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Authors

Wang, Crystal X

Gouda, Harsha

Scheurink, Toon Aw

et al.

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Genomics, Proteomics, and Metabolomics

Fecal Metabolomics–Based Dietary Profiling Reveals Food Markers of HIV Brain Health Disorders

Crystal X Wang [1,*], Harsha Gouda [2], Toon AW Scheurink [3], Jasmine Zemlin [2], Christine E Spaven [2,4], Helena Mannochio-Russo [2], Jennifer E Iudicello [1], Robert K Heaton [1], David J Moore [1], Scott L Letendre [5], Mariana Cherner [1], Donald R Franklin [1], Monica Guma [5,6], Andrew H Miller [7], Rob Knight [8,9,10,11,12,13], Pieter C Dorrestein [2,8,14,15], Ronald J Ellis [1,16]

[1] *Department of Psychiatry, University of California, San Diego, CA, United States;* [2] *Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California, San Diego, CA, United States;* [3] *Center for Clinical Neuroscience and Cognition, University Medical Centre Groningen, University of Groningen (RUG), Groningen, The Netherlands;* [4] *Department of Biological Sciences, University of California, San Diego, CA, United States;* [5] *Department of Medicine, University of California, San Diego, CA, United States;* [6] *Division of Rheumatology, Autoimmunity and Inflammation, UCSD School of Medicine, University of California, San Diego, CA, United States;* [7] *Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA, United States;* [8] *Department of Pediatrics, University of California, San Diego, CA, United States;* [9] *Center for Microbiome Innovation, University of California, San Diego, CA, United States;* [10] *Department of Computer Science and Engineering, University of California, San Diego, CA, United States;* [11] *Halıcıoğlu Data Science Institute, University of California, San Diego, CA, United States;* [12] *Shu Chien-Gene Lay Department of Bioengineering, University of California, San Diego, CA, United States;* [13] *Hong Kong University of Science and Technology Jockey Club Institute for Advanced Study, Hong Kong University of Science and Technology, Hong Kong SAR, China;* [14] *Collaborative Mass Spectrometry Innovation Center, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California, San Diego, CA, United States;* [15] *Department of Pharmacology, University of California, San Diego, CA, United States;* [16] *Department of Neurosciences, University of California, San Diego, CA, United States*

A B S T R A C T

Background: Despite widespread viral suppression, nearly half of people with human immunodeficiency virus (PWH) experience brain health disorders, such as neurocognitive impairment and depression. Dietary interventions can improve neuropsychiatric outcomes in other populations, but there is limited research in PWH.

Objectives: Recent advances allow the detection of food molecules from fecal samples to provide semiquantitative, high-resolution measures of dietary exposure. We applied a metabolomics-based method to identify food items associated with brain health outcomes in PWH.

Methods: Participants were 170 PWH (mean age = 56; 84% males; 97% virally suppressed) enrolled in the University of California, San Diego cohort studies (2019–2022). Fecal samples were analyzed using liquid chromatography tandem mass spectrometry. A food readout tool mapped fecal metabolomics features to ~6000 dietary molecular ions, predicting exposure with "food scores" scaled from 1 (lowest) to 4 (highest). Neurocognition was assessed with demographically adjusted T-scores across 7 ability domains. Depressive symptoms were measured by the Beck's Depression Inventory–II and its subscales (i.e., affective, apathy, cognitive, and somatic). Correlation analysis was followed by multivariate analysis adjusting for relevant covariates. Exploratory analysis in a subgroup of 37 participants with repeated neurocognitive measures examined longitudinal diet–neurocognition relationships.

Results: Eighty-six unique food items were detected based on fecal metabolomics profiles. Higher abundance of certain vegetables/herbs, fruits, eggs, and grains was associated with better neurocognitive outcomes, with longitudinal patterns consistent with possible diet–neurocognition relationships. As for depression, higher abundance of eggs, shrimp, and certain vegetables/fruits was associated with lower depression, particularly affective, apathy, and somatic symptoms.

Conclusion: Metabolomics-based dietary profiling revealed differential food–brain health associations in PWH that align with prior self-report studies. This approach provides semiquantitative estimates, suggesting that even modest differences in food exposure may meaningfully relate to brain health outcomes. These results provide preliminary evidence toward potential dietary targets for future interventions aimed at improving the brain health of at-risk PWH.

Abbreviations: ART, antiretroviral therapy; BDI-II, Beck's Depression Inventory–II; GDS, Global Deficit Score; HNRC, HIV Neurobehavioral Research Center; LME, linear mixed-effects; log2FC, log2 fold change; NCI, neurocognitive impairment; PWH, people with HIV; UCSD, University of California, San Diego.

* Corresponding author. *E-mail address:* crwang@health.ucsd.edu (C.X. Wang).

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Keywords: diet, untargeted metabolomics, foodomics, HIV brain health disorders, HIV-associated neurocognitive impairment, HIV-associated depression

Introduction

Despite significant advances in HIV treatment that have led to widespread viral suppression, brain health disorders remain highly prevalent among people with HIV (PWH), most notably neurocognitive impairment (NCI) and depression [1–3]. Nearly half of PWH meet criteria for either NCI or depression, highlighting the need to identify modifiable factors that may support brain health in this population. Nutrition is one potential modifiable factor, with diet increasingly recognized as an important contributor to brain health outcomes in populations without HIV [4–8].

Chronic systemic inflammation may represent an important mechanism linking diet to brain health in PWH. Despite effective antiretroviral therapy (ART), persistent inflammation remains a hallmark of HIV and has been implicated in both NCI and depression among PWH [9–11]. Diet can influence systemic inflammation, providing a potential pathway through which dietary factors may affect brain health. In the general population, dietary interventions showed efficacy in improving depressive and neurocognitive outcomes, as well as reducing risk of disorders, such as major depressive disorder and all-cause dementia [6–8]. In general, processed meats and foods high in sugar and fat have been associated with greater inflammation and worse depression or NCI [12–15], whereas vegetables, fruits, whole grains, nuts, and lean meats have been associated with lower inflammation and more favorable brain health outcomes [16–18]. Some interventional studies further support a role for inflammation in brain health outcomes, with anti-inflammatory interventions associated with symptom improvement [19].

