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Food insecurity and neurocognitive function among women living with or at risk for HIV in the United States

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ABSTRACT

Background: Neurocognitive impairment (NCI) persists among women living with HIV. Food insecurity is also common among women and may be an important modifiable contributor of NCI.

Objective: The goal of this study was to determine the association of food insecurity with neurocognitive function among women living with or without HIV.

Methods: From 2013 to 2015, we analyzed data from a cross-sectional sample from the Women's Interagency HIV Study (WIHS). Measures included food insecurity and a comprehensive neuropsychological test battery assessing executive function, processing speed, attention/working memory, learning, memory, fluency, and motor function. We conducted multivariable linear regressions to examine associations between food insecurity and domain-specific neurocognitive performance, adjusting for relevant sociodemographic, behavioral, and clinical factors.

Results: Participants ($n = 1,324$) were predominantly HIV seropositive (68%), Black/African-American (68%) or Hispanic (16%), and low income (48% reported <$12,000/y), with a median age of 49.6 y (IQR = 43.1, 55.5). Approximately one-third (36%, $n = 479$) were food insecure. Food insecurity was associated with poorer executive function ($b = -1.45$, SE = 0.58, $P \leq 0.01$) and processing speed ($b = -1.30$, SE = 0.59, $P \leq 0.05$). HIV serostatus modified the association between food insecurity and learning, memory, and motor function (P values <0.05). Food insecurity was positively associated with learning among women living with HIV ($b = 1.58$, SE = 0.77, $P \leq 0.05$) and negatively associated with motor function among HIV-negative women ($b = -3.57$, SE = 1.08, $P \leq 0.001$).

Conclusions: Food insecurity was associated with domain-specific neurocognitive function in women, and HIV serostatus modified associations. Food security may be an important point of intervention for ethnically diverse women with low socioeconomic status. Longitudinal studies are warranted to determine potential pathways by which food insecurity is associated with neurocognitive function among women living with or at risk for HIV. *Am J Clin Nutr* 2020;112:1280–1286.

Keywords: food insecurity, HIV, neurocognitive function, neurocognitive impairment, women

Introduction

Food insecurity, defined as limited access to and ability to acquire food, is highly prevalent among women in the United States (1). As a major contributor to poorer health outcomes, food insecurity disproportionally affects women due to gender-based inequality in access to and control over resources (1–3). Emergent research demonstrates that food insecurity is associated with neurocognitive impairment (NCI) across different age groups, which may further deleterious health outcomes. For example, food insecurity may compromise domain-specific neurocognitive functions that are important for food procurement and preparation, potentially contributing to a vicious cycle of food insecurity, NCI, and poor health. In a recent systematic review of food insecurity and cognitive function across 10 studies, food insecurity was associated with lower executive function, and findings across studies were mixed regarding associations with memory and attention (4). In 1 study, Gao and colleagues (5) found food insecurity to be associated with lower executive function but not memory or attention. In a longitudinal study with the same dataset, food insecurity was not only associated with neurocognitive decline over time but faster decline in visual-spatial ability, verbal fluency, and general neurocognitive

function among individuals reporting very low food security (6). Altogether, the evidence indicates an association between food insecurity and domain-specific neurocognitive function.

NCI is common among people living with HIV (7, 8). NCI is associated with HIV-related risk factors that compromise HIV care and treatment (9). Food insecurity among women living with HIV is associated with higher viral load, lower CD4 counts, increased acute care use, and higher mortality (10–13). Compared with their male counterparts, women living with HIV demonstrated poorer neurocognitive performance on procedural learning tasks (14) and may be more vulnerable to developing verbal learning and verbal memory deficits (15) due to social-structural inequality (e.g., educational attainment) and gender-based violence (16).

Women living with HIV may be particularly vulnerable to food insecurity (17). Little research has focused on the role of food insecurity in neurocognitive function in women, and even less is known regarding its potential interaction with living with HIV (18). The only known study of food insecurity and NCI that included a subset of people living with HIV showed that food insecurity was significantly associated with delayed recall but not with verbal fluency; HIV serostatus was not a significant effect modifier (19).

