BRACE-ing for the future: Establishing iPad-based norms for cognitive function in the MACS/WIHS Combined Cohort Study

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Abstract

Background: Digital cognitive assessments are increasingly used in large-scale studies to assess brain health, offering scalable, standardized, and self-directed testing solutions. Cognitive function remains a concern for people with HIV (PWH) despite antiretroviral therapy. The BrainBaseline Assessment of Cognition and Everyday Functioning (BRACE) is a validated tablet-based screener for cognition in PWH. Preliminary pilot norms were established in a small sample (n=144), but full regression-based normative data have not been developed. Consequently, HIV serostatus differences based on standardized BRACE scores and cognitive correlates have not been systematically examined.

Objective: To develop regression-based normative data for BRACE performance in people without HIV (PWoH) who were demographically and behaviorally comparable to PWH within biological sex; to examine differences in cognitive performance by HIV status and biological sex; and to evaluate sociodemographic, behavioral, and clinical correlates of BRACE performance.

Methods: A total of 2,937 participants (1063 PWoH [499 women] and 1,874 PWH [1,053 women]) in the Multicenter AIDS Cohort Study/Women's Interagency HIV Study Combined Cohort Study completed BRACE once between November 2020 and March 2025. BRACE includes Trail Making Test (A&B), Stroop-Color, and Visual-Spatial Learning. Regression-based norms were derived from PWoH using multiple demographic models (e.g., age-only, age+education, age+education+sex). The age+education model was selected for primary analyses to maximize generalizability and avoid race-based corrections. HIV serostatus and sex differences were examined using analysis of variance and chi-square tests, with effect sizes calculated using Cohen's d.

Results: Cognitive performance was largely comparable between PWH and PWoH across all BRACE outcome measures.

Statistically significant differences were small in magnitude (effect sizes< 0.11) and primarily observed among men on Stroop-Color. Across groups, older age and fewer years of education were associated with poorer raw BRACE performance, while these associations attenuated after demographic adjustment using T-scores. Most clinical and behavioral factors (e.g., hypertension, smoking, and non-cannabis substance use) were related to poorer raw but not standardized performance. However, diabetes and cannabis use remained independently associated with T-scores across multiple measures—diabetes with poorer and cannabis use with better performance. HIV-specific clinical factors such as nadir CD4 count and ART duration were linked primarily to raw scores.

Conclusions: This study establishes the first regression-based normative data for BRACE derived from a large, demographically diverse PWoH cohort and demonstrates its applicability for evaluating cognitive function in PWH. Findings indicate minimal cognitive differences between PWH and PWoH and highlight the influence of common sociodemographic and metabolic factors. These results support BRACE as a scalable, reliable, and self-administered digital tool for assessing cognitive health in diverse populations and underscore its potential for longitudinal monitoring and precision phenotyping in both research and clinical contexts. Clinical Trial: NA

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BRACE-ing for the future: Establishing iPad-based norms for cognitive function in the MACS/ WIHS Combined Cohort Study

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ABSTRACT (450/450-word limit)

BACKGROUND: Digital cognitive assessments are increasingly used in large-scale studies to assess brain health, offering scalable, standardized, and self-directed testing solutions. Cognitive function remains a concern for people with HIV (PWH) despite antiretroviral therapy. The BrainBaseline Assessment of Cognition and Everyday Functioning (BRACE) is a validated tablet-based screener for cognition in PWH. Preliminary pilot norms were established in a small sample

(n=144), but full regression-based normative data have not been developed. Consequently, HIV serostatus differences based on standardized BRACE scores and cognitive correlates have not been systematically examined.

OBJECTIVES: To develop regression-based normative data for BRACE performance in people without HIV (PWoH) who were demographically and behaviorally comparable to PWH within biological sex; to examine differences in cognitive performance by HIV status and biological sex; and to evaluate sociodemographic, behavioral, and clinical correlates of BRACE performance.

METHODS: A total of 2,937 participants (1063 PWoH [499 women] and 1,874 PWH [1,053 women]) in the Multicenter AIDS Cohort Study/Women's Interagency HIV Study Combined Cohort Study completed BRACE once between November 2020 and March 2025. BRACE includes Trail Making Test (A&B), Stroop-Color, and Visual-Spatial Learning. Regression-based norms were derived from PWoH using multiple demographic models (e.g., age-only, age+education, age+education+sex). The age+education model was selected for primary analyses because it provided the best balance of interpretability, parsimony, and generalizability while avoiding race-based corrections. HIV serostatus and sex differences were examined using analysis of variance and chi-square tests, with effect sizes calculated using Cohen's *d*.

RESULTS: Cognitive performance was largely comparable between PWH and PWoH across all BRACE outcome measures. Statistically significant differences were very small in magnitude (all effect sizes < .11) and primarily observed among men on Stroop-Color. Across groups, older age and fewer years of education were associated with poorer raw BRACE performance, while these associations attenuated after demographic adjustment using T-scores. Most clinical and behavioral factors (e.g., hypertension, smoking, and non-cannabis substance use) were related to poorer raw but not standardized performance. However, diabetes and cannabis use remained independently associated with T-scores across multiple measures—diabetes with poorer and cannabis use with higher scores, an association that should be interpreted cautiously. HIV-specific clinical factors such

as nadir CD4 count and ART duration were linked primarily to raw scores.

CONCLUSION: This study establishes the first regression-based normative data for BRACE derived from a large, demographically diverse PWoH cohort and demonstrates its applicability for evaluating cognitive function in PWH. Findings indicate minimal cognitive differences between PWH and PWoH and highlight the influence of common sociodemographic and metabolic factors. These results support BRACE as a scalable, reliable, and self-administered digital tool for assessing cognitive health in diverse populations and underscore its potential for longitudinal monitoring and precision phenotyping in both research and clinical contexts.

KEY WORDS: digital health, cognition, HIV, normative data, regression models, tablet-based testing

INTRODUCTION

Cognitive health is a central aspect of aging and chronic disease management, yet comprehensive neuropsychological (NP) assessments remain resource-intensive. Traditional paper-and-pencil NP batteries are the gold standard for assessing and staging cognitive impairment because of their reliability, validity, and established normative data. However, the staff training, cross-site standardization, and administration required for traditional NP testing limit scalability. This challenge is particularly relevant in HIV, where cognitive health remains a concern for people with HIV (PWH) despite effective antiretroviral therapy (ART).

Tablet-based cognitive assessments offer scalable, standardized, self-directed testing. These tools provide automated scoring and data aggregation, reducing staff burden and enabling broader implementation. The BrainBaseline Assessment of Cognition and Everyday Functioning (BRACE, Clinical Ink, Inc, Winston-Salem, NC) is a brief, iPad-based cognitive evaluation. In a study of 404

PWH receiving outpatient clinical care in Baltimore, Maryland, BRACE demonstrated excellent test-retest reliability, minimal practice effects over 30-day and 10-month intervals, strong correlations with a gold standard NP battery, and good classification accuracy for cognitive impairment [1]. To extend its use in HIV research and clinical settings, normative data reflecting the demographic and clinical diversity of PWH and people without HIV (PWoH) are needed. Norms for PWoH, particularly among women, may differ from those in the general population because comparison groups in HIV research often have a high prevalence of risk factors associated with cognitive dysfunction including lower educational attainment, mental health burden, substance use, and socioeconomic disadvantage [2].

In 2019, the Multicenter AIDS Cohort Study (MACS) and Women's Interagency HIV Study (WIHS) merged to form the MACS/WIHS Combined Cohort Study (MWCCS). Before the merger, each cohort administered comprehensive NP batteries every 24 months. During the COVID-19 pandemic, the iPad-based BRACE tool was introduced to reduce face-to-face contact and shorten testing time. Here we present the initial cross-sectional BRACE data from the MWCCS. We developed regression-based normative data in PWoH, examined HIV serostatus differences in cognitive performance using both raw and standardized (T-scores) metrics, evaluated whether HIV serostatus differences varied by biological sex given prior findings in this cohort [2, 3], and examined additional covariates that may inform future BRACE-based analyses stratified by HIV serostatus and biological sex.

METHODS

Participants and Data Source

In 2019, the MWCCS combined two long-running prospective, multicenter U.S. sex-specific cohorts of PWH and PWoH, the MACS (men) and WIHS (women). The combined cohort also enrolled

additional PWH and demographically similar PWoH across 14 clinical research sites located in the Mid-Atlantic/Northeast (New York-Brooklyn and Bronx; Baltimore, MD; Washington, DC), South (Birmingham, AL; Jackson, MS, Atlanta, GA; Chapel Hill, NC; Miami, FL), Midwest (Pittsburgh, PA; Columbus, OH; Chicago, IL), and West Coast (California-San Francisco and Los Angeles). Participant characteristics have been previously described in detail [4].

Data collected at annual in-person or semiannual interim telephone study visits included physical examinations, medical and psychosocial interviews, and blood draws. Measures included socio-demographics (self-reported date of birth, race/ethnicity, education), behavioral factors (substance use), clinical measures (Center for Epidemiological Depression Scale [CES-D]), and reproductive history (hysterectomy, menopause status according to the Staging of Reproductive Aging in women [STRAW+10][5]).