Despite this evidence, relatively little is known about the relationships between specific foods and brain health among PWH. The vast majority of dietary studies examining NCI and depression have focused on populations without HIV, and associations with dietary factors may differ across disease conditions. For example, some studies have found ketogenic diets rich in dairy products to be associated with better neurocognitive outcomes in an Alzheimer's disease cohort, whereas dairy was considered proinflammatory in a dietary intervention for rheumatoid arthritis [20,21]. Moreover, many nutritional studies conducted among PWH have not included brain health outcomes [22]. To our knowledge, only 3 recent studies have investigated associations between specific foods or food categories and NCI, depression, or anxiety among PWH. Although findings have not been entirely consistent, these studies suggest that greater reported intake of meats and sweetened beverages may be associated with poorer brain health, whereas vegetables, fruits, and eggs may be associated with better outcomes [23–26]. Importantly, these studies relied primarily on self-reported dietary assessments, which can be susceptible to some recall error and reporting bias [27].

The current study aimed to address the limited evidence linking specific foods with brain health in PWH and the reliance of prior studies on self-reported dietary assessments by leveraging foodomics technology to characterize fecal metabolomics-based signatures of specific foods in 170 PWH. We examined associations between these food scores and 2 major domains of HIV brain health: neurocognitive function and depressive symptoms. We further compared the foods identified through these associations with prior findings from dietary studies in the general population. This approach provides a complementary, metabolomics-based perspective on relationships between food-associated molecular signatures and brain health among PWH and identifies candidate foods for further investigation using longitudinal study designs.

Methods

Participants

Participants were 170 PWH enrolled in cohort studies at the University of California, San Diego (UCSD) HIV Neurobehavioral Research Center (HNRC; P30MH062512-24) who provided 222 fecal samples between 2019 and 2022 for untargeted metabolomics assays. The sample of 170 PWH was predominantly male (87%) and diverse in racial/ethnic background (55% non-White). Participants were a mean age of 56 y (SD = 11.67), with a mean of 14 y of education (SD = 2.90). There was an average of 1.31 visits per participant, with 37 (21.76%) participants who were part of the full cohort contributing repeated measures. The 37 participants with repeated measures had an average of 2.41 visits (range = 2–4 visits; mean time between visits = 0.93 y). During every visit, participants provided fecal samples for untargeted metabolomics profiling and completed comprehensive neuropsychiatric and neuromedical evaluations. See Figure 1 for the participant flowchart.

All participants provided informed consent to participate in these cohort studies, which included consent for the use of their data in future research. The UCSD Institutional Review Board approved all procedures. As per HNRC parent study guidelines, inclusion criteria included the following: *1*) to be aged ≥18, *2*) ability to provide informed consent, *3*) HIV-positivity via ELISA and Western blot confirmation or the MedMira Rapid test; and exclusion criteria included the following: *1*) inability to provide informed consent, *2*) history of significant confounding conditions that could impact interpretation of data (e.g., severe neurological or psychiatric conditions with current psychotic features, or ongoing substance use disorders).

Measures

Primary predictor: food scores

Fecal samples from HNRC participants were collected, extracted, and analyzed using ultra-HPLC-MS/MS as described previously [26]. The raw MS/MS data were uploaded to the Mass Spectrometry Interactive Virtual Environment, a publicly available data repository for metabolomics data, then processed using MZmine version 4.7.8 [28]. For details on the MZmine batch specifications, see Supplemental Methods.

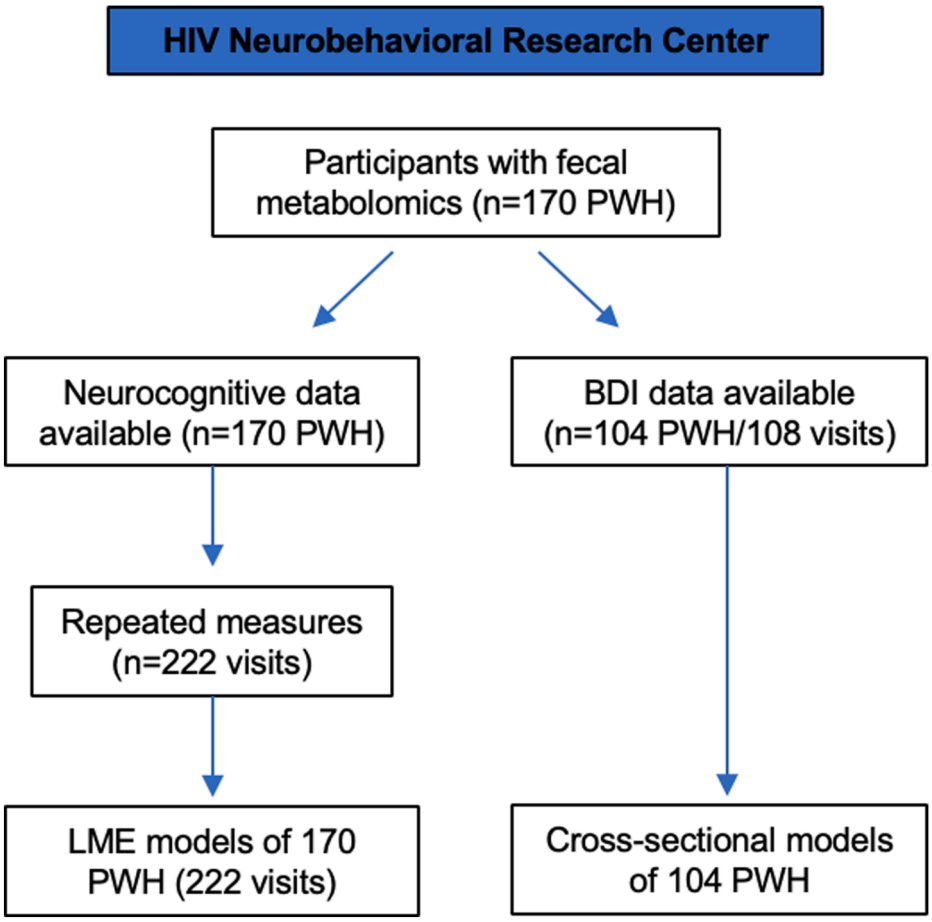

FIGURE 1. Participant flowchart. BDI-II, Beck's Depression Inventory–II; LME, linear mixed-effects; PWH, people with HIV.

