate our findings along the AD pathology continuum, as well as utilize other plasma and CSF biomarkers (e.g., p-tau217, 213), glial fibrillar acidic protein (GFAP) and neurofilament light (NfL), as they may provide greater insight into the progression of cerebral amyloid and tau pathology, and cognitive decline in SSA populations, in addition to potentially exploring novel highly promising serum-based synaptic biomarkers (e.g., β -synuclein and other aggregates in dopaminergic neurons), neuroinflammation, and GFAP as a biomarker for microglia and astrocyte reactivity. Therefore, the exploration of these plasma biomarkers in African populations may identify potential inter-individual differences and modifiable factors that account for the similarity or the differences in AD pathogenesis and may implicate safe and effective interventions for AD pathology and cognition among Africans and other ethnic groups.

In conclusion, this is the first study in which the association between plasma AD biomarkers and ANB tests are explored within an elderly adult population from Democratic Republic of Congo in the SSA. We demonstrated the value of plasma AD biomarkers and ANB cognitive scores in classifying dementia in older adults in SSA populations.

2 | METHODS

2.1 | Participants

We screened 1432 Congolese participants for dementia using the Community Screening Instruments for Dementia (CSID), which has been extensively used in many international studies,²⁸ and Alzheimer's Questionnaire (AQ) measures.^{23,24} Participants were first classified using CSID scores, with scores <25.5 classified as cognitively impaired

and scores ≥ 25.5 considered cognitively unimpaired (see Figure 1). Participants were subsequently classified within each category of cognitively impaired and cognitively unimpaired by AQ scores of >13 or ≤ 13 , which yielded 4 groups: major neurocognitive disorder/dementia (CSID < 25.5 and AQ > 13), mild neurocognitive disorder (MND; CSID < 25.5 and AQ ≤ 13), subjective cognitive impairment (CSID ≥ 25.5 and AQ > 13), and healthy control (HC), that is, normal cognition (CSID ≥ 25.5 and AQ ≤ 13). Only those with major neurocognitive disorder or dementia and normal cognition or HC were

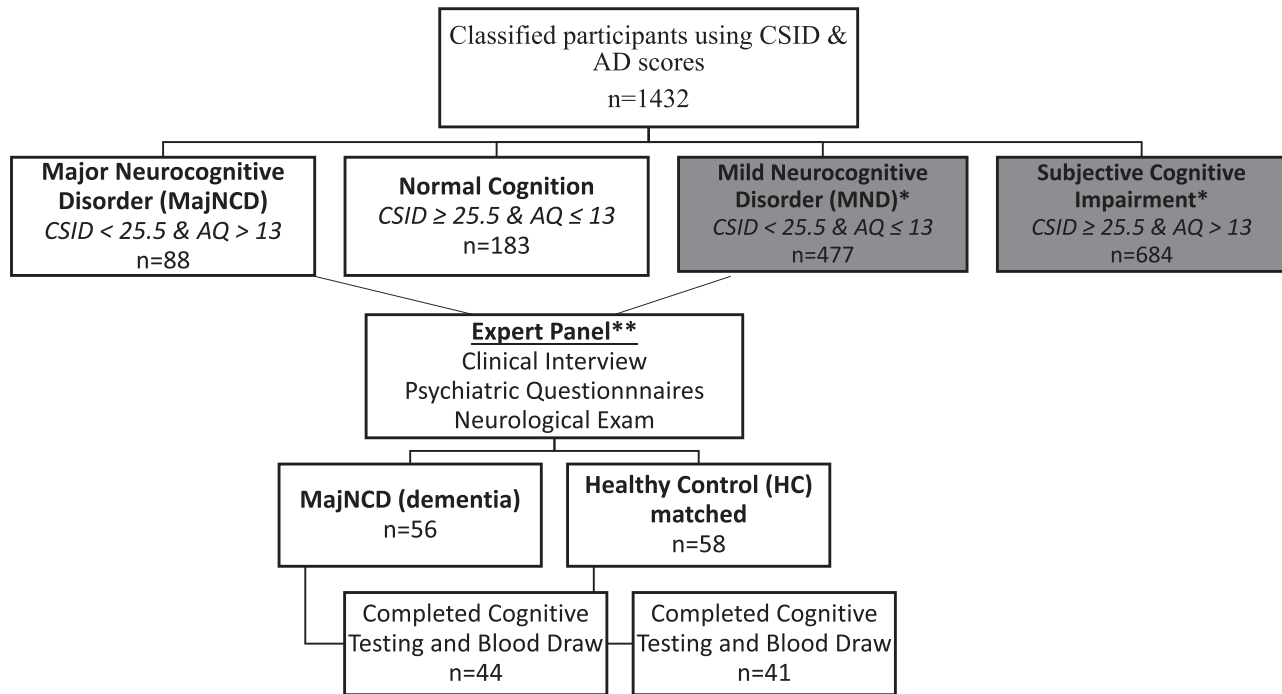


FIGURE 1 Flow diagram of participant classifications using the CSID and the AQ in the current study. *Groups that were excluded from study sample; **Expert panel consisted of neuropsychologist, neurologist, psychiatrist. AQ, Alzheimer's Questionnaire; AUC, area under the curve; CSID, Community Screening Instruments for Dementia; HC, healthy controls; MajNCD, major neurocognitive disorder; MND, mild neurocognitive disorder; pAD, possible Alzheimer's disease

