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Sex Differences in the Association Between Cerebrovascular Function and Cognitive Health in People Living With HIV in Urban China

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Abstract

Background: Cardiometabolic and cerebrovascular disease are strong independent contributors to cognitive impairment in people living with HIV. Data suggest that cardiovascular risk may play a greater role in cognitive health in women than in men with HIV.

Methods: We performed a cross-sectional study of 104 participants with virologically suppressed HIV from 2 clinics in urban China. Participants underwent neuropsychological testing from which we calculated T scores globally and in 5 cognitive domains. We assessed cerebral vasoreactivity of the middle cerebral arteries in response to breath holding. We constructed linear regression models to determine associations between cerebrovascular and cognitive function overall and stratified by sex.

Results: Women were younger than men (48 versus 51 years, $P = 0.053$), had fewer years of education (9 years versus 12 years, $P = 0.004$), and fewer cardiometabolic risk factors (0 versus 1 factor, $P = 0.008$). In a model with all participants, cerebrovascular function was significantly associated with global cognition (2.74 higher T score per 1-point higher cerebral vasoreactivity [SE 1.30], $P = 0.037$). Cerebrovascular function remained significantly associated with global cognition among women (4.15 higher T score [SE 1.78], $P = 0.028$) but not men (1.70 higher T score [SE 1.74], $P = 0.33$). The relationships between cerebrovascular function and specific cognitive domains followed a similar pattern, with significant associations present among women but not men.

Conclusions: Women with well-controlled HIV may be more vulnerable to the effect of cerebrovascular injury on cognitive health than men. Studies evaluating strategies to protect against cognitive impairment in people living with HIV should include adequate representation of women and stratification of analyses by sex.

Keywords

HIV; cerebrovascular disease; cognition; cognitive function; sex differences; sex disparities

INTRODUCTION

Progress toward reducing the overall burden of HIV-associated cognitive impairment has been limited. Even among individuals on antiretroviral therapy (ART) with sustained virological suppression,[1] cognitive impairment affecting every day function[2] and quality of life[3] afflicts as many as nearly 50% of people living with HIV (PWH).[4,5] In diverse low-income and middle-income settings, the prevalence of HIV-associated cognitive impairment is comparably high.[6,7] In a multicenter study from China, more than 1 in 3 PWH met criteria for HIV-associated neurocognitive disorders.[8]

Cardiometabolic comorbidities are consistently identified as strong independent contributors to HIV-associated cognitive impairment[9,10] and decline[11,12] and may play a greater role than HIV-related variables in the development or trajectory of cognitive impairment.[9,10] The effect of cardiovascular disease (CVD) may be especially salient for women living with HIV whose cognitive health has been shown to be more negatively affected by cardiometabolic risk factors than men.[13,14] Emerging evidence specifically implicates cerebrovascular disease, rates of which are higher in PWH than HIV-uninfected individuals,[15–17] as a determinant of HIV-associated cognitive impairment.[18,19] Little is known, however, about whether the link between cerebrovascular and cognitive health differs between women and men with HIV. We investigated sex differences in the association of cerebral vasoreactivity, a dynamic measure of cerebrovascular function, and cognitive health in virologically suppressed PWH on ART.

METHODS

Study Population

We recruited a convenience sample of PWH from 2 outpatient clinics in urban China, one at the Peking Union Medical College Hospital in Beijing, China, and the other at the Shenzhen Third People's Hospital in Shenzhen, Guangdong, China. Inclusion criteria were age older than 40 years and on stable ART with undetectable plasma viral load (<20 copies/mL) for a minimum of 24 weeks. Exclusion criteria included the following: (1) stroke, brain infection, or new neurologic deficit in the 12 weeks before enrollment or (2) any condition that could affect neuropsychological test performance (eg, active substance use and untreated psychiatric illness). All PWH followed in the clinic who met eligibility criteria were invited to participate. The Peking Union Medical College Hospital and Shenzhen Third People's Hospital Ethics Committees and the University of California San Francisco Institutional Review Board approved the study.