After processing the untargeted metabolomics data, a novel food readout tool was used to derive food scores from the fecal metabolomics data [29]. Briefly, this readout tool identifies the food-specific molecular ion features from untargeted metabolomics data using MS/MS spectral matching with a reference library of 6128 MS/MS food biomarkers from 130 unique, simple food items (e.g., single-ingredient foods like apple, beef, and milk). After detection, total ion count-normalized feature intensities were used to obtain food scores using the equation below:

$$\text{Food score for food(x)} = \frac{1}{N}\sum_{f=1}^{n} I_{(f)}$$

($I_{(f)}$= intensity of MS/MS food biomarker feature, N = total number of features detected for food type).

The food readout tool has been validated using animal and human nutritional intervention trials, and is able to retrospectively estimate relative dietary composition information using fecal metabolomics data [29]. Briefly, the food scores represent the joint outcome of food composition in fecal samples after ingestion, digestion, absorption, microbial and host biotransformation, transit, and stool water content, and are the semi-quantitative scores of the fecal abundance of food-associated spectral features, rather than direct measures of consumed quantity. However, our paper validating the food readout tool shows that the food scores still match well to relative consumption quantities in controlled diet studies, showing that they may still indirectly estimate intake [29]. The food readout tool is publicly available at https://foodreadouts.gnps2.org/.

For our study, after food scores were obtained from fecal metabolomics data of PWH, they were minimum–maximum transformed on a scale from 0 to 10 and then additionally categorized into quartiles ranging from 1 (lowest) to 4 (highest intensity) for increased interpretability. See Figure 2 for a workflow of food score calculations.

Neurocognition

All participants completed a comprehensive neurocognitive battery spanning the 7 ability domains most impacted by HIV (i.e., processing speed, executive functioning, verbal fluency, learning, working memory, delayed recall, and motor speed) [3]. Raw scores for each neurocognitive test were converted to T-scores that correct for relevant demographics, such as race/-ethnicity, sex, age, and education, as appropriate [30–32]. Global cognition was calculated as the average across the 7 ability domains. Global and domain-specific T-scores served as our measure of neurocognitive functioning. NCI was operationalized as having a Global Deficit Score (GDS; the average of deficit scores calculated from domain-specific T-scores across the 7 ability domains) of $\geq$0.50 [30,33,34].

Depression

A subset of 104 participants (108 visits) completed the Beck's Depression Inventory–II (BDI-II). The BDI-II is a self-report questionnaire of 21 items related to different depressive

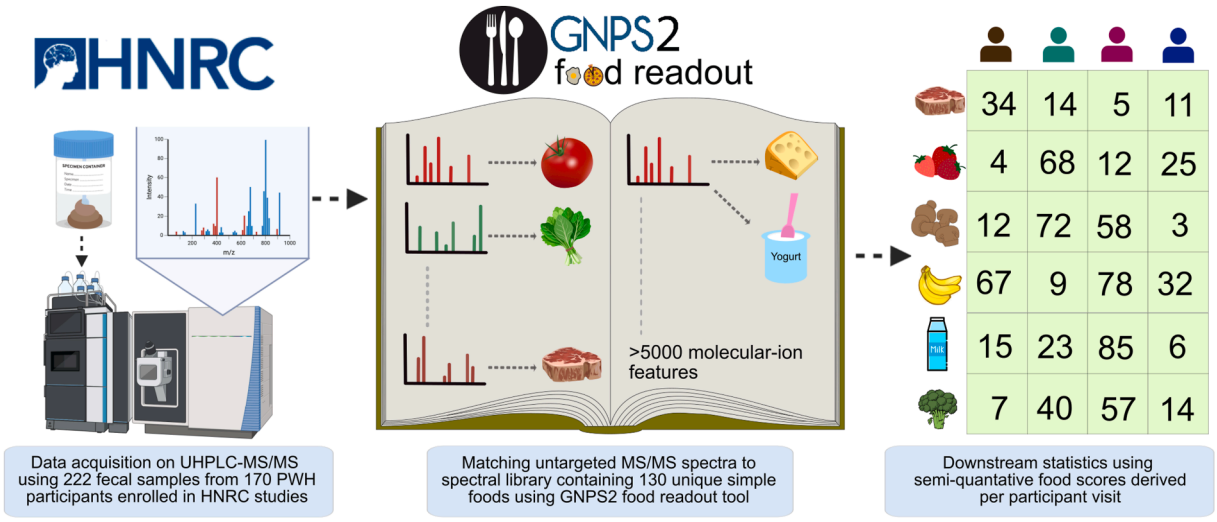

FIGURE 2. Workflow of methods to calculate food scores from fecal metabolomics data, including sample processing and feature annotation methods. Abbreviations: HNRC, HIV Neurobehavioral Research Center; GNPS, Global Natural Product Social Molecular Networking.

symptoms for which participants rate the severity of their experience over the past 2 wk on a 4-point scale (ranging from 0 to 3) [35]. Higher BDI-II scores (ranging from 0 to 63) indicate greater depressive symptom severity, with a score >13 indicating at least mild depression. The strong psychometric properties of the BDI-II have been well-documented across diverse clinical populations, including PWH [36]. The BDI-II can be further divided into subscales for affective, apathy, cognitive, and somatic depressive symptoms [36,37]. Given evidence showing differences in depressive symptom profiles in PWH [38], both BDI-II total and subscale scores were analyzed.

Covariates

All multivariate models controlled for covariates empirically linked to dietary habits or HIV brain health outcomes, including age, biological sex, race/ethnicity, education, BMI, HIV viral suppression, and Nadir CD4+ T-cell counts. Plasma viral RNA levels were quantified through a blood sample, and undetectable HIV viral load was operationalized as having ≤ 50 copies/mL. The demographic covariates were determined using self-report questionnaires that are well-established, validated, and commonly used across HNRC studies [39].