included in this study. Of the 1432 initial subjects, 271 individuals met the above criteria of dementia (88 subjects) and controls (183 participants). After expert panel assessment based on screening tests, clinical interview, and neurological examination, 56 were confirmed with a diagnosis of dementia and 58 were considered as HC matched based on age, education, and gender. Plasma biomarkers were then measured in 85 subjects (75%), resulting in the final sample of 44 dementia and 41 HC. The remaining 29 subjects refused to provide blood samples. Participants were at least 65 years or older, had a family member or close friend to serve as an informant, and fluent in French or Lingala to be included. Participants were excluded if they had a subjective memory complaint, mild neurocognitive disorder, history of schizophrenia, neurological, or other or medical conditions potentially affecting the CNS. Written informed consent was obtained prior to participants' undergoing any study procedures. All participants were financially compensated for their time. All procedures were approved by the Ethics Committee/Institutional Review Boards of the University of Kinshasa.

2.2 | Procedure

Subjects were administered the dementia screening measures (CSID and AQ) to assign them into one of the four groups. Only those who met the criteria of major neurocognitive disorder/dementia and normal cognition according to DSM-5 underwent clinical evaluation, cognitive testing, self-report questionnaires, standard psychiatric and neurological evaluations to be diagnosed with dementia or to be con-

sidered as HC. An expert panel [neurologist (E.E.), psychiatrist (G.G.), and neuropsychologist (J.I.)] conducted this diagnostic procedure. Subjects meeting criteria for either subjective cognitive complaint, mild neurocognitive disorder/MCI, and major neurocognitive disorder/dementia with clear etiology other than Alzheimer's disease were given a brief explanation for why they were not eligible to participate further, thanked for their willingness to participate, and reimbursed for transportation cost. Subjects meeting criteria for group assignment (HC and dementia) were interviewed to obtain demographic, socioeconomic, and medical history. These subjects were administered the ANB, demographic, medical history, and lifestyle questionnaires in a single session independently from the diagnostic workup. A second visit was scheduled to obtain a blood sample at Medical Center of Kinshasa (CMK). During this second visit, a phlebotomist obtained the blood sample. Following each session, subjects received the appropriate incentive payment based on parts of the study completed. Sample collection protocol and quantification of fluid biomarkers are presented below.

3 | MEASURES

3.1 | Cognitive measures

Cognitive function was evaluated using the ANB,²² which includes the: African Naming Test (ANT; confrontation naming; total unaided correct score), African List Memory Test (ALMT; verbal learning and memory;

total long delay free recall correct score), African Visuospatial Memory Test (AVMT; visuospatial memory; total long delay recall correct score), African Proverb Test (APT; abstract reasoning; total interpretation correct score), and African Card Game Test (ACGT; problem solving; total wins correct score). The ANB has demonstrated good psychometric properties in evaluating effects of aging and neurological disease alongside providing culturally and linguistically appropriate neuropsychological measures for SSA countries.²²

3.2 | Plasma biomarker analyses

Blood samples were drawn in the CMK blood laboratory by venipuncture into ethylene diamine tetraacetic acid (EDTA) tubes. Samples were centrifuged within 15 min, and 5 mL plasma was aliquoted into 0.5 mL polypropylene tubes and stored initially at -20°C for less than a week and then at -80°C at CMK laboratory freezer in Kinshasa for longer-term storage.²⁵ The samples were shipped on dry ice to Emory University and analyzed for p-tau181 (Quanterix) and $A\beta_{42/40}$ concentration ratio and APOE isoform-specific peptides (C_2N Diagnostics; St. Louis, Missouri, USA) as described.⁸ For the p-tau181, EDTA plasma samples were prepared according to manufacturer's instructions for p-tau181 kit v2 (Quanterix). Briefly, samples were thawed at room temperature for 45 min. They were then centrifuged at $5000\times g$ for 10 min at room temperature. The plasma samples were then diluted $4\times$ on board and measured on the Simoa HD-X platform.