Cognitive Function

A standardized neuropsychological test battery was administered in Mandarin. This abbreviated battery arose out of a systematic narrowing of a full battery of tests adapted from the HIV Neurobehavioral Research Center protocol.[20] The methods for selection and adaptation of tests for use in China have been described.[21] The battery comprised 8 tests evaluating 5 cognitive domains: learning and memory, speed of information processing, attention and working memory, verbal fluency, and motor function. Neuropsychological test examiners at both clinics were trained in testing and scoring procedures by a psychiatrist (C.S.) with experience in the HIV Neurobehavioral Research Center methods.[20]

Raw test scores were standardized using Chinese population–specific normative mean values adjusted for age, sex, and years of education to create demographically corrected T scores. We calculated individual T scores for the 5 cognitive domains, which were then averaged to create a global T score. A higher T score indicates better cognitive function. Participants also completed the Patient's Assessment of Own Functioning Inventory of self-reported cognitive difficulties and the Beck Depression Inventory-II.

Cerebral Vasoreactivity

To evaluate cerebrovascular function, we assessed cerebral vasoreactivity of the middle cerebral arteries in response to a breath-holding challenge,[22] which has good short-term and long-term reproducibility.[22–24] The primary measure of cerebral vasoreactivity was the breath-holding index, defined as the percentage change in mean flow velocities on transcranial Doppler (TCD) ultrasound per second of breath holding. A lower index correlates with worse cerebrovascular function. Normal breath-holding indices for adults aged 30–69 years range from 1.27 to 1.44.[25] Two ultrasound technologists performed all TCDs after undergoing training in the breath-holding challenge. The breath-holding challenge was performed on the same day as neuropsychological testing. Results from 2 consecutive breath-holding trials were averaged.

Statistical Analysis

We compared demographic and clinical characteristics between women and men using the Student *t*, χ^2, Fisher exact, and Wilcoxon rank sum tests, as appropriate. We constructed linear regression models in the overall cohort to determine the association of the breath-holding index with global cognitive function and with the 5 cognitive domains. We then stratified analyses by sex. Models were adjusted for age, sex (in the model that included all participants), education, study site, and change in the mean arterial pressure with breath holding. In addition, we considered the following plausible determinants of cognitive function, collected through medical records or self-report, as candidate covariates in models using forward stepwise selection with $P < 0.05$ as the entry criterion and $P > 0.1$ as the exit criterion.

- Cardiometabolic variables: total number of cardiometabolic risk factors (eg, hypertension, dyslipidemia, diabetes mellitus, a history of coronary heart disease, and a history of stroke), ranging from 0 to 5 factors; aspirin use, statin use, and physical activity[26]
- Health-related behaviors: ever versus never smoking, or ever versus never substance use, and current alcohol use
- Psychiatric comorbidities: a history of depression and the Beck Depression Inventory-II score
- HIV-specific variables: duration of infection; duration of ART; current use of efavirenz, integrase inhibitor, or protease inhibitor; most recent CD4 count; and CD4 to CD8 ratio

In the entire cohort, we tested a multivariable model that forced the inclusion of variables that were not retained in the forward stepwise selection but had face validity as factors that affect global cognition (cardiovascular risk, smoking, alcohol use, and the Beck Depression Inventory-II score). We evaluated whether sex modified the association between cerebrovascular and global cognitive function by entering a 2-way statistical interaction term into the multivariable model. *P* values were 2-sided with ≤0.05 considered statistically significant. Statistical analyses were performed using Stata 12.1 (Stata Corporation, College Station, TX).

RESULTS

A total of 111 participants were recruited for the study, of whom 37 (33%) were women. Seven participants (mean age 59 years, 57% women) were unable to complete the TCD due to temporal window failure. Demographic and clinical characteristics of the 104 participants included in the analyses are summarized in Table 1. Women were younger than men and had fewer years of education. When comparing the total number of individual cardiometabolic risk factors per participant, women had significantly lower cardiovascular risk than men. In addition, women were less likely to report current alcohol use and current or past smoking.