Statistical analysis

All statistical analyses were conducted using R version 4.4.1 (R Core Team, Vienna, Austria). For neurocognitive outcomes, univariate Spearman correlations were first conducted to assess associations between the quartile food scores (modeled as ordinal numeric variables) and global and domain-specific neurocognitive T-scores. Neurocognitive analyses included 222 visits from 170 participants, with a subset of participants contributing repeated measures. Candidate foods were identified using a structured, multistep screening approach. A food was considered a candidate if: *1*) its food score was nominally associated with global neurocognitive T-scores (Spearman correlation, $P < 0.05$), *2*) its food score was also nominally associated ($P < 0.05$) with ≥ 2 domain-specific neurocognitive T-scores, and *3*) the signs of the Spearman correlation coefficients (ρ) were consistent across all neurocognitive outcomes (i.e., all positive or all negative). For each candidate food, linear mixed-effects models were subsequently fit for global and each domain-specific neurocognitive T-score. All linear mixed-effects (LME) models included participant as a random intercept to account for the within-participant variance due to repeated measurements, with food scores included as fixed effects. LME models were adjusted for relevant covariates empirically related to dietary habits or outcomes (i.e., age, biological sex, race/ethnicity, education, BMI, HIV viral suppression, and Nadir CD4+ T-cell counts). Models were fit with restricted maximum likelihood using the *lmerTest* package [40], and statistical inference was based on Wald tests. The fixed-effects β coefficient was interpreted as a difference in neurocognitive T-scores based on a one-quartile increase in food scores, adjusting for covariates, with a positive β coefficient indicating higher neurocognitive T-scores, and a negative coefficient indicating lower neurocognitive T-scores. Only candidate foods that reached significance in LME tests across ≥ 2 neurocognitive domains were interpreted as potential dietary markers of neurocognition in PWH.

Exploratory analyses focused on the subset of 37 participants with repeated dietary assessments (89 total visits) to follow up on the food items significantly associated with neurocognition in the full sample and examine potential longitudinal patterns. Consistency of food scores across visits was first assessed by calculating the median within-person SD for each food score, with values <0.5 on the 0 to 10 scale indicating high within-person consistency over time. To examine whether dietary changes were associated with subsequent neurocognitive changes, dietary change between visits 1 and 2 was quantified by log2 fold change (log2FC) in food scores. Linear regression models were then fit to investigate associations between food log2FC changes and visit 2 global- and domain-specific neurocognitive T-scores, adjusting for corresponding visit 1 neurocognitive scores. Similar to the LMEs conducted in the full sample, the longitudinal LMEs included a participant-specific random intercept.

Because only 4 of the 104 participants (3.8%) who completed the BDI-II had repeated assessments, there was insufficient repeated-measures information to support estimation of participant-level random effects. BDI-II analyses were, therefore,

conducted using a cross-sectional design, with only the first observation retained for the 4 participants with repeated assessments, resulting in an analytic sample of 104 independent observations from 104 participants. Spearman correlations were used to screen associations between food scores and the BDI-II total score and subscale scores. A food was considered a candidate if its food score was nominally associated with ≥1 BDI-II outcome (Spearman correlation, $P < 0.05$) and the signs of the Spearman correlation coefficients (ρ) were consistent across all BDI-II outcomes (i.e., all positive or all negative). For each candidate food, linear regression models were subsequently fitted for the BDI-II total score and each subscale score, adjusting for relevant covariates. Regression β coefficients represented differences in BDI-II scores per one-quartile increase in food scores, with positive coefficients indicating higher (worse) depression, and negative coefficients indicating lower (better) depression. Given the exploratory nature of this study and relatively small sample size, multiple comparison corrections were applied to results, but our final interpretations of findings were based on nominal results. Supplemental Table 1 summarizes the models conducted and findings.

Results

Participant characteristics

Table 1 presents participant clinical and HIV disease characteristics. Global cognition T-scores were below average (mean = 46.10; SD = 7.69), and 42% of participants were classified as having NCI (GDS ≥0.50). Depressive symptoms were slightly elevated, with an average (BDI-II mean = 9.57; SD = 9.43), and 26% of participants endorsed at least mild depression on the BDI-II (>13). Considered together, nearly 50% of participants had evidence of brain health problems (cognitive impairment and/or at least mild depression). In terms of medical characteristics, nearly 40% of participants met criteria for metabolic syndrome (operationalized as ≥3 of the following: increased waist circumference, elevated triglycerides, low HDL-C, elevated blood pressure, and elevated fasting glucose) [41]. The mean BMI was in the overweight range (mean = 28.25; SD = 7.06), and average Charlson Comorbidity Index scores were in the severe range (mean = 5.52; SD = 4.59) [42]. In terms of HIV disease characteristics, 37% of participants had a historical diagnosis of AIDS, 90% were on ART, and virtually all participants on ART were virally suppressed (97%). The average estimated duration of HIV infection was 21 y (SD = 9.57). Participants' median current and Nadir CD4+ T-cell counts were 675.5 (IQR = 472–863.5) and 190 (IQR = 45–341), respectively.

TABLE 1
Participant demographics and clinical characteristics at visit 1 (N = 170)

Demographics	
Age (y), mean (SD)	55.86 (11.67)
Education, mean (SD)	13.89 (2.90)
Sex (% male)	84.12
Race/ethnicity, %	
White	46.47
Black	16.47
Hispanic/Latino	37.06
Neurocognitive	
Global cognition T-score, mean (SD)	46.10 (7.69)
Executive functioning T-scores, mean (SD)	46.09 (9.55)
Verbal fluency T-scores, mean (SD)	48.23 (9.35)
Processing speed T-scores, mean (SD)	48.00 (9.53)
Learning T-scores, mean (SD)	42.36 (10.16)
Working memory T-scores, mean (SD)	45.67 (9.25)
Recall T-scores, mean (SD)	43.71 (9.81)
Motor speed T-scores, mean (SD)	46.98 (11.85)
NCI (% GDS ≥0.50)	41.76
Depression[1]	
BDI-II total, mean (SD)	9.57 (9.43)
BDI-II affective subscale, mean (SD)	1.76 (2.13)
BDI-II apathy subscale, mean (SD)	2.16 (2.29)
BDI-II cognitive subscale, mean (SD)	2.73 (4.24)
BDI-II somatic subscale, mean (SD)	5.08 (4.02)
Depressed mood (% BDI-II >13)	26.17
Medical	
Metabolic syndrome (%)	38.83
Charlson Comorbidity Index, mean (SD)	5.52 (4.59)
BMI, mean (SD)	28.50 (7.25)
HIV disease/treatment	
AIDS diagnosis (%)	37.06
Est. duration HIV (y), mean (SD)	21.41 (9.57)
CD4+ T cells (cells/μL), median (IQR)	675.5 (472.0–863.5)
Nadir CD4+ T-cells (cells/μL), median (IQR)	190 (45–341)
ART (% on)	90
Plasma VL (log10), median (IQR)	0 (0–1.47)
Plasma VL (% < 50 cp/mL)	96.82

Abbreviations: ART, antiretroviral therapy; BDI-II, Beck's Depression Inventory–II; GDS, Global Deficit Score; NCI, neurocognitive impairment; VL, viral load.
[1] BDI-II scores were available for a subgroup of 104 participants.