For the $A\beta_{42/40}$ concentration ratios, plasma samples were spiked with known quantities of commercially available stable isotope labeled recombinant proteins (e.g., $U-^{15}\text{N}$ -amyloid- β -40 and -42; rPeptide, Watkinsville, Georgia). Plasma proteins were immunoprecipitated (extracted) using proprietary antibodies conjugated to magnetic beads, eluted from the beads, and digested with a site-specific protease (Lys-N; Thermo-Fisher Scientific, Waltham, MA) to form C-terminal peptides that were specific to amyloid- β -40 ($A\beta_{40}$) and -42 ($A\beta_{42}$) proteins. Peptides were separated using micro-flow liquid chromatography (Waters Corporation; Milford, Massachusetts, USA) and electrosprayed into the source of a high resolution orbitrap mass spectrometer (Thermo-Fisher Scientific; LC-MS/MS), which identified the peptides of interest based on known amino acid sequence and mass: charge (m/z) ratio, and quantified the ion signal intensity for the endogenous peptides by comparison to a calibration curve created with stable isotope labeled internal standard peptides.^{8,26,27} By comparing the signal intensities for the endogenous peptides to those obtained from the known amounts of stable isotope labeled proteins spiked into the sample, the concentrations for plasma $A\beta_{42}$ and $A\beta_{40}$ were quantified (in pg/mL). The plasma $A\beta_{42/40}$ concentration ratio was calculated by dividing the $A\beta_{42}$ concentration by the plasma $A\beta_{40}$ concentration. The APOE isoform-specific peptides (ϵ_2 , ϵ_3 , ϵ_4) were detected and identified using LC-MS/MS.⁸ The plasma $A\beta_{42/40}$ ratio, APOE proteotype, and the participant's age were incorporated into an algorithm that calculates the Amyloid Probability Score (APS); a value from 0–100 that reflects the likelihood that the participant will be amyloid positive or negative on an amyloid PET scan. These variables and

the APS value are branded the PrecivityAD test. They have been clinically validated against amyloid PET status in 60+ year old individuals with subjective cognitive decline or MCI. Precivity AD accuracy for determining brain amyloid positive versus negative was 86%; the positive predictive value was 92% and the negative predictive value was 77%, as tested in two cohorts including 378 subjects with amyloid PET confirmed AD pathology and 308 participants with negative amyloid PET results.⁸

3.3 | Statistical analyses

Statistical analyses were performed using SAS statistical software.³³ Multiple linear regression analyses were used to examine between group differences in demographic characteristics (age, gender, years of education), as well as cognitive test scores and plasma biomarkers, after adjusting for demographic covariates. Crude and adjusted linear regressions were also used to assess the association of plasma biomarkers with cognitive test scores while controlling for demographic characteristics. Z-scores were obtained for plasma biomarkers ($A\beta_{42/40}$, APS, p-Tau181) based on overall group means and standard deviations. Crude and adjusted logistic regressions were used to create ROC curve analyses and calculate AUCs to predict diagnostic accuracy of biomarkers for AD versus HC based on cognitive function testing (ANB).

Means and standard deviations needed to calculate power for between group comparisons of dementia and HC were obtained from the data. Using previous findings of APS⁸ to achieve a power of $> 80\%$ and $p < 0.05$, assuming a pooled standard deviation of 34, the study required a sample size of 66 overall, (33 per each group assuming equal group sizes) for detecting a true difference in means between the test and the reference group of -23.8 . Therefore, this study had adequate power with a sample of 85 subjects.

4 | RESULTS

4.1 | Demographic and clinical characteristics of sample

Baseline demographic, cognitive, and plasma biomarker characteristics are presented in Table 1. Groups did not significantly differ in age and education. Group differences were observed for all ANB cognitive measures, and group comparisons indicated that HC performed significantly better than the dementia group across all cognitive test measures. Regarding biomarkers, group differences were observed for $A\beta_{42/40}$ ratio and APS only, with significantly lower $A\beta_{42/40}$ and significantly higher APS and APOE ϵ_4 prevalence in dementia compared to HC. Groups did not differ in levels of $A\beta_{40}$, $A\beta_{42}$, or p-tau181. APOE allele frequencies are presented in Table 2.