In the present study, we examined the role of food insecurity on neurocognitive function among a cohort of largely low-income and ethnically diverse women living with or without HIV from the Women's Interagency HIV Study (WIHS). Based on the available research with HIV-seronegative individuals, we hypothesized that food insecurity would be associated with lower executive function and memory among both HIV-seropositive and HIV-seronegative women. We further hypothesized that HIV serostatus may modify the associations between food insecurity and neurocognitive function.

Methods

Participants

Participants were from the WIHS, a multisite prospective cohort established in 1994 that enrolled women living with HIV and demographically similar controls without HIV infection (20). As part of this ongoing longitudinal study, women completed questionnaires, interviews, and laboratory investigations every 6 mo. A cross-sectional sample of 1346 (918 HIV seropositive) participants enrolled in the WIHS between April 2013 and March 2015 at 8 WIHS sites: San Francisco/Bay Area, CA; Bronx/Manhattan, NY; Brooklyn, NY; Washington, DC; Chicago, IL; Chapel Hill, NC; Miami, FL; and Atlanta, GA (see **Supplemental Figure 1** for study flow chart). Details of cohort recruitment, demographics, and retention have been previously published (20, 21). Participants provided written informed consent and were compensated for participation. This study was approved by the institutional review board at each study site's institution and by the WIHS Executive Committee.

Measures

Primary independent variables.

The 2 primary variables of interest were HIV serostatus and food insecurity, which were assessed using the Household Food Security Survey (HFSS) module, a validated scale considered the reference measure of food security in the United States (22, 23). This 18-item scale captures uncertainty about food supply, sufficiency of food quantity, and diet quality over the previous 12 mo (23). The internal consistency of the measure was high (Cronbach's $\alpha = 0.90$), and the measure contained

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WIHS (Principal Investigators): UAB-MS WIHS (Mirjam-Colette Kempf and Deborah Konkle-Parker), U01-AI-103401; Atlanta WIHS (Ighovwerha Ofotokun, Anandi Sheth, and Gina Wingood), U01-AI-103408; Bronx WIHS (Kathryn Anastos and Anjali Sharma), U01-AI-035004; Brooklyn WIHS (Deborah Gustafson and Tracey Wilson), U01-AI-031834; Chicago WIHS (Mardge Cohen and Audrey French), U01-AI-034993; Metropolitan Washington WIHS (Seble Kassaye and Daniel Merenstein), U01-AI-034994; Miami WIHS (Maria Alcaide, Margaret Fischl, and Deborah Jones), U01-AI-103397; UNC WIHS (Adaora Adimora), U01-AI-103390; Connie Wofsy Women's HIV Study, Northern California (Bradley Aouizerat and Phyllis Tien), U01-AI-034989; WIHS Data Management and Analysis Center (Stephen Gange and Elizabeth Golub), U01-AI-042590; Southern California WIHS (Joel Milam), U01-HD-032632 (WIHS I–WIHS IV). The WIHS is funded primarily by the National Institute of Allergy and Infectious Diseases (NIAID), with additional co-funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), the National Cancer Institute (NCI), the National Institute on Drug Abuse (NIDA), and the National Institute on Mental Health (NIMH). Targeted supplemental funding for specific projects is also provided by the National Institute of Dental and Craniofacial Research (NIDCR), the National Institute on Alcohol Abuse and Alcoholism (NIAAA), the National Institute on Deafness and Other Communication Disorders (NIDCD), and the NIH Office of Research on Women's Health. WIHS data collection is also supported by UL1-TR000004 (UCSF CTSA), P30-AI-050409 (Atlanta CFAR), P30-AI-050410 (UNC CFAR), and P30-AI-027767 (UAB CFAR).

Supplemental Figure 1 is available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

LHR and SDW are co-senior authors.