Participants in this cross-sectional analysis completed BRACE during their first in-person MWCCS visit between November 30, 2020-March 28, 2025. As BRACE was only available in English, analyses were restricted to English-speaking participants. The study received institutional review board approval from each MWCCS clinical research site and all participants provided written informed consent.

Cognitive Assessments

Cognitive function was assessed using BRACE (Clinical Ink, Inc., Winston-Salem, NC), a self-administered iPad-based tool with automated audio and video instructions. BRACE includes four widely used cognitive tests assessing processing speed, executive function, and visuospatial learning —Trail Making Test (TMT)-A, TMT-B, Stroop-Color, and a Visual-Spatial Learning Test (VSLT) (**Table 1**).

Table 1. Cognitive tests in BRACE.

Test	Measures	Outcome(s)
TMT-A	psychomotor speed	time to completion
TMT-B	psychomotor speed;	time to completion
	executive function, particularly set-shifting and mental flexibility	TMT-B minus A
STROOP-Color	psychomotor speed	time to completion
		number of accurate trials
VSLT	visuospatial learning and attention	total correctly placed items minus incorrectly placed items

TMT=Trail Making Test

VSLT= Visual-Spatial Learning Test

Raw BRACE data were transmitted from Clinical Ink and processed locally using the custom graphical user interface (GUI) developed by Dastgheyb [6]. This GUI parses trial-level output files, applies quality control (QC) algorithms, and generates the primary performance metrics (time to completion and/or accuracy) for each test. QC procedures were used to ensure that participants interacted with the tasks as intended, including completing > 15 Stroop-color trials accurately and making < 5 errors on TMT-A and < 10 errors on TMT-B. For timed outcomes, lower raw scores indicate faster (better) performance. Normative standards (T-scores) were derived from the MWCCS PWoH sample, with higher T-scores indicating better performance.

Statistical Analysis

Descriptive statistics summarized sociodemographic, behavioral, and clinical characteristics by HIV serostatus and biological sex. Group differences (by HIV serostatus; sex stratified by HIV serostatus; or HIV serostatus stratified by sex) were examined using Wilcoxon rank-sum tests for continuous variables and χ^2 tests for categorical variables. Regression-based normative equations were developed in the PWoH sample and applied to both PWoH and PWH to generate standardized T-scores for each BRACE outcome. Analyses were then conducted using both raw BRACE performance metrics and demographically adjusted T-scores derived from the MWCCS PWoH reference group. Raw and T-scores were examined continuously. Binary indicators of BRACE impairment were defined as T-scores below 40 (≥ 1 SD below the normative mean) and below 35 (≥ 1.5 SD below). Group differences in BRACE performance (e.g., PWH vs. PWoH) were tested using ANOVA for continuous outcomes and χ^2 for categorical outcomes. Effect sizes for between-group differences were calculated using either Cohen's *d* or eta^2. Effect sizes of approximately .10 were interpreted as very small. Associations between sociodemographic, behavioral, and clinical variables and BRACE performance were examined separately in PWH and PWoH and further stratified by biological sex. Continuous variables were evaluated using Pearson correlations and binary categorical variables using point-biserial correlations. Results for variables with more than two categories were summarized descriptively across groups. Analyses were performed using all available data for each test. All statistical tests were two-tailed, with significance set at $\alpha = .05$, and analyses were conducted in R Version 4.3.3 and the SciDataReportR package [7], which now includes the custom function used for the regression-based normative modeling.

RESULTS

Sample Characteristics

Overall, 1874 PWH (1053 women) and 1063 PWoH (499 women) from the MWCCS completed the BRACE battery at a single time point between November 30, 2020-March 28, 2025. Compared to PWoH, PWH were slightly younger, completed fewer formal years of education, were more likely to be Black/African American (AA) and women, and were less likely to use substances (**Table 2**). The distribution of these characteristics differed by HIV serostatus when stratified by biological sex (**Table 3**). Among PWH, the majority (1488 out of 1602 [93%]) had a viral load $\leq$ 200 copies/ml and reported greater than or equal to 95% adherence to ART (1414 out of 1607 [88%]). Women with HIV were more likely to be postmenopausal and were also more likely to have had a hysterectomy compared to women without HIV.

Table 2. Sample characteristics by HIV status.

Characteristic	**PWoH** N = 1,063[1]	**PWH** N = 1,874[1]	***P*-value**[2]
Women	499 (47%)	1,053 (56%)	**<.001**
Clinical site			**<.001**
Bronx	94 (8.8%)	131 (7.0%)	
Brooklyn	78 (7.3%)	201 (11%)	
Washington DC	53 (5.0%)	128 (6.8%)	
San Francisco	92 (8.7%)	137 (7.3%)	
Chicago Cook County	48 (4.5%)	131 (7.0%)	
Chapel Hill	54 (5.1%)	191 (10%)	
Atlanta	91 (8.6%)	206 (11%)	
Miami	67 (6.3%)	133 (7.1%)	
Birmingham	36 (3.4%)	90 (4.8%)	
Jackson	43 (4.0%)	88 (4.7%)	
Baltimore	117 (11%)	136 (7.3%)	
Chicago Northwestern	85 (8.0%)	128 (6.8%)	
Pittsburgh/Ohio	93 (8.7%)	58 (3.1%)	
Los Angeles	112 (11%)	116 (6.2%)	
Age (years)	56.95 (12.34)	54.22 (10.61)	**<.001**
Initial study cohort			**<.001**
MACS	398 (40%)	410 (23%)	
WIHS	359 (36%)	826 (47%)	
New MWCCS Recruits	246 (25%)	509 (29%)	
Black/AA race	466 (44%)	1,042 (56%)	**<.001**
Hispanic/Latinx ethnicity	117 (11%)	230 (12%)	.336
Years of education			**<.001**
Less than high school	152 (14%)	318 (17%)	
Completed high school	201 (19%)	428 (23%)	
Some College	307 (29%)	635 (34%)	

Graduated College	142 (13%)	180 (9.6%)	
>College	258 (24%)	306 (16%)	
CES-D	10.79 (10.44)	10.76 (10.61)	.956
Body mass index, kg/m^2	30.62 (7.85)	31.16 (8.34)	.101
Diabetes	173 (18%)	342 (21%)	.142
Hypertension	637 (68%)	1,139 (68%)	.946
Current smoker	240 (26%)	441 (27%)	.532
Ever smoker	632 (67%)	1,073 (65%)	.281
Current heavy alcohol use	103 (12%)	155 (9.6%)	.113
Recent heroin use	314 (35%)	542 (33%)	.279
Recent crack use	30 (3.4%)	22 (1.4%)	**.001**
Recent cocaine use	90 (10%)	130 (8.1%)	.076
Recent cannabis use	90 (10%)	130 (8.1%)	.076
Ever cannabis use	619 (70%)	1,032 (63%)	**<.001**
Ever crack, cocaine, &/or heroin use	448 (45%)	686 (40%)	**.008**
Plasma HIV RNA viral load (cp/ml)			
<=20		931 (58%)	
21-200		557 (35%)	
201-500		24 (1.5%)	
501-1000		11 (0.7%)	
>1000		79 (4.9%)	
CD4+ count, c/mm^3		761 (379.49)	
CD8+ count, c/mm^3		828 (433)	
Nadir CD4+ count, c/mm^3		285 (227)	
ART adherence ≥95%		1,414 (88%)	
Years on ART		17.11 (8.96)	
HIV duration (years)		29.35 (5.77)	

[1] n (%); Mean (SD)

[2] Categorical: Pearson's Chi-squared test/Fisher's exact test; Continuous: Wilcoxon rank sum test

AA=African-American; ART=antiretroviral therapy; CES-D=Center for Epidemiological Studies-Depression; PWH=people with HIV; PWoH=people without HIV

Heavy alcohol use is defined as ≥7 standard drinks for women and ≥17 for men per week.

Table 3. Sample characteristics by HIV status and biological sex.

	Women			Men				
	PWoH	**PWH**		**PWoH**	**PWH**			
Characteristic	N = 499[1]	N = 1,053[1]	***P*-value**[2]	N = 464[1]	N = 821[1]	***P*-value**[2]		
Clinical site						**.011**		**<.001**
Bronx			66 (13%)	102 (9.7%)		28 (6.3%)	29 (4.2%)	
Brooklyn			78 (16%)	201 (19%)		0 (0%)	0 (0%)	
Washington DC			53 (11%)	127 (12%)		0 (0%)	1 (0.1%)	
San Francisco			61 (12%)	113 (11%)		31 (6.9%)	24 (3.5%)	
Chicago Cook County			48 (9.6%)	131 (12%)		0 (0%)	0 (0%)	
Chapel Hill			38 (7.6%)	94 (8.9%)		16 (3.6%)	97 (14%)	
Atlanta			70 (14%)	130 (12%)		21 (4.7%)	76 (11%)	
Miami			44 (8.8%)	51 (4.8%)		23 (5.1%)	82 (12%)	
Birmingham			16 (3.2%)	47 (4.5%)		20 (4.5%)	43 (6.3%)	
Jackson			25 (5.0%)	57 (5.4%)		18 (4.0%)	31 (4.5%)	
Baltimore			0 (0%)	0 (0%)		117 (21%)	136 (17%)	
Chicago Northwestern			0 (0%)	0 (0%)		85 (19%)	128 (19%)	
Pittsburgh/Ohio			0 (0%)	0 (0%)		93 (21%)	58 (8.5%)	

Table 3. Sample characteristics by HIV status and biological sex.