Most of our cohort (i.e., 55.6% of the sample) had $A\beta_{42/40}$ less than 0.0991 with 59.1% of the dementia and 17.1% of the HC. One quarter of the sample (25% of the individuals) had APS more than 58 with

TABLE 1 Demographic, cognitive, and biomarker characteristics of study groups

Variable	Overall ^a Mean (SD) [Range] n = 85	HC ^a Mean (SD) [Range] n = 41	Dementia ^a Mean (SD) [Range] n = 44	p-Value ^b
<i>Demographics</i>				
Age (years)	72.9 (7.8) [50–88]	72.0 (7.8) [50–83]	74.0 (8.0) [53–88]	0.31
Gender (M:F)	47:38	23:18	24:20	0.89
Education (years)	8.5 (5.4) [0–17]	9.4 (5.2) [0–17]	7.8 (5.5) [0–17]	0.16
ANT	18.7 (6.3) [0–29]	21.7 (4.0) [10–29]	15.8 (7.1) [0–27]	<0.0001
ALMT	3.5 (3.4) [0–11]	6.7 (1.6) [4–11]	0.3 (0.6) [0–2]	<0.0001
AVMT	4.3 (4.7) [0–16]	7.6 (4.4) [1–16]	1.1 (1.7) [0–6]	<0.0001
APT	4.6 (4.4) [0–18]	6.8 (5.0) [1–18]	2.5 (2.2) [0–10]	<0.0001
ACGT	25.0 (8.9) [8–49]	28.3 (9.5) [13–49]	21.7 (6.9) [8–36]	<0.0001
<i>Biomarkers</i>				
Aβ40 pg/mL	480.1 (110.4)	470 (102.8)	487.0 (116.6)	0.876
Aβ42 pg/mL	48.3 (10.3)	48.7 (9.3)	48.0 (11.0)	0.260
Aβ42/40	0.10 (0.01) [0.08–0.12]	0.11 (0.01) [0.09–0.12]	0.09 (0.01) [0.08–0.11]	<0.0001
APS ^c	25.5 (30.7) [0–95]	13.3 (21.3) [0–84]	37.1 (34.0) [0–95]	<0.0001
p-tau 181 ng/mL	1.5 (1.3) [0.2–7.7]	1.4 (1.4) [0.2–7.7]	1.6 (1.3) [0.2–6.0]	0.25

Abbreviations: ACGT, African Card Game Test; ALMT, African List Memory Test; ANT, African Naming Test; APS, Amyloid Probability Score; APT African Proverb Test; AUC, area under the receiver operating characteristic curve; AVMT, African Visuospatial Memory Test; Aβ42/40, amyloid β42/40; F, females; HC, healthy controls; M, males; p-tau181, phosphorylated-tau181.

^aFor all groups, mean (SD) and ranges are listed for all demographic, cognitive, and biomarker characteristics unless otherwise specified.

^bGroup comparisons were analyzed between dementia and HC groups using linear regressions adjusting for age, gender, and education, *p*-value for significance <= 0.05.

^cAPS scores: 0–35 = low APS indicative of low likelihood of amyloid plaques; 36–57 = intermediate APS which does not distinguish between the presence or absence of amyloid plaques; 58–100 = high APS indicative of high likelihood of amyloid plaques.⁸

TABLE 2 Frequencies of APOE allele stratified by neurological status

Variable, n (%)	Healthy controls (n = 38)	Dementia cases (n = 43)	Overall (n = 81)
<i>APOE e4</i>			
Presence of ≥ e4 Allele ^a	21 (25.9%)	19 (23.5%)	40 (49.4%)
e2/e2 Genotype	0 (0%)	2 (4.7%)	2 (3%)
e2/e3 Genotype	6 (16.7%)	0 (0)	6 (7.4%)
e3/e3 Genotype	2 (5.2%)	14 (32.6%)	16 (19.8%)
e3/e4 Genotype	17 (44.7%)	13 (30.2%)	30 (38%)
e4/e4 Genotype	4 (10.5%)	4 (9.3%)	8 (10%)

Note: APOE (heterozygote and homozygote apolipoprotein E4). We described the absolute and relative frequencies of homozygote and heterozygote alleles. Abbreviation: APOE, apolipoprotein E.

^aThese values may not sum to the total due to missing data.

TABLE 3 Linear regression analyses between plasma biomarkers and demographic variables

Variables	Ab42/40 Beta (95% CI), <i>p</i> -value	p-tau 181 Beta (95% CI), <i>p</i> -value	APS Beta (95% CI), <i>p</i> -value	APOE4 Beta (95% CI), <i>p</i> -value
Age, per 1-year	-0.07 (-0.11, -0.04), <i>p</i> < 0.0001	0.02 (-0.01, 0.06), <i>p</i> = 0.15	0.08 (0.05, 11), <i>p</i> < 0.0001	0.01 (-0.01, 0.03), <i>p</i> = 0.13
Sex, F versus M	-0.02 (-0.58, 0.55), <i>p</i> = 0.95	-0.11 (-0.65, 0.43), <i>p</i> = 0.69	-0.05 (-0.47, 0.38), <i>p</i> = 0.82	-0.17 (-0.45, 0.10), <i>p</i> = 0.21
Education year	-0.02 (-0.08, 0.04), <i>p</i> = 0.59	-0.02 (-0.09, 0.03), <i>p</i> = 0.29	0.03 (-0.02, 0.07), <i>p</i> = 0.19	0.002 (-0.03, 0.031), <i>p</i> = 0.87

Note: *p* < 0.05 (bolded). We described crude association between biomarkers and individual demographics. Abbreviations: APOE4, apolipoprotein E4; APS, Amyloid Probability Score; CI, confidence interval.

