Higher suPAR Relates to Domain-Specific Cognitive Function In Virally Suppressed Women With HIV

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BACKGROUND

Chronic inflammation is a key driver of cognitive decline in people with HIV (PWH), persisting despite effective antiretroviral therapy (ART). Soluble Urokinase Plasminogen Activator **(suPAR)** is a biomarker of chronic inflammation previously associated with cognitive impairment in a small study of men with HIV. Our study aimed to examine whether elevated suPAR levels are associated with domain-specific cognitive function in virologically suppressed women with HIV (VS-WWH), potentially providing a pre-clinical indicator for cognitive complications.

METHODS

suPAR levels were assessed in duplicate via ELISA (ViroGates; Denmark) from stored (-80ºC) plasma in a sample of **188 VS-WWH** (all participants had VL <200 copies/mL) participating in the Chicago Cook County site of the **MACS-WIHS Combined Cohort Study(MWCCS)**. Blood samples were collected between November 2004 and September 2017 at either the same visit as the cognitive assessment for 179 (95%) participants or from the visit immediately prior (within 6 months of assessment) from the remainder. Participants completed biennial cognitive testing. Cognitive domains included attention, executive function, psychomotor speed, verbal memory, verbal learning, verbal fluency, and motor function. Domain-specific cognitive impairment was defined as demographically adjusted **T-scores ≤40 at ≥1 visit**. Multivariable linear regression models assessed associations between log-transformed suPAR levels and cognitive domain T-scores adjusting for potential confounders such as age and race. Standardized beta-coefficients (β) were calculated to determine the strength and direction of associations, with negative values indicating poorer cognitive performance with increasing suPAR levels.

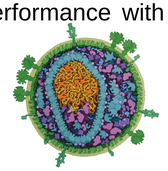


Table 2. Association Between Log-Transformed suPAR Levels and Cognitive Domain Performance. Standardized beta coefficients with 95% confidence intervals for the association between log suPAR and domain-specific T-scores.

Domain	β[1]	95% CI[2]	p-value
Psychomotor speed	-0.18	-0.31, -0.04	**0.01**
Verbal and learning memory	-0.15	-0.29, -0.02	**0.03**
Verbal fluency	-0.14	-0.27, -0.01	**0.04**
Motor function	-0.13	-0.26, 0.00	**0.05**
Memory	-0.11	-0.25, 0.03	0.11
Executive function	-0.11	-0.24, 0.03	0.13
Attention/working memory	-0.03	-0.17, 0.10	0.65

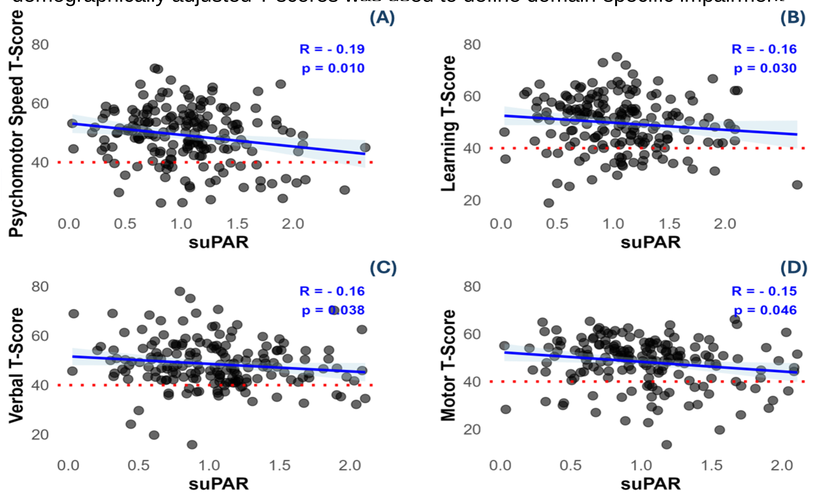
[1]Standardized β
[2]CI = Confidence Interval

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Figure 1. Association Between Log-Transformed suPAR Levels and Domain-Specific Cognitive T-Scores.. Scatter plots with fitted regression line and 95% confidence interval (light blue), depicting a negative linear correlation between log suPAR and domain-specific T-scores. A cutoff of ≤40 (red line) in demographically adjusted T-scores was used to define domain-specific impairment



Higher log *soluble urokinase plasminogen activator receptor* (**suPAR)** levels **negatively correlate** with *domain-specific* cognitive performance in *virally-suppressed* women with HIV

Figure 2. Distribution of Log-Transformed suPAR Levels in Participants With and Without Domain-Specific Cognitive Impairment. Violin plots comparing log suPAR levels between participants with (orange) and without (green) impairment in psychomotor (A) and motor (B) domains using a demographically-adjusted T-score cutoff of ≤40.