	Women			Men					
	PWoH	**PWH**		**PWoH**	**PWH**				
Characteristic	N = 499[1]	N = 1,053[1]	***P*-value**[2]	N = 464[1]	N = 821[1]	***P*-value**[2]			
Los Angeles				0 (0%)	0 (0%)		112 (25%)	116 (17%)	
Age				52.96 (9.81)	54.52 (9.18)	**.003**	60.49 (13.25)	53.84 (12.20)	**<.001**
Initial study cohort						.458			**<.001**
MACS				0 (0%)	0 (0%)		398 (75%)	410 (57%)	
WIHS				336 (85%)	785 (84%)		0 (0%)	0 (0%)	
New MWCCS Recruits				57 (15%)	153 (16%)		135 (25%)	315 (43%)	
Black/AA race				325 (65%)	691 (66%)	.934	141 (25%)	351 (43%)	**<.001**
Hispanic/Latinx ethnicity				59 (12%)	112 (11%)	.541	58 (10%)	118 (14%)	.031
Years of education						.102			**<.001**
Less than high school				108 (22%)	245 (23%)		44 (7.8%)	73 (8.9%)	
Completed high school				126 (25%)	256 (24%)		75 (13%)	172 (21%)	
Some college				191 (38%)	382 (36%)		116 (21%)	253 (31%)	
Graduated College				17 (3.4%)	18 (1.7%)		125 (22%)	162 (20%)	
>College				55 (11%)	149 (14%)		203 (36%)	157 (19%)	

Table 3. Sample characteristics by HIV status and biological sex.

	Women			Men					
	PWoH	PWH		PWoH	PWH				
Characteristic	N = 499[1]	N = 1,053[1]	***P*-value**[2]	N = 464[1]	N = 821[1]	***P*-value**[2]			
CES-D			12.16 (10.43)	10.66 (10.40)	**.028**	9.23 (10.09)	10.95 (11.02)	**.018**	
BMI, kg/m^2			32.66 (8.71)	32.90 (9.12)	.667	28.69 (6.05)	28.24 (5.97)	.197	
Diabetes			93 (26%)	238 (28%)	.518	86 (17%)	111 (16%)	.884	
Hypertension			245 (64%)	613 (70%)	.076	334 (68%)	441 (65%)	.295	
Current smoker			134 (34%)	240 (27%)	**.014**	81 (16%)	171 (25%)	**<.001**	
Ever smoker			270 (68%)	581 (65%)	.316	326 (66%)	439 (65%)	.724	
Heavy alcohol use			63 (16%)	104 (12%)	.050	33 (7.4%)	39 (5.8%)	.368	
Recent heroin use			15 (3.9%)	13 (1.5%)	**.016**	161 (36%)	285 (43%)	**.025**	
Recent crack use			45 (11%)	82 (9.3%)	.284	15 (3.4%)	9 (1.4%)	**.042**	
Recent cocaine use			21 (5.4%)	50 (5.7%)	.935	40 (9.1%)	57 (8.6%)	.879	
Recent cannabis use			138 (35%)	239 (27%)	**.004**	40 (9.1%)	57 (8.6%)	.879	
Ever cannabis use			175 (42%)	318 (34%)	**.007**	352 (78%)	524 (79%)	>.999	
Ever crack, cocaine, &/or heroin use			81 (19%)	144 (15%)	.085	252 (48%)	368 (52%)	.183	
STRAW+10 menopause status					**<.001**				
Premenopausal			98 (25%)	146 (16%)					

Table 3. Sample characteristics by HIV status and biological sex.

	Women			Men		
	PWoH	**PWH**		**PWoH**	**PWH**	
Characteristic	N = 499[1]	N = 1,053[1]	***P*-value**[2]	N = 464[1]	N = 821[1]	***P*-value**[2]
Perimenopause				47 (12%)	76 (8.5%)	
Postmenopausal				243 (63%)	669 (75%)	
Hysterectomy				59 (15%)	205 (23%)	**.002**
Ever pregnant				382 (93%)	859 (93%)	.917
Plasma HIV RNA Viral load (cp/ml)						
<=20					522 (60%)	359 (56%)
21-200					284 (33%)	240 (37%)
201-500					15 (1.7%)	9 (1.4%)
501-1000					5 (0.6%)	5 (0.8%)
>1000					45 (5.2%)	32 (5.0%)
CD4+ count, cell/mm^3					797 (398)	710 (343)
CD8+ count, cell/mm^3					846 (465)	801 (395)
Nadir CD4+ count, cell/mm^3					284 (242)	305 (221)
ART adherence ≥95%					743 (87%)	597 (90%)

Table 3. Sample characteristics by HIV status and biological sex.

	Women			Men		
	PWoH	**PWH**		**PWoH**	**PWH**	
Characteristic	N = 499[1]	N = 1,053[1]	***P*-value**[2]	N = 464[1]	N = 821[1]	***P*-value**[2]
Years on ART					16.34 (7.98)	
						18.25 (10.15)
HIV duration (years)					29.60 (4.95)	
						28.99 (6.81)

[1] n (%); Mean (SD)

[2] Categorical: Pearson's Chi-squared test/Fisher's exact test; Continuous: Wilcoxon rank sum test

AA=African-American; ART=antiretroviral therapy; CES-D=Center for Epidemiological Studies-Depression; PWH=people with HIV; PWoH=people without HIV

Heavy alcohol use is defined as ≥7 standard drinks for women and ≥17 for men per week.

Development of BRACE Normative Data

Regression-based normative equations were generated for each raw BRACE outcome using data from PWoH who met QC criteria on all outcomes (n=1063). Timed outcomes were converted to seconds, log transformed, and reverse scored so that higher values indicated better performance across all measures. Log transformation reduced skewness in the timed outcomes, whereas non-timed outcomes were already approximately normally distributed (**Supplemental Figure 1**).

Each outcome was regressed on age and years of education (categorized as less than high school, high school, some college, completed/graduate with 4-year college degree, attended/completed graduate school). The resulting unstandardized beta weights for each predictor, the constant, and standard error were used to compute predicted scores for each test (**Table 4**). Differences between predicted and observed scores (or residual scores) were divided by the standard error of the estimate of the regression to generate standardized T-scores with a mean of 50 and standard deviation of 10. Distribution plots for the derived T-scores are shown in **Supplemental Figure 2** and indicate that the normative transformation produced approximately normally distributed T-scores. These age- and education-adjusted T-scores were then applied to both PWoH and PWH. A Global T-Score was calculated by averaging the four individual test T-scores (TMT-A, TMT-B, and Stroop-Color time to completion, and VSLT).

Table 4. Regression coefficients, constants, and standard errors for regression models for the normative sample of people without HIV (n=1063).

			Education (referent =completed high school)				
Outcome	Intercept	Age	Less than high school	Some college	Completed/ Graduated with 4-year college degree	Attended/ completed graduate school	SE
TMT-A	-1.066***	-0.004***	-0.026	0.065***	0.126***	0.126***	0.187
TMT-B	-1.474***	-0.004***	-0.013	0.075***	0.162***	0.158***	0.14
TMT-B - A	-19.494***	-0.170***	-0.026	3.625**	8.809***	8.645***	13.749
Stroop-Color duration	0.247***	-0.004***	-0.010	0.026***	0.057***	0.056***	0.08
Stroop-Color accuracy	36.166***	-0.155***	-0.500	1.054**	2.686***	2.784***	3.752
VSLT	2.035***	-0.045***	-0.420	0.836***	1.403***	1.862***	2.453

***P<.001; **P<.01; *P<.05; SE=standard error; TMT-Trial Making Test; VSLT=Visual spatial learning Test

The primary normative model included age and education because this model provided the best balance of interpretability, parsimony, and generalizability. Race/ethnicity was not included in the primary model given longstanding concerns in neuropsychology regarding race-based corrections [8-10]. Biological sex was also not included in the primary model because a study aim was to evaluate HIV serostatus differences within sex using a common normative framework. Alternative normative equations were also derived using age only; age + education + biological sex; age + education + race/ethnicity; and age + education + biological sex + race/ethnicity, and are presented in **Supplemental Tables 1-4**, but were not used in the primary analyses.