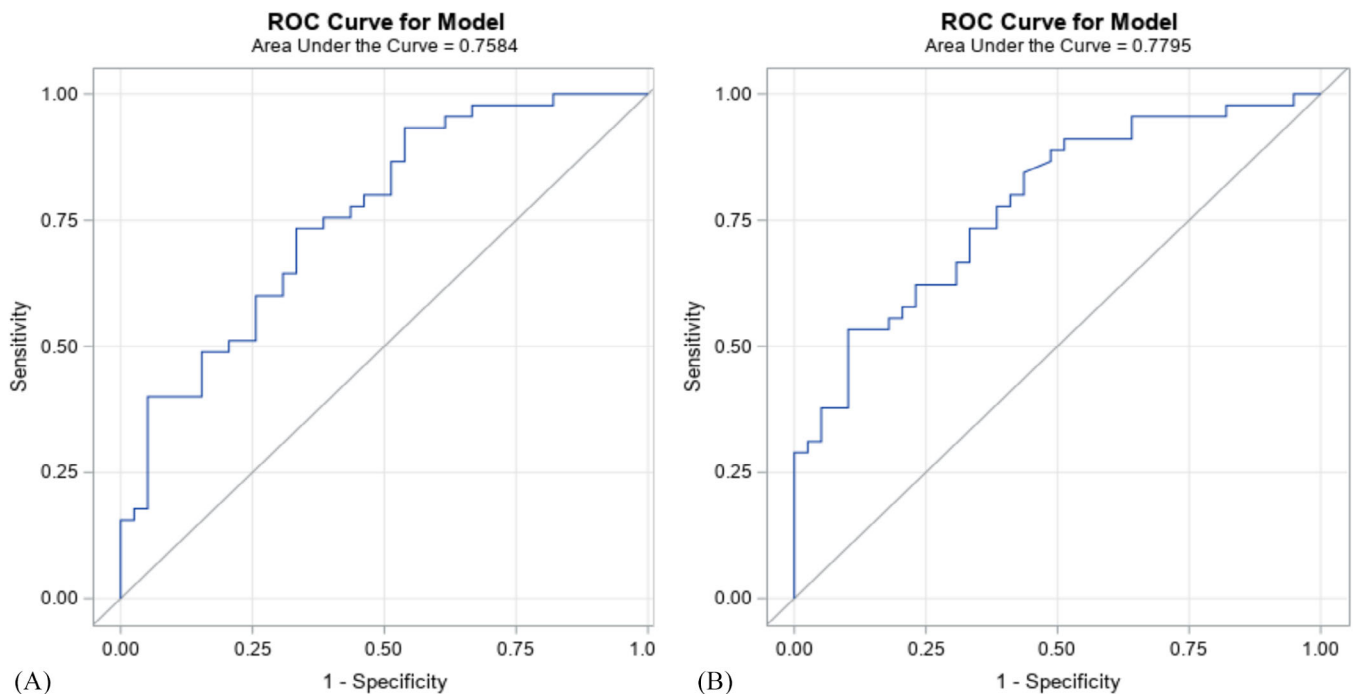


FIGURE 2 ROC curves for diagnostic accuracy of plasma biomarkers (A) A β 42/40 and (B) APS to distinguish pAD (possible AD dementia) from HC (healthy controls) determined using ANB. AD, Alzheimer's disease; APS, amyloid probability score; AUC, area under the curve; A β 42/40, amyloid β 42/40; HC, healthy controls; pAD, possible Alzheimer's disease; ROC, receiver operating characteristic curve

43.2% of dementia and 4.9% of HC. We have run a linear regression using biomarkers and demographic variables. We found that age was associated with A β 42/40 and APS (see Table 3).

There was no significant difference in results between crude and adjusted models. Adjusted ROC curves demonstrating diagnostic accuracy of plasma biomarkers for discriminating cognitive function in dementia versus HC are shown in Figure 2. Across biomarkers in the adjusted model, APS showed the highest AUC value (AUC = 0.78, 95% CI: 0.68–0.88) followed by A β 42/40 (AUC = 0.75, 95% CI: 0.66–0.86) and APOE ϵ 4 allele (AUC = 0.69 (CI 0.57–0.81) in discriminating dementia from HC (See Figure 2). Higher APS levels were associated with 4.5-fold increased odds of dementia (OR = 4.45 per standard deviation, *p* < 0.0006), APOE ϵ 4 was associated with 4-fold increased odds of dementia (OR = 3.99, *p* < 0.02), while lower A β 42/40 was

associated with a significantly 61% increase odds of having dementia (OR = 0.39 per standard deviation, *p* < 0.0008). However, in both crude and adjusted models, p-tau 181 was not significantly associated with the prevalence of dementia in this sample (OR = 1.06, *p* = 0.83) (see Table 4).