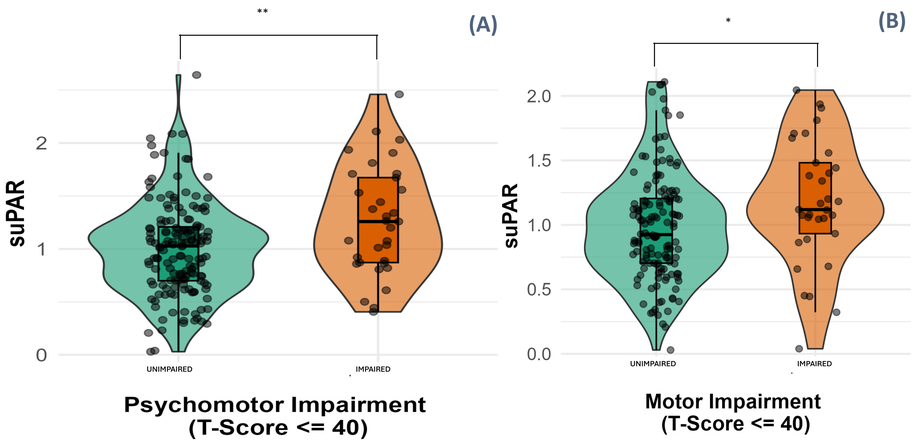


Table 1. Baseline Characteristics of Study Participants. Demographic and clinical characteristics of virally suppressed women included in the study

Characteristic	N=188[1]
Age	52 (46, 57)
Race	
Black	135 (72%)
Hispanic	16 (8.5%)
Other	2 (1.1%)
White	35 (19%)
Education	
Above high school	78 (41%)
Below high school	61 (32%)
High school	49 (26%)
CD4+	693 (421, 922)
CD4+ Nadir	291 (185, 422)
CD4+ Nadir unknown	6
Viremic status >200 copies/mL	
Aviremic	188 (100%)

[1]Median (Q1, Q3); n (%)

RESULTS

VS-WWH had a mean age of 52, a mean CD4⁺ of 693, 72% were Black, and 67% had completed high school education**(Table 1)**. The median suPAR level was 2.87 ng/mL (variation coefficient 56.8%). Higher log suPAR levels were associated with poorer psychomotor speed (β=-0.18, 95%CI -0.31, -0.04, P=0.01), verbal learning (β=-0.15, 95%CI -0.29, -0.02, P=0.029), verbal fluency (β=-0.14, 95%CI -0.27, -0.01, P=0.038), and motor function (β=-0.13, 95%CI -0.26, -0.00, P=0.045)**(Table 2).** We found a negative linear relationship between log suPAR levels and psychomotor speed (R=-0.19, P=0.00999), verbal learning (R=-0.16, P=0.03), verbal fluency(R=-0.16, P=0.038) and motor function(R=-0.15, P=0.0468)**(Figure 1).** We observed statistically significant differences in log suPAR levels between participants with impairment in the psychomotor speed and motor domains as compared to those without impairment in those specific domains**(Figure 2)**. There were no associations with other cognitive domains.

CONCLUSIONS

These findings suggest that suPAR, a known marker of systemic chronic inflammation, offers potential as an indirect biomarker for psychomotor speed, verbal learning, verbal fluency, in this population. Although the effect sizes were small, prospective studies are warranted as suPAR may be useful as part of a comprehensive pre-clinical predictive model of cognitive changes in this population. Elucidating the mechanisms of suPAR production in this context will contribute to our overall understanding of its applicability.