In an adjusted model that included all participants, cerebral vasoreactivity was significantly associated with global cognitive function (Table 2). A higher breath-holding index, indicative of greater cerebral vasoreactivity, corresponded to a higher global cognitive T score. The association between cerebrovascular and cognitive function remained significant after forced inclusion of cardiovascular risk, smoking status, current alcohol use, and the Beck Depression Inventory-II score (Table 2). In an adjusted model restricted to women, cerebral vasoreactivity was again significantly associated with global cognitive function, with an approximately 2-fold greater estimated effect of cerebrovascular function on cognition than in the overall cohort (Table 2). The association between cerebrovascular and global cognitive function in women remained significant after further adjusting for current alcohol use, as identified by forward stepwise selection. No statistically significant associations between cerebrovascular and cognitive function were observed in men (Table 2). In the adjusted model that included all participants, the interaction of sex and cerebral vasoreactivity with global cognitive function did not reach statistical significance ($P = 0.20$).

We noted a similar pattern in the relationships between cerebrovascular and cognitive function in the overall cohort compared with among women and men when examining specific cognitive domains (Table 2). In the overall cohort, cerebrovascular function was positively associated with processing speed. Among women, higher cerebral vasoreactivity was associated with better performance on not only testing of processing speed but also attention/working memory and motor function. Conversely, cerebrovascular function was not significantly associated with cognitive performance in any domain for men. We did not observe any significant change in the relationships between cerebral vasoreactivity and any cognitive domain when cardiovascular risk, smoking status, current alcohol use, and the Beck Depression Inventory-II score were forced into the models.

DISCUSSION

The relationship between cerebrovascular function and cognitive health differed between ART-treated, virologically suppressed women and men with HIV. We observed a stronger link between cerebrovascular and cognitive function in women, suggesting that cerebrovascular injury may have a more marked negative effect on cognition in women than in men living with HIV. One potential clinical implication of this finding is that strategies targeting cerebrovascular health as a means to prevent cognitive decline in PWH may be more beneficial for women than for men.

These findings align with our previous work in the AIDS Clinical Trials Group demonstrating a negative effect of several cardiometabolic risk factors (eg, fewer than 3 days of physical activity, lower HDL cholesterol, and diabetes mellitus) on cognitive health in women but not in men with HIV.[13] We also found that the deleterious effect of a higher CVD risk score on cognitive function was nearly 3-fold greater in women than in men.[14] Similar sex differences in the association of CVD risk with cognition have been observed in the general population, in which an unfavorable cardiometabolic risk profile or individual cardiometabolic factors more adversely affect cognitive health in women than in men.[27–31]

The dissimilar effect of CVD risk on cognitive health in women with HIV may be mediated by greater cerebrovascular injury caused by cardiometabolic risk factors in women than in men. Several large cohort studies in the general population support this hypothesis, pointing to more marked effects of various CVD risk factors (eg, hypertension, pulse pressure, smoking, and diabetes mellitus) on incident stroke risk and microstructural brain injury in women compared with men.[32–34] In a study of PWH and HIV-uninfected individuals in the Partners HealthCare system, the excess risk of ischemic stroke associated with hypertension and atrial fibrillation was 18% and 25% higher for women, respectively.[15]

Proposed sex differences in vascular physiology, including smaller arterial size and greater arterial stiffness in women, may heighten the susceptibility of women with HIV to the negative effects of CVD risk factors.[35,36] In combination with more prominent remodeling of the cerebral vasculature in women than in men,[37] these factors could predispose women to higher age-adjusted prevalence, severity, and progression of cerebrovascular injury, which has been observed in large population-based studies,[38–40] and subsequent cognitive impairment. Monocyte activation, which may decline less in response to initiation of ART in women than in men[41] and has been linked to HIV-associated cognitive impairment,[42,43] may further exacerbate the effect of cerebrovascular injury on cognition in PWH.

Our results should be interpreted in the context of several limitations. The cross-sectional design precludes drawing conclusions regarding causation or the utility of cerebral vasoreactivity to predict changes in cognition over time. Furthermore, use of a convenience sample may have introduced sampling bias that could threaten the generalizability of our findings on a population level. Finally, the modest sample size limited our ability to simultaneously adjust for multiple potential confounders, especially in the analyses restricted to women, and limited our power to detect significant effect modification by sex. Although we did not find a statistically significant interaction effect of sex on the association of cerebrovascular and cognitive function, we believe these preliminary findings are compelling because the estimate of the association was larger or more robust for women than for men despite women comprising a smaller proportion of the cohort. Confirmation of these findings in a larger sample and investigation into the mechanisms driving these observed sex differences will be critical to translate this work into more personalized treatment and prevention guidelines for women and men with HIV.