Data are from the Women's Interagency HIV Study (WIHS), whose authors may be contacted atJHSPH.wdmac@jhu.edu. Data are available to all investigators in 2 ways. The WIHS Public Data Set provides de-identified data (meeting HIPAA criteria) that may assist anyone interested in public health research. Access to the WIHS Public Data Set may be obtained by filling out the WIHS Public Use Data Set Request form at https://statepi.jhsph.edu/wihs/wordpress/, under "Investigators". Data are updated annually. Alternatively, the WIHS welcomes collaborations with investigators and with other cohorts, both nationally and internationally, who can access the entire richness of data and specimens that are available. To collaborate, a concept sheet must be submitted, reviewed, and approved by the WIHS Executive Committee. This is a requirement of cohort institutional review board (IRB) approvals ensuring secure, timely, and ethical sharing of the cohort's data.

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Abbreviations used: aOR, adjusted OR; HVLT, Hopkins Verbal Learning Test; NCI, neurocognitive impairment; PTSD, post-traumatic stress disorder; WIHS, Women's Interagency HIV Study.

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separate items for adults and children to assess household food insecurity (23). Preliminary examination did not demonstrate a reliable dose-response relation between food insecurity and NCI across domains. To aid in interpretability of current results, we treated the construct of food insecurity as a binary variable, with high food security (or being food secure) as the reference category compared with marginal, low, and very low food security (i.e., being food insecure), consistent with prior research (24).

Primary outcome.

We assessed neurocognitive performance via a comprehensive neuropsychological test battery that evaluated 7 domains cross-sectionally: *1*) executive function assessed with Trail Making Test Part B (25) and the Stroop Test interference trial (26), *2*) fine motor skills using the Grooved Pegboard test (27), *3*) learning via the Hopkins Verbal Learning Test (HVLT) (28), *4*) memory via the HVLT (28), *4*) attention/working memory using the Letter-Number Span Task (29), *5*) verbal fluency using the Controlled Oral Word Association Test and animal fluency (30), *6*) processing speed using the Stroop Test Trial 2 (26), and *7*) the Symbol Digit Modalities Test (31). A global performance score for participants with data for ≥4 domains was created (32).

Consistent with prior studies (33–35), neurocognitive measures were quantified via continuous T-scores (mean = 50, SD = 10) that are demographically corrected normative standards that adjusted for age, race/ethnicity, education, and previous administration of the neurocognitive battery (36–38). Due to the time-intensive nature of administering the neurocognitive battery with the entire sample of women, it was administered to a subset (~25%) of the participants at each of the 4 semiannual assessment visits. Thus, a complete cross-sectional dataset was constructed from 4 consecutive assessment visits; details on the study design are published elsewhere (33).

Covariates.

We selected potential covariates based on previous research and included annual household income, employment status, smoking status (current smoker vs. not), heavy alcohol use (defined as ≥7/wk) (39), recent illicit drug use (cocaine, crack, or heroin use in the last 6 mo or since the last WIHS assessment), and BMI categories (continuous per kg/m^2). Mental health covariates included depression measured using the Centers of Epidemiology Study–Depression (CES-D) scale (40), and post-traumatic stress disorder (PTSD) measured using the PTSD checklist, or PCL-C (41). Study site was not considered as a confounder as adjusting for it could potentially remove some of the association of empirical interest in the present study and since most salient socioeconomic status features are controlled by income, race, and age. Finally, we did not consider HIV-related outcomes (e.g., time on antiretroviral therapy, virologic suppression, CD4 count, adherence to antiretroviral therapy) as potential confounders because they are either not associated with food insecurity in the present analyses or as shown by prior research (10) or they are potentially on the causal pathway in our conceptual model (17).