Candidate foods for neurocognition and depression

Using the food readout tool, 86 unique food items (out of a possible 130) were detected across 222 fecal metabolomics samples of 170 PWH. The detected single-food items (e.g., melon) were then organized into mid-level (e.g., pepo) and high-level (e.g., fleshy fruit) categories based on an established food ontology framework [29]. The same MS/MS features present in carrot, cauliflower, and dill were detected; hence, these foods were categorized into a single category labeled "carotenoid-rich vegetables." For the purposes of this study, only food items spanning low-to-high levels of the ontology were assessed. See a study by Dorrestein et al. [29] for more details on the classification and ontology of food items.

On the basis of univariate screening analyses, 13 food items and 6 higher-level food categories met the multistep criteria for neurocognition and were identified as candidate foods for subsequent linear mixed-effects models, and 5 food items and 4 categories met the multistep criteria for depressive symptoms and were identified as candidate foods for subsequent regression analyses. A complete list of all detected food items from fecal samples across PWH, as well as candidate food items and categories for neurocognition and depression, can be found in Supplemental Data Tables.

Associations of candidate foods with neurocognitive outcomes

Of the 19 candidate food items or categories, the following 7 were found to be significant across ≥2 neurocognitive domains in LME models controlling for relevant covariates (i.e., age, sex, race/ethnicity, education, BMI, HIV viral suppression, and

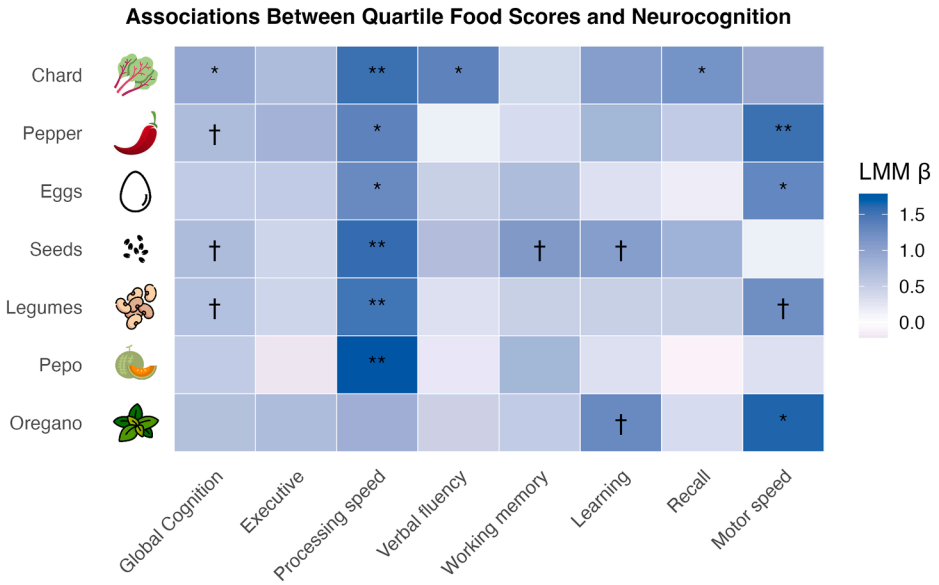

FIGURE 3. Heatmap depicting the positive associations of chard, pepper, eggs, seeds, legumes, pepo, and oregano with global and domain-specific neurocognition. Results of linear regression models controlling for age, sex, race/ethnicity, education, BMI, HIV viral suppression, and Nadir CD4+ T-cell counts, with darker blue colors indicating stronger negative associations with depressive scores (*x*-axis) for each food item (*y*-axis). LMM, linear mixed models. *$P < 0.05$, **$P < 0.01$, $^{\dagger}P < 0.10$.

Nadir CD4+ T-cell counts): *1*) chard, *2*) pepper, *3*) eggs, *4*) seeds, *5*) legumes, *6*) pepo (e.g., watery, fleshy fruits such as melon), and *7*) oregano. Figure 3 shows a summary of food associations with global and domain-specific neurocognitive T-scores. Results by neurocognitive domain are reported below.

Global cognition

The results of LME models adjusted for covariates showed that chard was significantly associated with higher global cognition ($\beta = 0.92$, SE = 0.43, $P = 0.03$). There were also marginally significant associations with pepper ($\beta = 0.70$, SE = 0.38, $P = 0.07$), seeds ($\beta = 0.69$, SE = 0.39, $P = 0.08$), and legumes ($\beta = 0.65$, SE = 0.38, $P = 0.097$). There were no significant associations of eggs, pepo, or oregano with global cognition.

Processing speed

Chard ($\beta = 1.53$, SE = 0.59, $P < 0.01$), pepper ($\beta = 1.36$, SE = 0.53, $P = 0.01$), eggs ($\beta = 1.27$, SE = 0.56, $P = 0.03$), seeds ($\beta = 1.56$, SE = 0.55, $P < 0.01$), legumes ($\beta = 1.50$, SE = 0.54, $P < 0.01$), and pepo ($\beta = 1.78$, SE = 0.54, $P < .01$) were significantly associated with higher processing speed. There was no significant association of oregano with processing speed.

Motor speed

Pepper ($\beta = 1.55$, SE = 0.55, $P < 0.01$), oregano ($\beta = 1.64$, SE = 0.66, $P = 0.02$), and eggs ($\beta = 1.30$, SE = 0.64, $P = 0.05$) were significantly associated with higher motor speed. There was also a marginally significant association of legumes with higher motor speed ($\beta = 1.22$, SE = 0.63, $P = 0.06$). There were no associations of chard, seeds, or pepo with motor speed T-scores.

Other neurocognitive domains

Findings in other domains were less consistent. For verbal fluency, only chard was significantly associated ($\beta = 1.36$, SE = 0.53, $P = 0.01$). Chard was also significantly associated with higher recall ($\beta = 1.17$, SE = 0.59, $P = 0.05$), and oregano was associated with higher learning ($\beta = 1.27$, SE = 0.64, $P = 0.05$). There were no significant associations of food scores with executive functioning or working memory, although seeds were marginally associated with higher working memory ($\beta = 1.09$, SE = 0.58, $P = 0.06$) and learning T-scores ($\beta = 1.05$, SE = 0.59, $P = 0.08$). After False Discovery Rate (FDR) correction, none of the nominally significant models remained significant.