4.2 | Association of plasma biomarkers with ANB test scores

We calculated simple correlations to examine the relationship between plasma biomarkers. The relationship was negative, moderate in strength, and statistically significant between A β 42/40 and p-tau181 (*r* = -0.46, *p* = 0.0003), positive and moderate between p-tau181 and

TABLE 4 Odds ratio estimates of biomarkers

Biomarker	Crude model			Adjusted model		
	OR estimates	95% CI	p-Value	OR estimates	95% CI	p-Value
A β 42/40 ratio ^a	0.44	0.28, 0.70	0.0006	0.39	0.23, 0.68	0.0008
APS ^a	2.95	1.56, 5.55	0.0008	4.45	1.91, 10.39	0.0006
p-tau181 ^a	1.15	0.71, 1.86	0.5817	1.06	0.62, 1.80	0.83
APOE4 allele	3.76	1.53, 9.26	0.0039	3.09	1.19, 8.0	0.02

Note: We adjusted for age, gender, and years of education.

Abbreviations: APOE4, apolipoprotein E4; APS, Amyloid Probability Score; CI, confidence interval; OR, odds ratio.

^aPer 1-standard deviation increase.

TABLE 5 Linear regression analyses using plasma biomarkers to predict cognitive scores

Cognitive score	Estimate	A β 42/40 Ratio			Adjusted analysis		
		Crude analysis	95% CI	p-Value	Estimate	95% CI	p-Value
ANT	2.58	1.41, 3.76	<0.0001	2.27	0.10, 3.54	0.0007	
ALMT	1.29	0.68, 1.89	<0.0001	1.29	0.62, 1.97	0.0003	
AVMT	1.84	1.01, 2.66	<0.0001	1.79	0.95, 2.63	0.0001	
APT	1.03	0.19, 1.187	<0.0170	0.75	-0.03, 1.54	0.06	
ACGT	1.10	-0.65, 2.85	0.2131	0.76	-1.09, 2.62	0.41	
APS							
ANT	-3.27	-4.73, -1.81	<0.0001	-3.24	-4.94, -1.56	0.0003	
ALMT	-1.63	-2.38, -0.88	<0.0001	-1.86	-2.75, -0.98	<0.0001	
AVMT	-2.13	-3.18, -1.08	0.0001	-2.41	-3.54, -1.28	<0.0001	
APT	-1.18	-2.23, -0.13	0.0284	-0.10	-2.06, 0.60	0.06	
ACGT	-1.72	-3.89, 0.44	0.1175	-1.69	-4.17, 0.78	0.17	
P-tau 181							
ANT	-2.20	-3.74, -0.64	0.006	-1.56	-3.12, 0.01	0.05	
ALMT	-0.07	-0.88, 0.73	0.855	-0.08	-0.73, 0.90	0.84	
AVMT	-1.08	-2.19, 0.03	0.0578	-0.65	-1.68, 0.38	0.21	
APT	-0.62	-1.54, 0.30	0.1820	0.01	-0.88, 0.90	0.98	
ACGT	-1.24	-3.43, 0.94	0.2608	-0.64	-2.74, 1.46	0.54	
APOE4							
ANT	-5.13	-7.85, -2.41	0.0003	-5.34	-7.90, -2.79	<0.0001	
ALMT	-2.27	-3.69, -0.85	0.0021	-2.02	-3.36, -0.67	0.004	
AVMT	-2.48	-4.48, -0.48	0.0158	-2.33	-4.03, -0.63	0.008	
APT	-1.64	-3.57, 0.29	0.0953	-1.67	-3.17, -0.17	0.03	
ACGT	-2.98	-6.90, 0.95	0.1353	-2.08	-5.68, 1.53	0.25	

Note: $p < 0.05$ (bolded). We adjusted for age, gender, and years of education.

Abbreviations: ACGT, African Card Game Test; ALMT, African List Memory Test; ANT, African Naming Test; APS, Amyloid Probability Score; APT African Proverb Test; AVMT, African Visuospatial Memory Test; p-tau181, phosphorylated-tau181.