CONCLUSIONS

Among older PWH from urban China with virologically suppressed infection, women were more vulnerable to the effect of cerebrovascular injury on cognitive health than men. Disentangling potential biological mechanisms underlying observed sex differences in the link between cerebrovascular disease and cognitive health will require adequate representation of women in clinical research studies and stratification of analyses by sex. If women with HIV are confirmed to be more vulnerable to the effects of modifiable CVD risk factors and cerebrovascular injury on cognitive health, an interventional trial targeting these factors to prevent cognitive decline in PWH must include adequate representation of women.

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TABLE 1.

Demographic and Clinical Characteristics of PWH From Two Outpatient Clinics in Urban China

No. (%) Unless Otherwise Noted	All (n = 104)	Women (n = 33)	Men (n = 71)	*P*
Demographics				
Age (yr), mean (SD)	50 (8)	48 (7)	51 (8)	0.053
Education (yr), median (interquartile range)	12 (9–17)	9 (9–12)	12 (9–17)	0.004
Cardiometabolic variables				
Hypertension	17 (16)	4 (12)	13 (18)	0.71
Dyslipidemia	34 (32)	8 (24)	26 (37)	0.23
Diabetes mellitus	9 (9)	1 (3)	8 (11)	0.27
A history of previous myocardial infarction	6 (6)	2 (6)	4 (6)	1.00
A history of previous stroke	5 (5)	0 (0)	5 (7)	0.32
Cardiovascular risk index (ie, total number of cardiometabolic risk factors per participant), median (interquartile range)	1 (0–1)	0 (0–1)	1 (0–1)	0.008
Aspirin use	7 (7)	0 (0)	7 (10)	0.097
Statin use	16 (15)	3 (9)	13 (18)	0.38
Health-related behaviors, mental health, and functional status				
Alcohol use	54 (51)	11 (33)	43 (61)	0.012
Cigarette smoking				
Current	17 (16)	2 (6)	15 (21)	<0.001
Past	20 (19)	1 (3)	19 (27)	
Current or past substance use	1 (1)	1 (1)	0 (0)	1.00
Moderate physical activity (eg, daily walking or biking for at least 10 minutes continuously)	93 (89)	28 (85)	65 (92)	0.51
Vigorous physical activity (eg, lifting or carrying a heavy load; housecleaning; construction work; any activities that cause increase in heart rate for at least 10 min continuously)	19 (18)	4 (12)	15 (21)	0.41
A history of depression	9 (9)	4 (12)	5 (7)	0.30
The Beck Depression Inventory-II score, mean (SD)	11.8 (9.0)	11.6 (10.1)	11.9 (8.5)	0.87
Number of clinically significant cognitive symptoms on the Patient Assessment of Own Functioning Inventory (PAOFI) score, median (interquartile range) *	1 (0–7)	2 (0–9)	1 (0–6)	0.56
HIV-related variables				
CD4 count (cells/mm^3), mean (SD)	510 (214)	461 (204)	532 (217)	0.11
Undetectable plasma viral load (<20 copies/mL)	104 (100)	33 (100)	71 (100)	1.00
HIV duration (yr), mean (SD)	6.9 (4.9)	8.1 (6.1)	6.4 (4.2)	0.11

No. (%) Unless Otherwise Noted	All (n = 104)	Women (n = 33)	Men (n = 71)	*P*
ART duration (yr), mean (SD)	6.1 (4.6)	6.6 (5.6)	5.9 (4.2)	0.52
Efavirenz use	52 (50)	18 (55)	34 (48)	0.27
Protease inhibitor use	26 (25)	11 (33)	15 (21)	0.13
Integrase inhibitor use	6 (6)	1 (3)	5 (7)	0.33
Cerebrovascular function				
Cerebral vasoreactivity assessed by the breath-holding index, mean (SD)	1.29 (0.53)	1.25 (0.59)	1.31 (0.51)	0.59
Global cognitive function				
Global T score across domains, mean (SD)	49.6 (6.1)	50.3 (6.5)	49.3 (5.9)	0.43
Number of neuropsychological tests with T score <40, median (interquartile range)	1 (1–3)	1 (0–3)	2 (1–3)	0.10

* Items on the Patient Assessment of Own Functioning Inventory (PAOFI) endorsed as “fairly often” or more frequent are considered to be clinically significant cognitive symptoms.