BRACE Performance

Table 5 presents comparisons of cognitive performance between PWH and PWoH. Overall, group differences were minimal. On Stroop-color duration and accuracy, PWH showed slightly lower performance than PWoH on standardized T-scores, although no significant differences were observed for raw scores. Effect sizes were very small (all < .11). When examining impairment on Stroop-color duration, significant differences were observed at the 1 SD and 1.5 SD cutoffs (P =.03 and P =.04). For accuracy, there was a trend for a difference at the 1 SD cutoff (P =.059). When stratified by biological sex (**Table 6**), the Stroop-Color difference was largely driven by men. Among women, no significant differences were detected across tests. Across both sexes, the direction and magnitude of serostatus differences were very small (all effect sizes < .11), underscoring the generally comparable BRACE performance between PWH and PWoH in this sample.

Table 5. Differences in cognitive performance by HIV status.

Test/outcomes	**PWoH** N = 1,063[1]	**PWH** N = 1,874[1]	***P*-value**[2]	**Effect Size**[3]
TRAIL MAKING TEST (TMT)				
TMT-A				
Raw score: time to completion (ms)	19,490 (11,196)	19,467 (10,999)	.956	.00
T-Score	50.00 (9.98)	49.98 (9.83)	.954	.00
Impaired (< 1 SD)	163 (15%)	275 (15%)	.676	.01
Impaired (<1.5 SD)	103 (9.7%)	170 (9.1%)	.631	.01
TMT-B				
Raw score: time to completion (ms)	44,331 (15,116)	45,404 (14,975)	.064	.07
T-Score	50.00 (9.98)	49.52 (10.06)	.213	.05
Impaired (< 1 SD)	177 (17%)	333 (18%)	.466	.01
Impaired (<1.5 SD)	55 (5.2%)	107 (5.7%)	.594	.01
TMT-B minus A				
Raw score	24,841 (14,189)	25,966 (14,423)	**.040**	.08
T-Score	50.00 (9.98)	49.49 (10.25)	.186	.05
Impaired (< 1 SD)	199 (19%)	390 (21%)	.185	.03
Impaired (<1.5 SD)	81 (7.6%)	177 (9.5%)	.105	.03
STROOP-COLOR				
Raw score: average response time per trial (ms)	879.46 (192.96)	884.98 (191.65)	.455	.03
T-Score	50.00 (9.98)	49.08 (10.14)	**.018**	.09
Impaired (< 1 SD)	152 (14%)	325 (17%)	**.035**	.04
Impaired (<1.5 SD)	69 (6.5%)	162 (8.7%)	**.043**	.04
Raw score: % accuracy across trials	28.61 (4.26)	28.38 (4.42)	.162	.05
T-Score	50.00 (9.98)	48.96 (10.86)	**.009**	.10

Table 5. Differences in cognitive performance by HIV status.

Test/outcomes	**PWoH** N = 1,063[1]	**PWH** N = 1,874[1]	***P*-value**[2]	**Effect Size**[3]
Impaired (< 1 SD)	142 (13%)	300 (16%)	.059	.04
Impaired (<1.5 SD)	79 (7.5%)	160 (8.6%)	.322	.02
VISUAL-SPATIAL LEARNING TEST (VSLT)				
Raw score: correct minus incorrect	0.31 (2.59)	0.13 (2.54)	.068	.07
T-Score	50.00 (9.98)	49.43 (9.88)	.137	.06
Impaired (< 1 SD)	179 (17%)	314 (17%)	>.999	.00
Impaired (<1.5 SD)	73 (6.9%)	140 (7.5%)	.590	.01
GLOBAL				
T-Score	50.00 (6.88)	49.50 (6.87)	.061	.07
Impaired (< 1 SD)	76 (7.2%)	151 (8.1%)	.412	.02
Impaired (<1.5 SD)	17 (1.6%)	33 (1.8%)	.857	.01

[1]n (%); Mean (SD)

[2] Categorical: Pearson's Chi-squared test/Fisher's exact test; Continuous: independent sample t-test

[3] Effect size: Continuous--|Cohen’s d|; Categorical—Cramer’s V

PWH=people with HIV; PWoH=people without HIV; SD=standard deviation

Global is the average of TMT-A and TMT-B time to completion, Stroop-color time to completion, and VSLT raw score.

Table 6. HIV status differences in cognition in women and men separately.

	Women				Men			
Tests/Outcomes	**PWoH** N = 499[1]	**PWH** N = 1,053[1]	***P*-value**[2]	**Effect Size**[3]	**PWoH** N = 564[1]	**PWH** N = 821[1]	***P*-value**[2]	**Effect Size**[3]
TRAIL MAKING TEST (TMT)								
TMT-A								
Raw score: time to completion (ms)	21,283 (13,165)	20,739 (12,278)	.438	.04	17,905 (8,82)	17,835 (8,844)	.885	.01
T-Score	48.93 (11.01)	49.64 (10.60)	.228	.07	50.95 (8.87)	50.41 (8.74)	.266	.06
Impaired (< 1 SD)	96 (19%)	184 (18%)	.433	.02	67 (12%)	91 (11%)	.726	.01
Impaired (<1.5 SD)	71 (14%)	122 (12%)	.162	.04	32 (5.7%)	48 (5.9%)	.974	.00
TMT-B								
Raw score: time to completion (ms)	46,733 (15,178)	47,258 (14,732)	.521	.04	42,206 (14,751)	43,027 (14,957)	.312	.06
T-Score	49.31 (9.88)	49.31 (9.90)	.999	.00	50.61 (10.03)	49.80 (10.26)	.142	.08
Impaired (< 1 SD)	84 (17%)	180 (17%)	.964	.00	93 (17%)	153 (19%)	.326	.03
Impaired (<1.5 SD)	26 (5.2%)	50 (4.8%)	.785	.01	29 (5.2%)	57 (7.0%)	.206	.04
TMT-B minus A								
Raw score	25,450 (15,581)	26,560 (15,089)	.186	.07	24,301 (12,821)	25,205 (13,492)	.207	.07

Table 6. HIV status differences in cognition in women and men separately.

	Women					Men				
Tests/Outcomes	**PWoH** N = 499[1]	**PWH** N = 1,053[1]	***P*-value**[2]	**Effect Size**[3]		**PWoH** N = 564[1]	**PWH** N = 821[1]	***P*-value**[2]	**Effect Size**[3]	
T-Score			50.28 (11.14)	49.67 (10.90)	.314	.06	49.75 (8.82)	49.25 (9.35)	.310	.06
Impaired (< 1 SD)			112 (23%)	235 (22%)	.998	.00	87 (15%)	155 (19%)	.106	.05
Impaired (<1.5 SD)			50 (10%)	107 (10%)	>.999	.00	31 (5.5%)	70 (8.6%)	**.041**	.06
STROOP-COLOR										
Raw score: average response time per Trial (ms)			888.99 (190.45)	905.60 (183.70)	.105	.09	871.02 (194.93)	858.54 (198.39)	.245	.06
T-Score			48.87 (9.65)	48.54 (9.76)	.535	.03	51.00 (10.16)	49.78 (10.58)	**.032**	.12
Impaired (< 1 SD)			78 (16%)	186 (18%)	.361	.03	74 (13%)	139 (17%)	.060	.05
Impaired (<1.5 SD)			34 (6.8%)	90 (8.6%)	.285	.03	35 (6.2%)	72 (8.8%)	.095	.05
Raw score: % accuracy across trials			28.29 (4.19)	27.90 (4.21)	.090	.09	28.90 (4.29)	28.99 (4.61)	.695	.02
T-Score			49.01 (9.96)	48.55 (10.37)	.402	.05	50.87 (9.92)	49.48 (11.46)	**.016**	.13
Impaired (< 1 SD)			75 (15%)	175 (17%)	.476	.02	67 (12%)	125 (15%)	.087	.05
Impaired (<1.5 SD)			41 (8.2%)	83 (7.9%)	.894	.01	38 (6.7%)	77 (9.4%)	.095	.05
VISUAL-SPATIAL LEARNING TEST (VSLT)										

Table 6. HIV status differences in cognition in women and men separately.

	Women				Men			
Tests/Outcomes	**PWoH** N = 499[1]	**PWH** N = 1,053[1]	***P*-value**[2]	**Effect Size**[3]	**PWoH** N = 564[1]	**PWH** N = 821[1]	***P*-value**[2]	**Effect Size**[3]
Raw score: correct minus incorrect	-0.07 (2.60)	-0.17 (2.37)	.454	.04	0.64 (2.54)	0.51 (2.69)	.358	.05
T-Score	49.12 (10.11)	48.94 (9.43)	.744	.02	50.78 (9.80)	50.06 (10.40)	.192	.07
Impaired (< 1 SD)	94 (19%)	176 (17%)	.332	.03	85 (15%)	138 (17%)	.415	.02
Impaired (<1.5 SD)	48 (9.7%)	75 (7.1%)	.108	.04	25 (4.4%)	65 (8.0%)	**.013**	.07
GLOBAL								
T-Score	49.05 (6.80)	49.11 (6.71)	.887	.01	50.83 (6.85)	50.01 (7.05)	**.031**	.12
Impaired (< 1 SD)	45 (9.1%)	87 (8.3%)	.683	.01	31 (5.5%)	64 (7.8%)	.116	.05
Impaired (<1.5 SD)	9 (1.8%)	19 (1.8%)	>.999	.00	8 (1.4%)	14 (1.7%)	.835	.01

[1] Mean (SD); n (%)

[2] Categorical: Pearson's Chi-squared test/ Fisher's exact test; Continuous: independent sample t-test

[3] Effect size: Continuous—|Cohen's d|; Categorical—Cramer's V

PWH=people with HIV; PWoH=people without HIV; SD=standard deviation

Global is the average of TMT-A and TMT-B time to completion, Stroop-color time to completion and VSLT raw score.