Statistical analyses

First, we examined histograms and scatterplots (not shown) of the outcome variables, which showed scores to be normally distributed. Next, using bivariate and multivariable linear regression models, we examined the independent contribution of food insecurity and HIV serostatus on neurocognitive function. We then examined whether HIV serostatus modified associations between food insecurity and neurocognitive function by adding in an interaction term (HIV by food insecurity) into the models. Interaction terms that were not significant at $P < 0.05$ were removed from the models. BMI, mental health, alcohol use, and smoking covariates were excluded in the multivariable models as these covariates were not significantly associated with the outcomes in bivariate analyses (data not shown) and their presence did not promote parsimony in the multivariable models. In all models, we adjusted for annual household income, employment status, and illicit drug use since the last visit (6 mo ago). Race/ethnicity, age, and education attainment were accounted for during the construction of neurocognitive domain T-scores and were thus not included in the final multivariable models. We conducted analyses using StataCorp Stata Statistical Software, release 14 (StataCorp LP).

Results

A total of 1346 women were included in this study. Ages ranged from 29 to 81 y, with the median age being 49.6 y (IQR: 43.1, 55.5). The sample was predominantly HIV seropositive (68%), Black/African-American (68%), or Hispanic (16%). A majority of the sample reported low annual household income (69% reported <$24,000/y) and being unemployed (64%). **Table 1** presents demographic information for the overall sample and by food security status (food secure vs. food insecure).

Adjusted multivariable linear regression models revealed statistically significant negative associations between food insecurity and executive function ($b = -1.45$, SE = 0.58), processing speed ($b = -1.30$, SE = 0.59), and motor function ($b = -1.68$, SE = 0.62). Relative to being HIV seronegative, living with HIV was associated with poorer executive function ($b = -1.15$, SE = 0.59) and poorer attention/working memory ($b = -1.63$, SE = 0.62). An ordinal logistic regression analysis with 95% CIs revealed that living with HIV was also associated with lower odds of global function relative to being HIV seronegative [adjusted OR (aOR): 0.70; 95% CI: 0.56, 0.87]. Adjusted multivariable linear regression models with the interaction term (HIV by food insecurity) revealed statistically significant interaction effects on learning ($b = 3.09$, SE = 1.35), memory ($b = 2.76$, SE = 1.32), and motor function ($b = 2.76$, SE = 1.29). There were no statistically significant interaction effects on executive function ($b = -0.35$, SE = 1.22), processing speed ($b = 1.34$, SE = 1.22), attention/working memory ($b = 1.38$, SE = 1.27), verbal fluency ($b = -0.40$, SE = 1.18), or global function (aOR: 1.10; 95% CI: 0.70, 1.72) (all P values >0.10). **Table 2** presents only the adjusted multivariable linear regression models where the interaction effect was not statistically significant.

From the adjusted models for learning, memory, and motor function, we calculated the coefficients for food insecurity for

TABLE 1 Demographic characteristics by food-security status[1]

	All	Food secure	Food insecure	P[2]
n	1346	845	479	
HIV serostatus, n (%)				
Negative	428 (31.8)	273 (32.3)	146 (30.5)	0.49
Positive	918 (68.2)	572 (67.7)	333 (69.5)	
Median (IQR) age at visit, y	49.6 (43.1, 55.5)	50.3 (44.2, 56.0)	48.1 (41.9, 54.5)	<0.01
Race/ethnicity, n (%)				
White	146 (10.9)	91 (10.8)	51 (10.6)	0.01
Hispanic	220 (16.4)	152 (18.0)	66 (13.8)	
African-American/Black	914 (68.1)	574 (67.9)	330 (68.9)	
Other	62 (4.6)	28 (3.3)	32 (6.7)	
Employment status, n (%)				
Unemployed	854 (63.8)	480 (56.9)	359 (75.1)	<0.01
Employed	484 (36.2)	363 (43.1)	119 (24.9)	
Crack, cocaine, and/or heroin use since last visit, n (%)				
No	1225 (91.8)	791 (93.7)	424 (88.9)	<0.01
Yes	109 (8.2)	53 (6.3)	53 (11.1)	
Annual household income, n (%)				
≤$6000 or less	173 (13.3)	95 (11.4)	78 (16.5)	<0.001
$6001–$12,000	453 (34.8)	255 (30.7)	198 (42.0)	
$12,001–$18,000	172 (13.2)	104 (12.5)	68 (14.4)	
$18,001–$24,000	98 (7.5)	59 (7.1)	39 (8.3)	
$24,001–$30,000	87 (6.7)	57 (6.9)	30 (6.4)	
$30,001–$36,000	76 (5.8)	53 (6.4)	23 (4.9)	
$36,001–$75,000	159 (12.2)	124 (14.9)	35 (7.4)	
≥$75,001	85 (6.5)	84 (10.1)	1 (0.2)	