TABLE 2.

Relationship of Cerebral Vasoreactivity With Global Cognitive Function and T Scores in Specific Cognitive Domains in Women and Men Living With HIV Infection. $P \leq 0.01$, $P \leq 0.05$

Estimate (SE)	All (n = 104)	*P*	Women (n = 33)	*P*	Men (n = 71)	*P*
Global cognition						
Global cognition: model 1 *	2.74 (1.30)	0.037	5.62 (1.97)	0.008	1.36 (1.76)	0.44
Global cognition: model 2 †	2.74 (1.30)	0.037	4.15 (1.78)	0.028	1.70 (1.74)	0.33
Global cognition: model 3 ‡	2.97 (1.41)	0.038	—	—	—	—
Cognitive domains						
Learning and memory §	1.08 (1.80)	0.55	2.04 (2.46)	0.42	0.30 (2.38)	0.90
Attention and working memory ‖	3.34 (2.02)	0.10	6.91 (2.93)	0.026	2.52 (2.67)	0.35
Speed of information processing ¶	0.47 (0.18)	0.012	0.90 (0.33)	0.010	0.40 (0.25)	0.12
Verbal fluency #	3.66 (2.49)	0.15	4.31 (3.99)	0.29	2.25 (3.26)	0.49
Motor function **	1.40 (1.74)	0.42	5.99 (2.70)	0.036	−0.21 (2.45)	0.93

SE, standard error.

*Model 1: adjusted for age, sex (in the model of all participants), education, site, change in the mean arterial pressure during breath holding.

†Model 2: All participants: adjusted for age, sex, education, site, change in the mean arterial pressure during breath holding. Women only: adjusted for age, education, site, change in the mean arterial pressure during breath holding, and alcohol use. Men only: adjusted for age, education, site, change in the mean arterial pressure during breath holding, and the Beck Depression Inventory-II score.

‡Model 3: All participants: adjusted for age, sex, education, site, change in the mean arterial pressure during breath holding, duration of ART use, cardiovascular risk index score, ever versus never smoking, alcohol use, and the Beck Depression Inventory-II score. Model 3 was tested only in the full cohort to avoid overfitting in the smaller samples after stratifying by sex.

§Model with all participants: adjusted for age, sex, education, site, change in the mean arterial pressure during breath holding, and HIV duration. Women only: adjusted for age, education, site, change in the mean arterial pressure during breath holding, and alcohol use. Men only: adjusted for age, education, site, and change in the mean arterial pressure during breath holding.

‖Model with all participants: adjusted for age, sex, education, site, and change in the mean arterial pressure during breath holding. Women only: adjusted for age, education, site, and change in the mean arterial pressure during breath holding. Men only: adjusted for age, education, site, and change in the mean arterial pressure during breath holding.

¶Model with all participants: adjusted for age, sex, education, site, change in the mean arterial pressure during breath holding, duration of ART, CD4 count, and aspirin use. Women only: adjusted for age, education, site, change in the mean arterial pressure during breath holding, and moderate physical activity. Men only: adjusted for age, education, site, change in the mean arterial pressure during breath holding, and aspirin use.

#Model with all participants: adjusted for age, sex, education, site, change in the mean arterial pressure during breath holding, cardiovascular risk index score, and alcohol use. Women only: adjusted for age, education, site, change in the mean arterial pressure during breath holding, and alcohol use. Men only: adjusted for age, education, site, change in the mean arterial pressure during breath holding, and cardiovascular risk index score.

** Model with all participants: adjusted for age, sex, education, site, change in the mean arterial pressure during breath holding, and the Beck Depression Inventory-II score. Women only: adjusted for age, education, site, change in the mean arterial pressure during breath holding, and protease inhibitor use. Men only: adjusted for age, education, site, change in the mean arterial pressure during breath holding, cardiovascular risk index score, and the Beck Depression Inventory-II score.