Longitudinal analyses with a subgroup of 37 participants

The 7 food items or categories found to be significantly associated with cognition in the full sample were then investigated further in a subset of 37 participants with repeated visits (total = 89 visits) to explore relationships between changes in food scores and neurocognition over time.

Consistency of food scores over time

Sixty-six foods were categorized as highly consistent (i.e., median within SD <0.5), 46 foods were categorized as moderately consistent (i.e., median within SD <1.0), only 12 foods were categorized as time-varying (i.e., median within 1.0–2.0 SD), and no foods were categorized as highly time-varying (i.e., median within SD ≥2.0). Of our candidate food items, only oregano was time-varying (median within SD = 1.181), whereas the others were all moderately consistent (i.e., chard, legumes, pepo, and pepper) or highly consistent (i.e., seeds, eggs, and betel nut leaf). Supplemental Figure 1 shows

increased, compared with decreased, fecal metabolomics-based food scores between visits 1 and 2 for the 7 candidate food items.

Food change scores and visit 2 neurocognition

Consistent with the LME models with the full sample, increased legume, egg, and pepo food scores were associated with better neurocognitive outcomes at visit 2, even when controlling for visit 1 neurocognition. Specifically, a 2-fold increase in egg metabolomics-based food scores from visit 1 to 2 was significantly associated with higher global cognition ($\beta = 0.724$, SE $= 0.241$, $P = 0.005$), working memory ($\beta = 1.529$, SE $= 0.495$, $P = 0.004$), and verbal fluency ($\beta = 0.990$, SE $= 0.354$, $P = 0.009$). Similarly, increased legume food scores were associated with higher global cognition ($\beta = 0.420$, SE $= 0.155$, $P = 0.010$), executive functioning ($\beta = 0.748$, SE $= 0.237$, $P = 0.003$), and motor speed ($\beta = 0.578$, SE $= 0.239$, $P = 0.023$), and increased pepo food scores were associated with higher executive functioning ($\beta = 0.564$, SE $= 0.220$, $P = 0.015$). Contrary to our findings in the overall sample, a 2-fold increase in pepper food scores was associated with lower global cognition ($\beta = -0.650$, SE $= 0.196$, $P = 0.002$) and processing speed ($\beta = -1.042$, SE $= 0.453$, $P = 0.028$). Figure 4 shows all associations of significant candidate foods with each neurocognitive domain over time. Only the 4 most significant findings remained significant after FDR correction.

Associations of candidate foods with depressive symptoms

Of the 9 candidate food items or categories, the following 6 were found to be associated with depressive outcomes in linear regression models controlling for relevant covariates (i.e., age, sex, race/ethnicity, education, BMI, HIV viral suppression, and Nadir CD4+ T-cell counts): *1*) shrimp, *2*) eggs, *3*) jicama, *4*) carotenoid-rich vegetables (e.g., carrots, cauliflower, and dill), *5*) persimmon, and *6*) berries. Figure 5 shows a summary of food associations with BDI-II total and subscale scores. No models remained significant after FDR correction. Results by depressive domain are reported below.

BDI-II total scores

The results of linear regression models controlling for relevant covariates showed that higher egg scores were significantly associated with lower (better) BDI-II total scores ($\beta = -2.09$, SE $= 0.91$, $P = 0.02$). There were also marginally significant negative associations of shrimp ($\beta = -1.70$, SE $= 0.93$, $P = 0.07$) and jicama ($\beta = -1.47$, SE $= 0.87$, $P = 0.10$) with BDI-II total scores.

Affective symptoms

Higher jicama ($\beta = -0.42$, SE $= 0.19$, $P = 0.03$) and egg food scores ($\beta = -0.41$, SE $= 0.20$, $P = 0.05$) were significantly associated with lower BDI-II affective subscale scores. There was also a marginally significant negative association of shrimp ($\beta = -.38$, SE $= 0.21$, $P = 0.07$) with BDI-II affective subscale scores.

Apathy symptoms

Higher shrimp ($\beta = -0.55$, SE $= 0.21$, $P = 0.01$), egg ($\beta = -0.46$, SE $= 0.21$, $P = 0.03$), and jicama food scores ($\beta = -0.40$, SE $= 0.20$, $P = 0.050$) were significantly associated with lower BDI-II apathy subscale scores.