Socio-demographic, clinical, and behavioral factors relating to BRACE performance

In both PWH and PWoH, a greater number of factors were associated with raw BRACE scores than with demographically adjusted T-scores. Associations for continuous variables and two-level categorical variables are shown in **Figure 1**, whereas results for categorical variables with more than two levels are presented in **Supplemental Tables 5-11**. Across serostatus groups, clinical research site, study cohort, and sociodemographic factors (age, race/ethnicity, education) were significantly related to raw test scores across most outcome measures. Older age, being Black/African American, and having fewer years of education were associated with poorer performance. These associations for race and sex were attenuated when using age- and education-adjusted T-scores. Behavioral and clinical factors including diabetes, hypertension, depressive symptoms, and substance use (except cannabis) were also consistently associated with poorer raw scores in both groups, although these relationships were often weakened when using T-scores. Among PWH, HIV-related factors such as nadir CD4 count, years of ART, and HIV duration were primarily associated with raw rather than T-score performance.

When analyses were stratified by biological sex, most associations with BRACE performance were again observed for raw scores rather than T-scores (**Figure 2, Supplemental Tables 12-27**). Across all four groups, age and education showed the most consistent associations with cognitive performance (**Supplemental Figure 1**, **Supplemental Tables 28-30**).

Among women, associations between demographic factors and cognitive performance were generally more extensive and stronger in PWH (**Figure 2A, Supplemental Tables 12-16**) than in

PWoH (**Figure 2B, Supplemental Tables 17-20**). Menopausal status was significantly related to raw scores, but not T-scores, in both women with and without HIV. In women with HIV, additional associations were observed with clinical research site and Black/AA race. Depressive symptoms (CES-D score) were associated with poorer performance on Stroop-color accuracy in PWH and VSLT in PWoH. Diabetes, hypertension, and smoking (current or ever) were associated with poorer raw scores in both groups of women, whereas other forms of substance use showed stronger associations in women without HIV.

Among men, cognitive performance was associated with a broader range of factors overall, with stronger associations observed among PWH (**Figure 2C, Supplemental Tables 21-24**) than among PWoH (**Figure 2D, Supplemental Tables 25-27**). In men with HIV, substance use, particularly cannabis, was significantly related to both raw and T-scores across multiple cognitive tests. Diabetes was also more strongly associated with poorer cognition in men with HIV compared to men without HIV. Additional results for the total sample and sex-stratified analyses are presented in **Supplemental Figures 3-5** and **Supplemental Tables 28-37**.

DISCUSSION

This study establishes the first regression-based normative framework for BRACE using data from a large and diverse sample of people with and without HIV. The analyses incorporated multiple demographic models (age only; age and education; age, education, and race/ethnicity; age, education, and biological sex; and age, education, race/ethnicity, and biological sex). Building on our prior work demonstrating that BRACE is easily self-administered, reliable, resistant to short-term practice effects, and strongly correlated with a standard NP battery [1], the

present study extends validation by examining HIV serostatus differences, within-sex comparisons, and demographic and clinical correlates of cognitive performance across four cognitive measures (TMT-A and B, Stroop-Color, VSLT). These norms provide a framework for interpreting BRACE performance relative to age and education and support standardized evaluation across research and clinical settings.

Overall, cognitive differences between PWH and PWoH were minimal, with very small effect sizes observed for Stroop-Color. Notably, these serostatus differences were predominantly observed in men. This finding contrasts with a systematic review suggesting women with HIV are more vulnerable to cognitive impairment than men with HIV [2, 11]. While many prior studies were underpowered to detect sex differences [2], one well-powered MWCCS analysis using traditional pencil-and-paper NP tests found a female disadvantage. Women with HIV had 2.5 times higher odds of scoring in the impaired range on the TMT-A and on the non-dominant hand of the Grooved Pegboard Test (not assessed in BRACE) [3]. However, that study included a younger cohort (mean age early 40s vs. 50s-60s here), lower ART adherence, higher CD4 counts, higher viral loads, and represented only about one fourth of the MWCCS. These differences may reflect differences in cohort composition, aging, improved viral suppression, and methodological differences between tablet-based and traditional testing.

Beyond serostatus and biological sex, cognitive performance was related to a broad set of sociodemographic, behavioral, and clinical factors across both PWH and PWoH. Consistent with prior work, older age, fewer years of education, and Black/AA race were associated with poorer performance, highlighting persistent disparities in cognitive health [12, 13]. These associations

likely reflect broader structural and contextual determinants of cognitive health rather than intrinsic group differences. Depressive symptoms and cardiometabolic comorbidities, particularly diabetes and hypertension, were also associated with worse cognition, reinforcing their role as modifiable risk factors for cognitive health in aging populations. Substance use patterns showed nuanced associations. Most substances were associated with poorer performance, whereas cannabis use was associated with better performance, consistent with some prior studies [14, 15]. This finding should be interpreted cautiously, as it may reflect residual confounding or other unmeasured behavioral or clinical factors rather than a beneficial effect of cannabis itself. These findings suggest that BRACE is sensitive to broader determinants of cognitive health that cut across serostatus.

A major strength of this study is the large (N=2937), diverse normative sample (mean age 56 years; 53% women; 51% Black/AA; 12% Hispanic/Latino) recruited across multiple U.S. sites, enhancing generalizability. Generating regression-based norms across multiple demographic models provides flexibility for future BRACE applications. To minimize residual confounding due to demographic and clinical differences between men and women, we examined HIV serostatus differences *within* sex rather than sex differences *within* HIV serostatus. This approach improves internal validity but limits direct inferences about sex differences among PWH and PWoH.

Several limitations should be considered. The cross-sectional design precludes causal inference and BRACE assesses a relatively narrow range of cognitive abilities compared to comprehensive NP batteries. Although tablet-based cognitive assessments such as BRACE offer advantages for scalability and standardized administration, they may also introduce modality-specific challenges

that are less common in traditional NP testing. In this study, administration difficulties were documented in routine coordinator notes including touchscreen or stylus interaction issues (e.g., among some participants with long fingernails or limited hand dexterity), intermittent software interruptions, and participant fatigue or drowsiness during testing. These observations should be interpreted cautiously, as they were not systematically measured; however, they highlight the importance of documenting testing context and user interaction when implementing digital cognitive assessments in research settings. Potentially relevant factors related to cognitive function, including sleep, HIV reservoir dynamics, and sex hormones, were not available in this analysis and warrant further investigation. As BRACE was only available in English, findings may not generalize to non-English speaking populations. Additionally, since the normative equations were derived in PWoH and then applied to both groups, observed HIV serostatus differences should be interpreted relative to the PWoH reference group. Accordingly, the present regression-based norms should be viewed as an initial framework requiring further refinement and validation. Future work should evaluate their performance including assessments of criterion and construct validity, potential adjustment for practice effects, and the incorporation of additional demographic or contextual factors. Although we intentionally did not use race-based corrections in the primary normative model, the current approach does not fully account for broader social and structural determinants that may shape cognitive performance. Future work should evaluate whether incorporating indicators of socioeconomic disadvantage, opportunity, and related contextual factors improves normative precision. Longitudinal analyses of BRACE data in the MWCCS will be essential to characterize cognitive trajectories in PWH and PWoH and to identify early markers of cognitive decline or resilience.

In conclusion, we developed and applied regression-based normative equations for BRACE

using data from PWoH, providing an initial framework for standardized evaluation of cognitive performance in PWH. Cognitive differences between groups were minimal overall and when present were largely driven by men with HIV. BRACE performance was also shaped by sociodemographic and clinical factors common to both groups, underscoring that cognitive difficulties likely reflect multiple intersecting influences. BRACE appears to be a promising tool for scalable cognitive assessment in large cohorts; however, additional external validation will be important before broader applicability can be established. Future cross-sectional and longitudinal studies are needed to further validate these norms and clarify sex- and serostatus-specific trajectories of cognitive performance.

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Conflicts of Interest

None Declared for Rubin, Severson, Lieberman, Shorer, Haberlen, Gustafson, Stosor, Mimiaga, Peven, Jones, Sheth, Spence, Sharma, Vance, and Dastgheyb. Dr. Maki receives consulting fees from Astellas and Bayer, and has equity in Midi Health, Estrigenix, and Respin. Dr. Floris-Moore has received consulting fees from ViiV Healthcare. Dr. Kathleen Weber reports the she is a Trustee of the Hektoen Institute of Medicine.