[1] $n = 1346$. Cells may not add up to total because of missing values.
[2] Statistical tests of difference were Pearson's chi-square except for age at visit, which was Wilcoxon rank-sum test.

each HIV serostatus (**Table 3**). We found a statistically significant positive association between learning and food insecurity for those living with HIV ($b = 1.58$, $P \leq 0.05$), but a statistically significant negative association between motor function and food insecurity for those who are HIV seronegative ($b = -3.57$, $P \leq 0.001$). There were no other statistically significant domain-specific effect modifications by HIV serostatus. HIV-seronegative women who were food insecure performed consistently worse than those who were food secure, although differences were only statistically significant for motor function. For HIV-seropositive women, patterns were not consistent across learning, memory, and motor function by food security. **Figures 1–3** show the estimated mean T-scores for learning, memory, and motor function by HIV serostatus and food security status.

Discussion

Food insecurity was associated with domain-specific neurocognitive performance among a sample of HIV-seronegative and -seropositive women who were predominantly Black/African American and living below the federal poverty level. Findings illustrate a complex interplay between food insecurity and neurocognitive function in relation to HIV among women. Our hypothesis that food insecurity would be associated with lower executive function, memory, and verbal fluency, irrespective of HIV serostatus, was partially supported: adjusted analyses showed that being food insecure (vs. food secure) in the past year was significantly associated with lower scores on executive function and processing speed. Relative to HIV-seronegative

TABLE 2 Adjusted associations between food security, HIV serostatus, and neurocognitive function outcomes[1]

	Food insecurity (high security ref)	HIV seropositive (HIV seronegative ref)
Executive function ($n = 1254$)	−1.45** (0.58)	−1.15* (0.59)
Processing speed ($n = 1267$)	−1.30* (0.59)	−0.83 (0.59)
Attention/working memory ($n = 1183$)	0.11 (0.61)	−1.63** (0.62)
Verbal fluency ($n = 1256$)	−0.33 (0.57)	−0.32 (0.57)
Global function ($n = 1260$)	0.97 (0.78, 1.20)	0.70** (0.56, 0.87)

[1] Values are *b* (SEs) unless otherwise indicated. *ref*, reference group in the regression analysis. The first 4 models were multivariable linear regression analyses with unstandardized regression coefficients (*b*) and SEs; the last model was an ordinal logistic regression, which produced an adjusted OR with 95% CI. All models adjusted for employment, crack cocaine and/or heroin use, and annual income. All T-scores were adjusted for age, race/ethnicity, education, and the number of times the measure was previously administered. Sample size (*n*) differs across neurocognitive domains because not all participants completed all cognitive tests due to participant refusal, neuropathy, or missed visit.
$^{**}P \leq 0.01$, $^{*}P \leq 0.05$.

TABLE 3 Adjusted associations between food insecurity and learning, memory, and motor function outcomes for HIV-seropositive and HIV-seronegative women[1]

	HIV-seropositive	HIV-seronegative
Learning (n_{HIV+} = 862; n_{HIV-} = 398)	1.58* (0.77)	− 1.51 (1.13)
Memory (n_{HIV+} = 860; n_{HIV-} = 395)	0.80 (0.75)	− 1.96 (1.11)
Motor function (n_{HIV+} = 851; n_{HIV-} = 397)	− 0.81 (0.73)	− 3.57*** (1.08)