APS (0.41, $p = 0.001$). The association was negative, strong, and statistically significant between A β 42/40 and APS ($r = -0.85$, $p < 0.0001$). Crude and adjusted linear regression models were used to evaluate associations between plasma biomarkers (in standard deviation units) and ANB cognitive performance while adjusting for age, education, and gender. There were no significant difference in scores between crude

and adjusted models (see Table 5). The results showed that A β 42/40 and APS were significantly associated with ANT, ALMT, and AVMT scores, while the presence of APOE ϵ 4 allele was significantly associated with ANT, ALMT, AVMT, and APT scores. There were no significant associations between p-tau181 and any ANB scores in both crude and adjusted models (see Table 5).

5 | DISCUSSION

In the current study, we examined the associations between plasma biomarkers and cognitive test scores, as well as the predictive ability of plasma biomarkers in differentiating dementia from HC in a sample of elderly Congolese adults from Kinshasa, Democratic Republic of the Congo. This study used CSID and AQ as the basis for determining if there is cognitive and functional impairment in these individuals. Since there are no established cutoffs for AD biomarker levels and related dementias in the SSA for the confirmation of a clinical diagnosis, we used screening measures to diagnose major neurocognitive disorders or dementia based on cognitive and functional deficits. Although amyloid and p-tau measures show some racial differences between African Americans and other ethnic groups,¹⁷ we predicted that a plasma A β 42/40 ratio cutoff value (< 0.090 for AD) derived previously on predominantly Caucasian cohorts⁸ would distinguish Africans with dementia from cognitively unimpaired Africans. The current findings support this hypothesis.

To our knowledge, this is the first study exploring these associations in SSA populations. Consistent with studies in non-SSA populations, HC performed significantly better across all ANB tasks.³⁴ Similarly, significantly lower A β 42/40, significantly higher APS levels,⁹ and greater frequency of APOE ϵ 4 allele were observed in persons with dementia compared to HC. These results also confirm previous research within SSA populations, which found that APOE ϵ 4 allele is more frequent among some Africans specifically in Ugandans (but not in Yoruba, Nigeria) than Whites or Asians.²⁸ No group differences were seen for plasma A β 40, A β 42, and p-tau181 biomarker concentrations. These results are not surprising given that p-tau measures show racial differences; the CSF p-tau181 levels are lower in African Americans with AD than in whites with AD.¹⁷ Hence, this might be similar in plasma in the Congo and, if so, there would not be as much difference between AD and control cases in the Congo. While many longitudinal and cross-sectional studies on populations from have established that p-tau181 levels discriminate between AD and non-AD patients,⁷ the lack of significant differences in the current study may be unexpected. It is expected that p-tau concentrations would be more strongly associated with neuropsychological test performance and clinical diagnosis than A β 42/AB40 levels. The assumption and accumulating evidence suggest that plasma A β 42/40 declines very early in the progression of amyloid pathology while individuals are asymptomatic, and this subsequently “triggers” or “ignites” tau tangle formation and elevations in plasma p-tau species that more closely coincide with symptoms, cognitive decline, and dementia. There are two tentative reasons why p-tau was not associated with cognitive tests. First, the difference in CV% between C2N diagnostics and Simoa assays needs to be taken into consideration. C2N analytical validation metrics for the mass spectrometry based on plasma a β 42/40 analytical platform (CV%) within-day precision varied from 1.5% to 3.0% (A β 40) and 2.5% to 8.4% (A β 42). Total (within-lab) variability was 2.7%–7.7% (A β 40) and 3.1%–9.5% (A β 42). APOE proteotypes were 100% concordant with genotype, while LoD (fM) was much lower than APOE concentrations observed in plasma (mM).²⁶ Analytical validation met-

rics of p-tau 181 of repeatability within-laboratory precision above the LoQ was found \leq 20%.²⁹ Recent publications support the superior diagnostic performance of the mass spectrometry-based analytical platforms for detecting brain amyloid pathology (by amyloid PET) for both plasma A β 42/40 and p-tau species.⁶ Therefore, this difference can account for our present findings. Second, we used plasma phospho-tau biomarker concentration, which we did not normalize it to the plasma total or non-phospho-tau concentration, and expressed it as a ratio (e.g., plasma A β 42/40). Recent evidence suggests that the plasma phospho-tau/non-phospho-tau concentration ratio may be a more reliable indicator of brain amyloid (and potentially tau) pathology than the simple phospho-tau concentration alone.⁶

This study also investigated the association between plasma AD biomarkers with ANB cognitive test scores. In concordance with results of previous studies, lower A β 42/40 and higher APS biomarker levels significantly predicted lower naming (ANT) and memory (ALMT, AVMT) scores. The presence of APOE ϵ 4 allele predicted significantly lower naming, memory (ALMT, AVMT) and mental abstraction (APT) subtests. Furthermore, these findings are consistent with previous studies highlighting APOE ϵ 4 as a risk factor for cognitive decline in African Americans¹² and its associations with cognitive deficits in AD patients.¹⁷ Most notably, these results support the value of both plasma biomarkers and cognitive testing for characterization of AD pathology in SSA populations.