Data Availability

Data used in this study were obtained from the MACS/WIHS Combined Cohort Study (MWCCS) database. Access to individual-level data from the MWCCS may be obtained upon review and approval of a MWCCS concept sheet. Links and instructions for online concept sheet submission are on the study website: https://statepi.jhsph.edu/mwccs/work-with-us/ Investigators within the MWCCS contributed to the design and implementation of MWCCS and/or provided data but did not participate in analysis or writing of this report. A complete listing of MWCCS investigators can be found at: https://statepi.jhsph.edu/mwccs/work-with-us/.

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Figure 1. Cognitive correlates among people with HIV (PWH) and people without HIV (PWoH). For each group, the top panel displays associations between the examined variables and cognitive performance (raw scores and T-scores). † Denotes raw scores that have been reverse scored so that higher scores indicate better performance. The bottom panel illustrates the direction and strength of associations. Pearson correlations were used for continuous variables (e.g., age), and point-biserial correlations for binary categorical variables. Significance thresholds are denoted as: ***P < .001; **P < .01; *P < .05; ns=not significant; Biological sex=male

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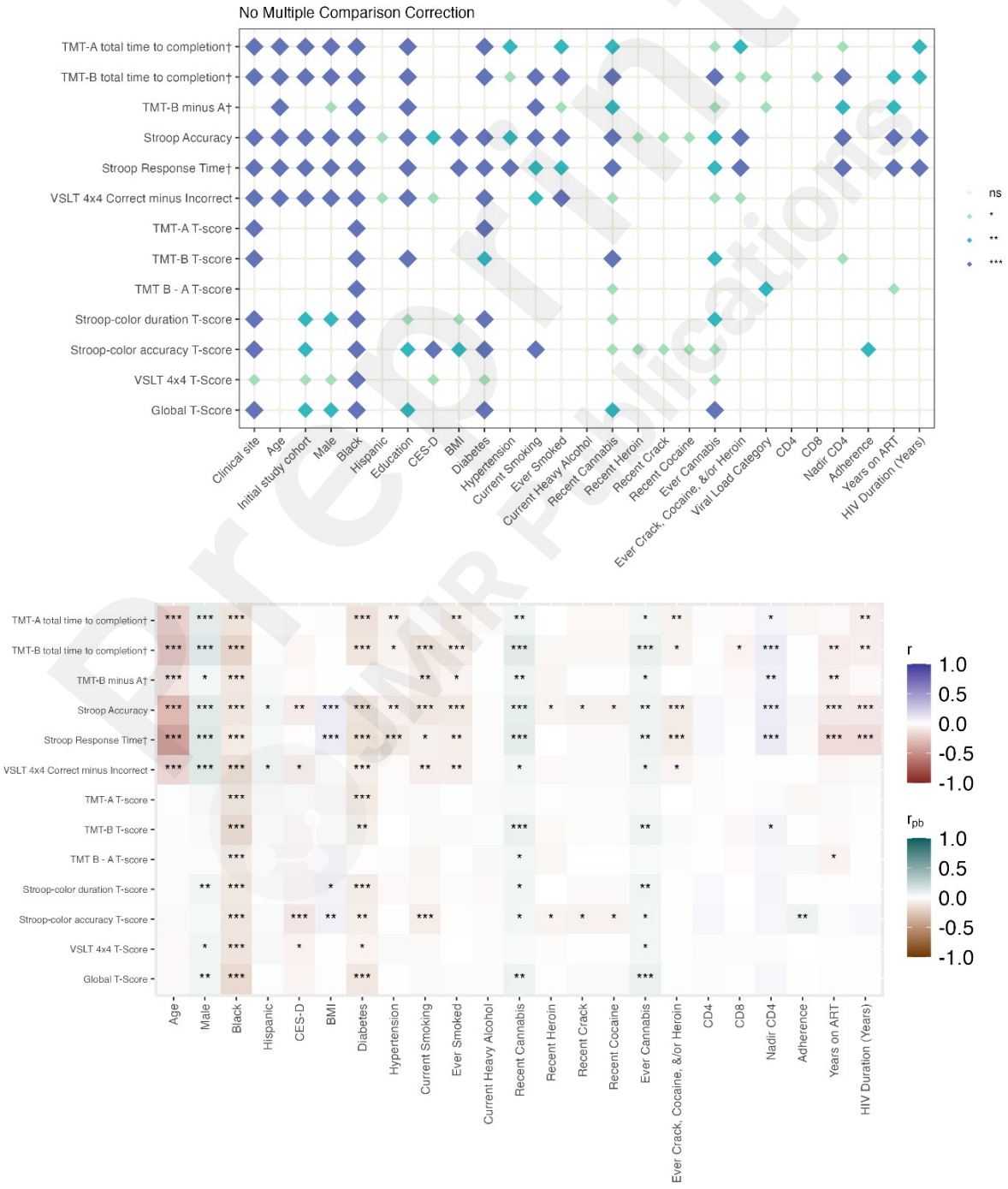


B. PWoH

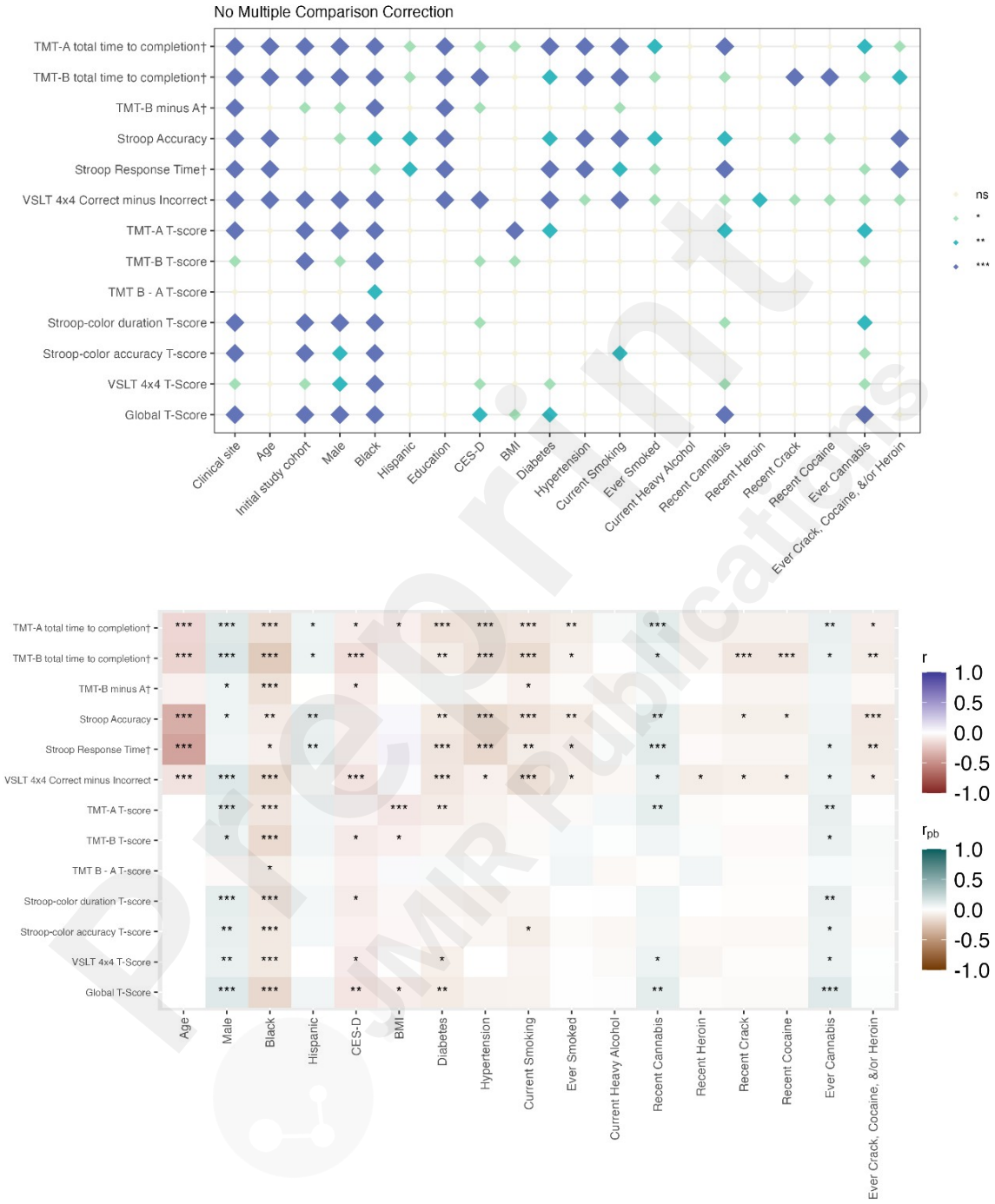
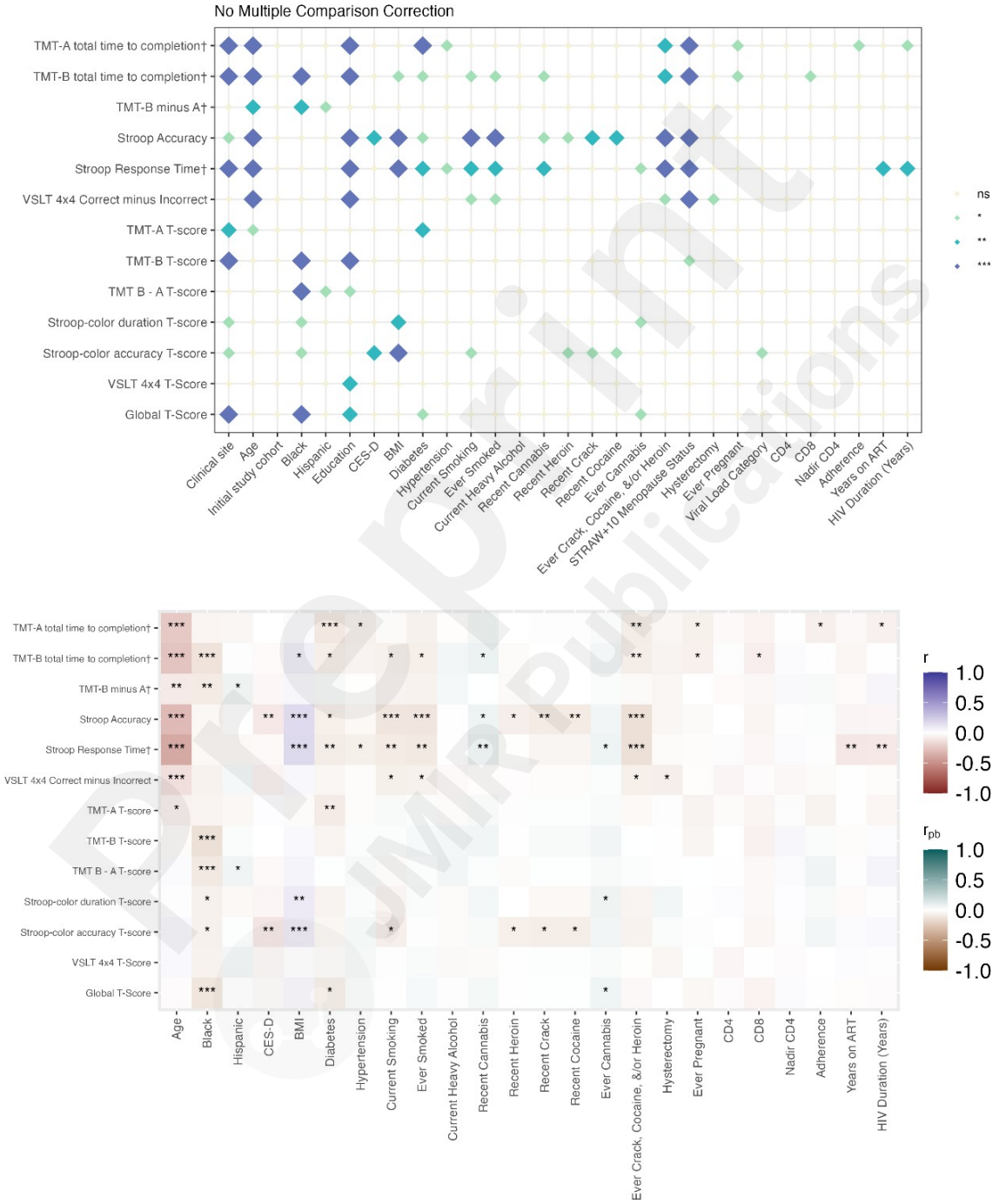