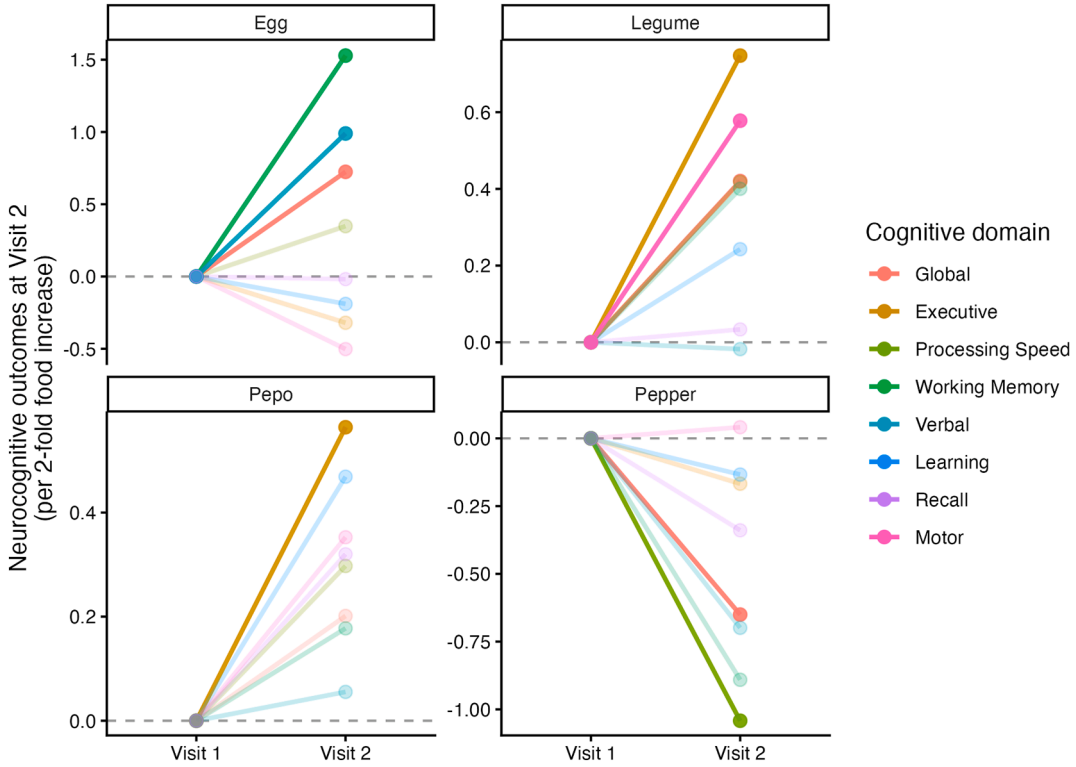

FIGURE 4. Associations between changes in food scores and neurocognitive outcomes over time. Results of linear regression models examining associations between log2 fold changes in food scores and visit 2 neurocognitive T-scores, adjusting for visit 1 neurocognitive T-scores. Slopes represent the direction and magnitude of associations, with darker lines indicating significant associations ($P < 0.05$).

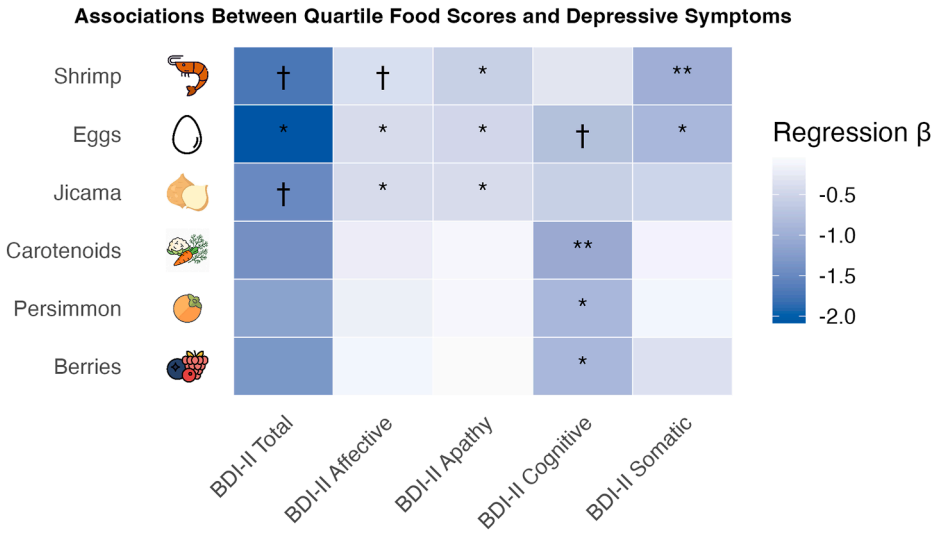

FIGURE 5. Heatmap depicting the associations of eggs, shrimp, jicama, carotenoid-rich vegetables, persimmon, and berries with lower (better) depressive total and subscale scores. Results of linear regression models controlling for age, sex, race/ethnicity, education, BMI, HIV viral suppression, and Nadir CD4+ T-cell counts, with darker blue colors indicating stronger negative associations with depressive scores (*x*-axis) for each food item (*y*-axis). *$P < 0.05$, **$P < 0.01$, $^{\dagger}P < 0.10$. BDI-II, Beck's Depression Inventory–II.

Cognitive symptoms

Higher carotenoid-rich vegetable ($\beta = -1.05$, SE = 0.40, $P < 0.01$), persimmon ($\beta = -0.89$, SE = 0.40, $P = 0.03$), and berry food scores ($\beta = -0.87$, SE = 0.41, $P = 0.04$) were significantly associated with lower BDI-II cognitive subscale scores.

Somatic symptoms

Higher shrimp ($\beta = -1.01$, SE = 0.37, $P < 0.01$) and egg food scores ($\beta = -0.89$, SE = 0.40, $P = 0.02$) were significantly associated with lower BDI-II somatic subscale scores.

Discussion

The current study leveraged a metabolomics-based tool to derive semiquantitative food scores from fecal samples and assess food-brain health associations across 222 samples provided by 170 PWH enrolled in cohort studies at the HIV Neurobehavioral Research Program (HNRP). Overall, the tool detected 86 simple foods and provided estimates of their relative fecal abundances across samples. For neurocognition, higher scores for vegetable/plant food items (e.g., chard, oregano), fruit (e.g., pepo), seeds, legumes, and eggs were associated with better neurocognitive outcomes, with preliminary evidence for longitudinal associations in a subset of participants with multiple study visits. Similarly, higher scores for vegetables (e.g., jicama, pepper, and carotenoid-rich vegetables), fruit (e.g., persimmon, berries), and eggs were associated with lower (better) depressive outcomes. In addition, higher shrimp scores were associated with fewer depressive symptoms.

Our findings using a metabolomics-based approach are generally consistent with prior dietary literature on brain health in both HIV-specific and non-HIV populations. Vegetables, fruits, legumes, seeds, and certain lean proteins (e.g., shrimp) are all considered healthy brain food by the Mediterranean-Dietary Approaches to Stop Hypertension (DASH) Intervention for Neurodegenerative Delay (MIND) diet and others [8,12]. Notably, vegetables, legumes, eggs, and fruit have previously been associated with brain health in PWH, although associations with vegetable intake have been the most consistently observed across neurocognitive and mental health [23–26]. Evidence from the general population also supports associations of fruits and vegetables, legumes, seeds, seafood, and eggs with favorable neurocognitive or mental health outcomes [14,43–47]. These foods have been linked to several biological processes potentially relevant to brain health, including inflammation, oxidative stress, and lipid metabolism [14,43–47]; however, these mechanisms were not examined in the current study, and whether they contribute to the associations observed among PWH remains unknown.