[1]Models are multivariable linear regression analyses with unstandardized regression coefficients (*b*) and SEs. All models adjusted for employment, crack cocaine and/or heroin use, and annual income, and included the interaction between food insecurity and HIV serostatus. All T-scores adjust for age, race/ethnicity, education, and the number of times the measure was previously administered . Sample size (*n*) differs across neurocognitive domains because not all participants completed all cognitive tests due to participant refusal, neuropathy, or missed visit. ***$P \leq 0.001$, *$P \leq 0.05$.

women, women living with HIV demonstrated lower performance on executive function, attention/working memory, and global function. Importantly, HIV serostatus was a significant effect modifier on the associations between food insecurity and neurocognitive performance in learning, memory, and motor function. Among HIV-seronegative women, those who were food insecure performed worse than those who were food secure on learning, memory, and motor function, although the differences were only statistically significant for motor function. Food-insecure HIV-seronegative women performed significantly worse on motor function compared with food-secure HIV-seronegative women. An unexpected finding was that food-insecure women living with HIV performed better on learning compared with food-secure women living with HIV. There is evidence that the expected inverse association between food insecurity and neurocognitive function (i.e., greater food insecurity is associated with worse NCI) is not always found (4). In some cases, greater food insecurity was associated with better neurocognitive function, while in other cases, there was no association (4, 5, 42). Further study is needed to examine these complex relations, accounting for the timing of food insecurity, diet, obesity, and stress—indicators previously found to be implicated in HIV serostatus, neurocognitive function, and food security (4, 5, 42, 43).

Our findings are partially consistent with prior research with HIV-seronegative or unknown serostatus individuals, which found that food insecurity was associated with poorer performance in executive function (4, 5). Gao and colleagues (5) found that food insecurity was associated with worse performance on 7 neuropsychological tests including total learning and percentage retention on the Mini-Mental State Examination, 16-word list learning test, letter fluency, and digit span forward and backward, Stroop test, clock drawing, or figure copying. It is important to consider these findings in light of differences in target populations: prior studies were conducted with Puerto Rican individuals living in the United States, while our study sample comprised HIV-seropositive and HIV-seronegative women who were predominantly Black/African American and living below the federal poverty level. Despite the fact that the magnitude of the effects of food insecurity on some of the neurocognitive domains were small, given the significant impact of food insecurity in the general population and especially among people living with HIV, the present effects have important implications if considered on a population basis.

To date, research evidence is scant for understanding how potential social-contextual factors that characterize the environments in which individuals live may interact with HIV to influence neurocognitive function (44). Our findings underscore a

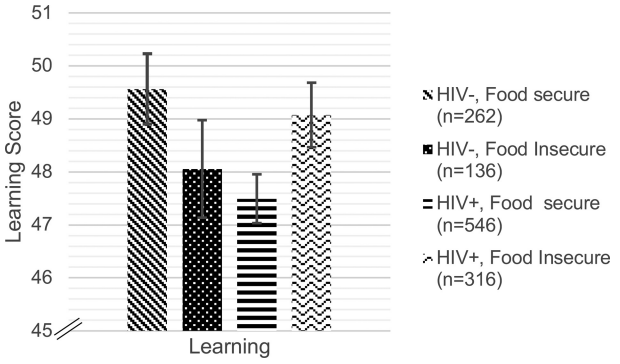

FIGURE 1 Estimated mean learning T-scores by food security status among HIV-seropositive and HIV-seronegative women. Estimated mean T-scores (mean = 50, SD = 10) are demographically corrected normative standards that adjusted for age, race/ethnicity, education, and previous administration of the neurocognitive battery. Learning scores are significantly higher only for HIV-seropositive women who were food insecure compared with those who were food secure.