A few important findings to note are the lack of significant associations between executive functioning subtests (APT and ACGT) with A β 42/40 and APS levels (and no associations with any biomarkers for the APT subtest) and lack of associations between p-tau181 and ANB subtests. Memory and executive functioning domains have demonstrated associations with these biomarkers in populations from high-income countries.^{31,32} Thus, the impact of our study is that it highlights ethnoracial underpinnings, such as decoupling of p-tau181 which was reported in African Americans and lower levels compared to other ethnic groups.^{14,33}

Regarding discrimination ability, APS demonstrated the highest performance in discriminating dementia from cognitively healthy individuals, closely followed by A β 42/40. This result is expected, since APS is based on A β 42/40, as well as age and APOE genotype. In the same vein, higher APS levels and APOE ϵ 4 presence showed a 4.5-fold and 3.99-fold increased odds of having dementia in the present sample, respectively. In contrast, higher A β 42/40 levels showed a significantly higher odds of currently having dementia (OR = 0.39 per 1 standard deviation unit increase). Thus, consistent with prior research,⁸ plasma A β 42/40, APS, and APOE ϵ 4 proteotype, combined in PrecivityAD, could be helpful and useful for differentiating AD pathology from healthy aging in SSA populations, and more specifically in the Congo.

5.1 | Limitations and future directions

Our findings should be interpreted in light of several limitations, such as the cross-sectional nature, low power and lack of amyloid PET

imaging confirming AD pathology. The degree to which the current associations between plasma biomarkers of AD pathology and cognitive scores reflect disease trajectory and progression should be further explored with longitudinal analyses. Second, the moderate sample size in both groups may have obscured significant associations among variables examined; thus, future studies should replicate these findings with larger sample sizes. Third, the prevalence of APOE ϵ 4 was high in this DRC sample (50%), with 24% among those with suspected dementia and 26% among those HCs. This prevalence is still higher compared to prevalence rates in the world alongside many other countries in Africa. Previous studies have shown that in the Yoruba region, the presence of an APOE ϵ 4 allele was significant for both incident AD ($p = 0.0489$) and cognitive decline ($p = 0.0425$) compared to African American cohorts.¹¹ On the other hand, Corbo and his colleagues comparing the distribution of APOE ϵ 4 allele in the world reported highest frequency of APOE ϵ 4 in the DRC/Zaire region, among populations such as Pygmies (0.407) compared to Khoi San (0.370), aborigines of Malaysia (0.240) and Australia (0.260), Papuans (0.368), some Native Americans (0.280), and Lapps (0.310).³⁴ Additionally, other studies have confirmed high frequency of APOE ϵ 4 in the DRC population, which is statistically different from the overall mean in Africa (Fon, 29.4%; Zairians, 33.3%; Tutsi, 38.5%). Future studies should investigate the frequency of APOE ϵ 4 in the Congo using large samples and between the four primary linguistic groups (Bantu, Nilotic, Sudanic, and Pygmies). Finally, this study analyzed only selected plasma AD biomarkers (A β 42/40, p-tau181, and APOE). Future studies should aim to replicate our findings along the AD pathology continuum, as well as utilize other plasma and CSF biomarkers (e.g., p-tau217, 231, glial fibrillar acidic protein [GFAP] and neurofilament light [NfL]), as they may provide greater insight into the progression of cerebral amyloid and tau pathology, and cognitive decline in SSA populations, in addition to potentially exploring novel highly promising serum-based synaptic biomarkers (e.g., β -synuclein and other aggregates in dopaminergic neurons), neuroinflammation, and GFAP as a biomarker for microglia and astrocyte reactivity. Therefore, the exploration of these plasma biomarkers in African populations may identify potential inter-individual differences and modifiable factors that account for the similarity or the differences in AD pathogenesis and may implicate safe and effective interventions for AD pathology and cognition among Africans and other ethnic groups.

In conclusion, this is the first study in which the association between plasma AD biomarkers and ANB tests are explored within an elderly adult population from Democratic Republic of Congo in the SSA. We demonstrated the value of plasma AD biomarkers and ANB cognitive scores in classifying dementia in older adults in SSA populations.

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CONFLICT OF INTEREST STATEMENT

Charlotte Teunissen serves on editorial boards of *Medicines* (Springer), *Alzheimer Research and Therapy*, *Neurology: Neuroimmunology & Neuroinflammation*. She had speaker contracts for Roche, Grifols, Novo Nordisk. KEY is employed full-time by and has equity interests in C₂N Diagnostics. Author disclosures are available in the [supporting information](#).

CONSENT STATEMENT

All human subjects in this study provided informed consent.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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