One major advantage of this study is the use of fecal metabolomics-based food scores as a complementary approach to traditional self-reported dietary assessments, which can be affected by recall and reporting error [27,48]. To our knowledge, this is the first study to use untargeted fecal metabolomics data to examine diet-related signatures in PWH, and one of the first to examine associations of specific food items with HIV brain health outcomes. The semiquantitative nature of the food scores allowed us to examine the magnitude of associations between food scores and brain health outcomes. For example, a one-quartile increase in the egg food score was associated with an over 1-point increase in processing speed and motor speed T-scores and a 2-point decrease in overall depressive symptoms. Many of the identified foods (e.g., vegetables/herbs, fruits, seeds, legumes, and eggs) are relatively inexpensive and could represent practical candidates for future dietary research in PWH. Focusing on specific food items instead of full diet changes

may also increase the feasibility of future intervention. Thus, the results of this study have implications for informing future neuroHIV dietary interventions, but longitudinal and interventional studies incorporating complementary measures of dietary intake are needed to confirm our findings.

Of note, the significant food-neurocognition associations were primarily observed in domains consistent with a subcortical pattern of deficits typically impacted by HIV disease [49]. Specifically, speeded neurocognitive domains, such as processing speed and psychomotor speed, had the strongest relationships with food. There is significant evidence that the subcortical brain regions carry the highest levels of HIV viral load, thereby contributing to neurocognitive and psychomotor slowing [50]. The chronic systemic inflammation associated with HIV infection may interact with or exacerbate this pattern of neurocognitive deficits, with prior studies showing strong relationships of elevated inflammation with neurocognitive and psychomotor slowing in PWH [10,50,51]. Future studies incorporating inflammatory biomarkers and control groups of people without HIV will be needed to determine whether HIV-related biological processes contribute to these associations.

As for depression, past studies have found >50% comorbidity between depression and NCI in PWH [1], likely due to their shared underlying mechanism of chronic systemic inflammation. Indeed, vegetables (e.g., carotenoid-rich vegetables and jicama), fruit (e.g., persimmon and berries), shrimp, and eggs were associated with reduced depressive symptoms, and a potential mechanism to explain this association may be their anti-inflammatory or neuroprotective properties [12,44,45,47]. However, future studies still need to examine causal relationships between these identified food items and neuropsychiatric outcomes in PWH via longitudinal methods or clinical diet trials.

Our study has several limitations. First, our study was primarily cross-sectional, with only a small subset (i.e., 37 participants) contributing repeated measures, which limits the interpretability of the findings. Although we found consistencies in associations of legumes, eggs, and fruit with outcomes, our findings regarding pepper were inconsistent, with our cross-sectional analyses finding consistent positive associations with neurocognition, and our longitudinal analyses finding consistent negative ones. It is possible that pepper quantity matters, such that only moderate amounts may confer benefits. Conversely, it is also possible that the participants with repeated measures consumed different forms of pepper with potentially harmful effects (e.g., habanero compared with bell peppers), but our food readout tool lacked the sensitivity to discriminate between different types. Second, we did not have information on participants' income levels. Although we controlled for other relevant socioeconomic variables, such as education, income could impact the participant's access to healthy foods as well as their brain health, thus serving as a potential confounder. Third, our sample was relatively small and consisted of predominantly male PWH in the Southern California areas, limiting the generalizability of our findings to female PWH or PWH in other geographic regions. However, it is notable that our findings closely mirrored those of Rubin et al. [23], which included only females with HIV from 6 sites across the United States, and those of Nie et al. [24], performed with male and female PWH in Jinhua City, China [23,24]. Fourth, our food readout tool was developed from untargeted metabolomic profiling of simple food items and does not provide information on complex, multi-ingredient foods. There is some evidence suggesting that overall diet quality or consumption of processed foods compared with unprocessed whole foods may be more relevant to some health outcomes than individual foods [4]. Future studies should incorporate complementary self-reported food diaries on complex foods and overall dietary patterns. Moreover, our food readout tool still lacked the specificity to discriminate between similar food items (e.g., carrot compared with cauliflower). We are currently working to improve our tool's detection abilities by refining our algorithmic classifications of food items and increasing the reference database over time. Fifth, this was a retrospective study of preexisting data, and the parent study did not incorporate food diaries or any other self-report measures to confirm dietary intake. Although our food readout tool has shown good concordance with self-reported intake in previous dietary interventions on people without HIV [29], more research is needed to confirm this in PWH. Finally, there were no available data on inflammation for the participants in this study. Inflammation, a key contributor to the elevated rates of NCI and depression in PWH [9], would be important for elucidating underlying mechanisms in the observed food-brain health associations.

In conclusion, the current study examined associations between fecal metabolomics-based signatures of specific foods or categories and neurocognitive and depressive symptoms among 170 PWH. Higher scores for several vegetables, fruits, seeds, legumes, eggs, and shrimp were associated with more favorable brain health outcomes. These findings identify candidate foods for further investigation and demonstrate the potential utility of fecal foodomics as a complementary approach for studying diet-related signatures in PWH. In future studies, we will measure inflammation as a mechanism of effects and employ a longitudinal design to assess causal relationships between the identified foods and brain health outcomes in a larger, more representative sample of PWH.

Author contributions

The authors' responsibilities were as follows – CXW, HG, PCD: designed research; CXW, HG, JZ, HM-R: conducted research; PCD, DJM, RJE: provided essential materials; CXW, HG: analyzed data; CXW, HG, TAWS: wrote the paper; CES, HM-R, JEI, RKH, DJM, SLL, MC, DRF, MG, AHM, RK, RJE: reviewed and edited the paper; PCD: took primary responsibility for final content; and all authors: read and approved the final manuscript.

Conflict of interest

PCD is a scientific advisor and have equity to Cybele, Sirenas, and BileOmix. PCD is a scientific co-founder, and an advisor, and holds equity and/or has received income through Enveda, Ometa, and Arome. Rob Knight reports a relationship with BiomeSense, Inc. that includes: board membership, consulting or advisory, and equity or stocks. Rob Knight reports a relationship with GenCirq that includes: board membership and equity or stocks. RK reports a relationship with Cybele that includes: consulting or advisory and equity or stocks. AHM reports a relationship with Freedom Biosciences that includes: consulting or advisory. AHM reports a relationship with Kyowa Kirin

that includes: consulting or advisory. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data described in the manuscript, code book, and analytic code will be made available upon request, pending a resource request that can be accessed at https://www.cognitoforms.com/HNRP/HIVNeurobehavioralResearchProgramResourceRequest.

Declaration of Generative AI and AI-assisted Technologies in the Writing Process

During the preparation of this work, the authors used ChatGPT to edit existing statistical R code, figures, and the manuscript. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tjnut.2026.101873.

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