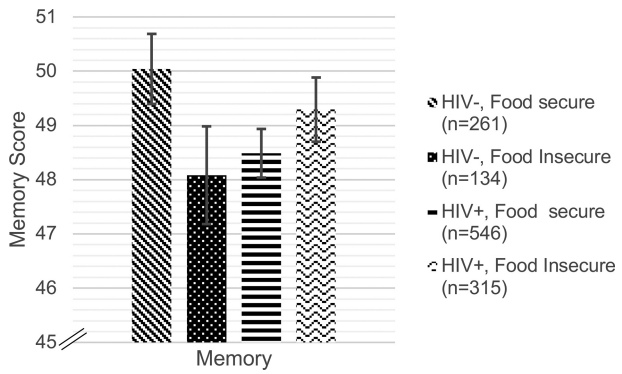

FIGURE 2 Estimated mean memory T-scores by food security status among HIV-seropositive and HIV-seronegative women. Estimated mean T-scores (mean = 50, *SD* = 10) are demographically corrected normative standards that adjusted for age, race/ethnicity, education, and previous administration of the neurocognitive battery. There are no statistically significant differences among the subgroups on memory scores.

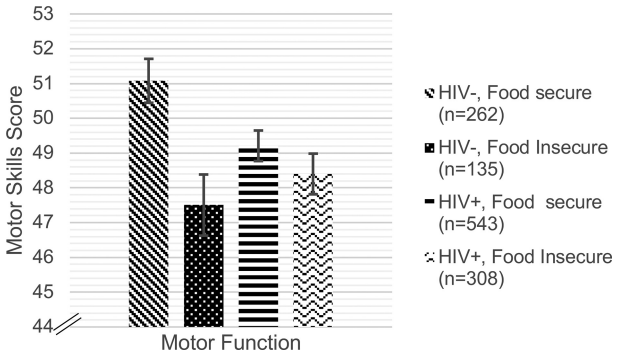

FIGURE 3 Estimated mean motor function T-scores by food security status among HIV-seropositive and HIV-seronegative women. Estimated mean T-scores (mean = 50, SD = 10) are demographically corrected normative standards that adjusted for age, race/ethnicity, education, and previous administration of the neurocognitive battery. Motor scores are lower among food-insecure women, although this difference was statistically significant only for women who were HIV seronegative.

potential bidirectional relation between food insecurity and NCI. For example, experiencing food insecurity may increase subsequent NCI, which, in turn, may compromise food procurement or access, further entrenching women in a persistent cycle of food insecurity and NCI (17, 45). The mechanisms underlying the associations between food insecurity and neurocognitive impairment likely involve multiple pathways such as stress, poor mental health, poor dietary intake, and inflammation (17, 46). In addition, food insecurity is a known contributor to worse HIV virologic control, mediated by nutritional (e.g., poor diet quality), mental health (e.g., stress), and behavioral (e.g., missed clinic visits) pathways, and poor virologic control may, in turn, partially mediate impacts of food insecurity on neurocognitive function (17, 46). Understanding the potential pathways by which food insecurity may impact NCI among people living with HIV, particularly those most vulnerable to its deleterious effects, is among the promising next steps in integrative HIV research.

Limitations

Causality cannot be inferred based on cross-sectional data in the current study. Poorer neurocognitive performance may lead to food insecurity; hence, the direction of the causal path is unclear. Residual confounding could have occurred, particularly from unmeasured underlying health conditions that affect both food insecurity and neurocognition (4). Future research is needed to fully examine mediational pathways of food insecurity on neurocognitive function using longitudinal data.

Conclusions

There is limited research for understanding how the social environment may be related to neurocognitive function among people living with HIV (44). Theoretical and practical considerations suggest that food insecurity represents a social, behavioral, and environmental aspect of HIV and related health outcomes (45). This study represents one of the first forays into examining food insecurity as a social-contextual factor in neurocognitive function among HIV-seropositive and -seronegative women at risk for HIV infection. More research is needed to elucidate potential synergistic effects of food insecurity and HIV on neurocognitive function given the prevalence and impact of food insecurity among women.

The authors' responsibilities were as follows—SDW, AAA, PCT, DK-P, ETG, DM, SL, MC, IO, and MAF: designed or conducted the research; LAS, EAF, LHR, and JYT: analyzed and interpreted the data; JYT, LHR, and SDW: wrote the manuscript; SDW: had primary responsibility for final content; and all authors: read and approved the final manuscript. The authors report no conflicts of interest.

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