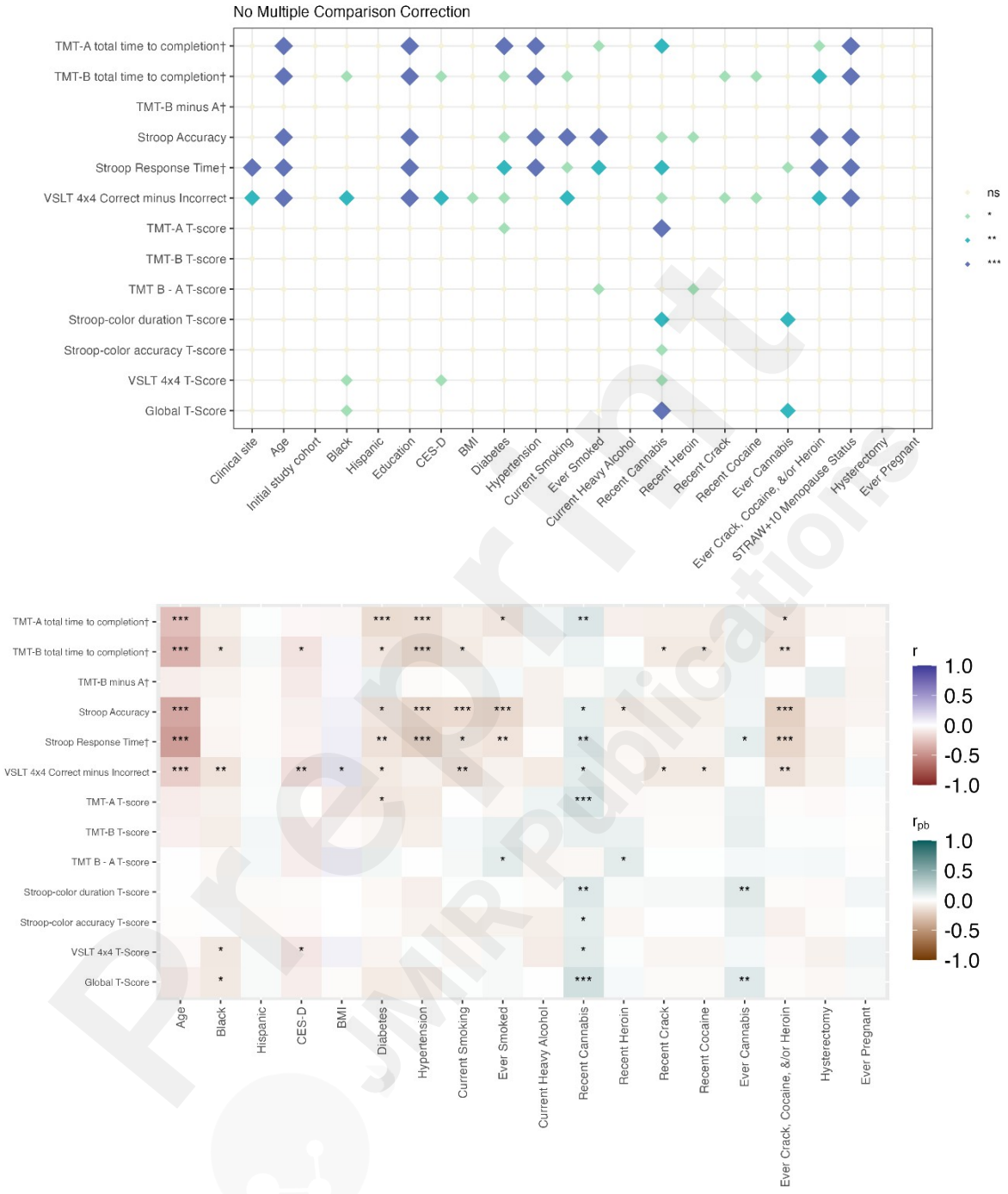
Figure 2. Cognitive correlates among people with HIV (PWH) and people without HIV (PWoH) by biological sex. For each group, the top panel displays associations between examined variables and cognitive performance (raw scores and T-scores). † Denotes raw scores that have been reverse scored so that higher scores indicate better performance. The bottom panel

illustrates the direction of and strength of associations: Pearson correlations were used for continuous variables (e.g., age), and point-biserial correlations for binary categorical variables. Significance thresholds are denoted as: ***$P < .001$; **$P < .01$; *$P < .05$; ns=not significant

A. Women-PWH



B. Women-PWoH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TMT-B total time to completion†
TMT-B minus A†
Stroop Accuracy
Stroop Response Time†
VSLT 4x4 Correct minus Incorrect
TMT-A T-score
TMT-B T-score
TMT B - A T-score
Stroop-color duration T-score
Stroop-color accuracy T-score
VSLT 4x4 T-Score
Global T-Score
Clinical site
Age
Initial study cohort
Black
Hispanic
Education
CES-D
BMI
Diabetes
Hypertension
Current Smoking
Ever Smoked
Current Heavy Alcohol
Recent Cannabis
Recent Heroin
Recent Crack
Recent Cocaine
Ever Cannabis
Ever Crack, Cocaine, &/or Heroin
STRAW+10 Menopause Status
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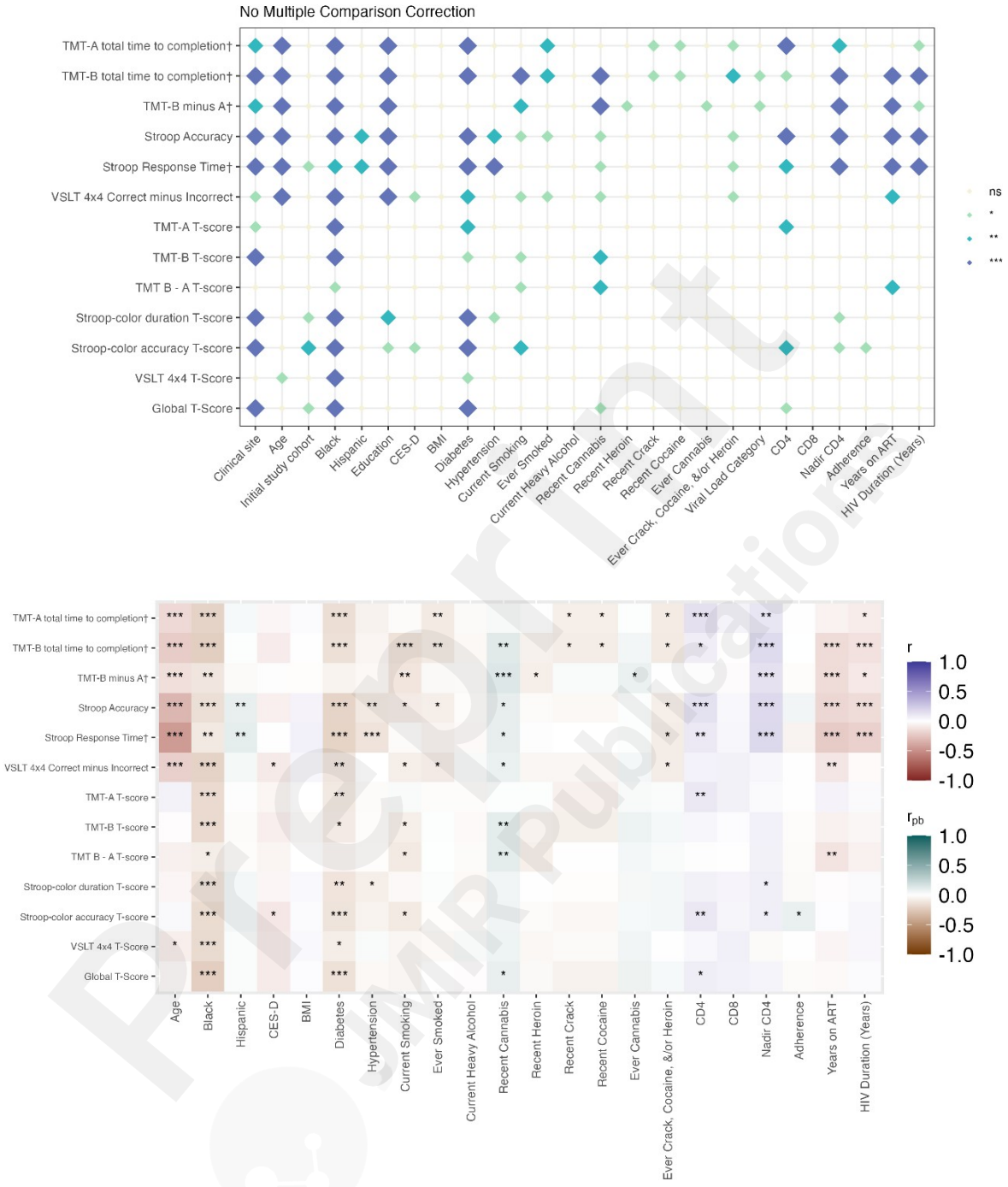
C. Men-PWH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TMT-B minus A†
Stroop Accuracy
Stroop Response Time†
VSLT 4x4 Correct minus Incorrect
TMT-A T-score
TMT-B T-score
TMT B - A T-score
Stroop-color duration T-score
Stroop-color accuracy T-score
VSLT 4x4 T-Score
Global T-Score
Clinical site
Age
Initial study cohort
Black
Hispanic
Education
CES-D
BMI
Diabetes
Hypertension
Current Smoking
Ever Smoked
Current Heavy Alcohol
Recent Cannabis
Recent Heroin
Recent Crack
Recent Cocaine
Ever Cannabis
Ever Crack, Cocaine, &/or Heroin
Viral Load Category
CD4
CD8
Nadir CD4
Adherence
Years on ART
HIV Duration (Years)
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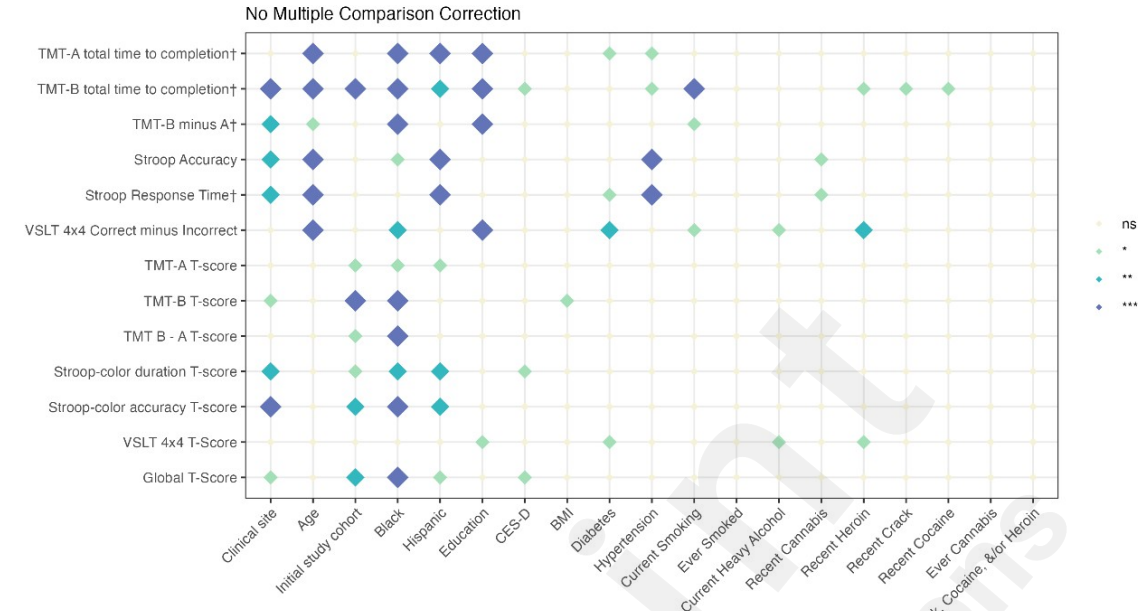
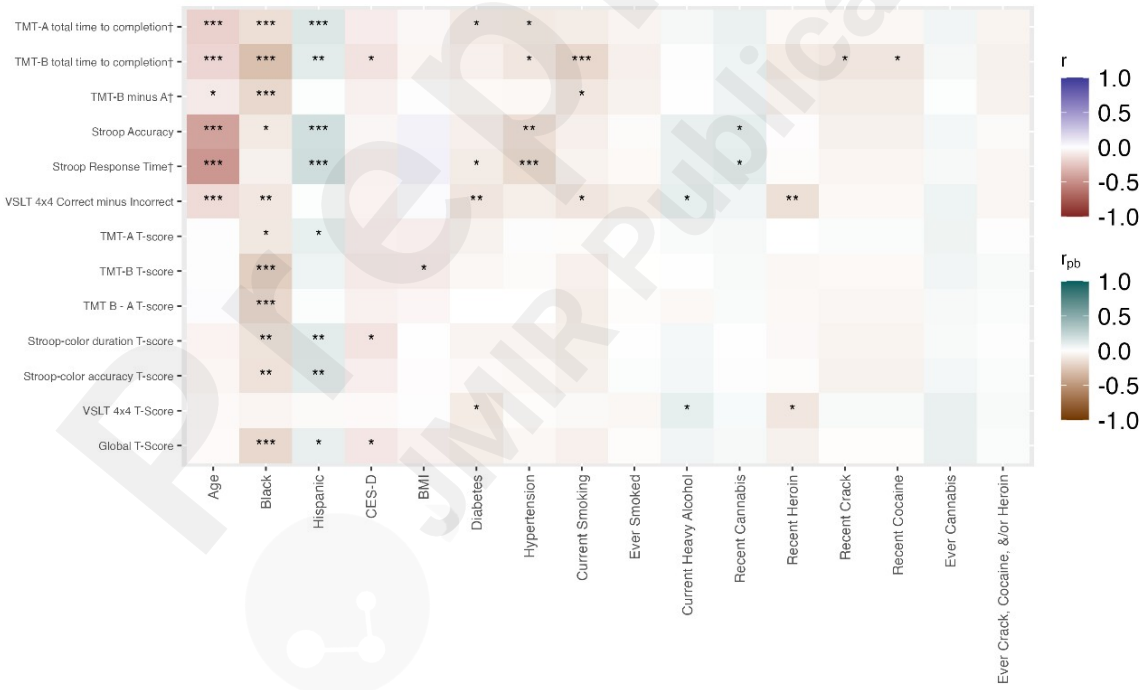
D. Men-PWoH





Supplementary Files

Untitled.
URL: http://asset.jmir.pub/assets/13d7f98952d8a6e7f1ee99ae81312c92.docx