

Modifiable Factors Could Mitigate Greater Burden of Brain Small Vessel Injury in Women with HIV

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Women living with HIV have a greater burden of cerebral small vessel disease than men. The impact of certain modifiable factors, such as smoking and injection drug use, on cerebrovascular injury may differ between women and men and could serve as therapeutic targets to narrow this risk gap.

BACKGROUND

PWH have a high burden of subclinical cerebrovascular disease on imaging, but little is known about whether this burden differs by sex.

OBJECTIVES

1. Compare imaging markers of cerebral small vessel disease (SVD) and large artery disease (LAD) between women and men living with HIV.
2. Examine differential associations of modifiable risk factors on subclinical cerebrovascular disease in women and men living with HIV.

METHODS

- Participants on ART and at moderate to high cardiovascular disease (CVD) risk were enrolled from 3 sites of the MACS/WIHS Combined Cohort Study (MWCCS).
- Participants underwent brain MRI, MRA, and vessel wall imaging (VWI).
- White matter hyperintensity (WMH) volume quantified with open-source automated segmentation tool for SPM.
- SVD score derived from visual rating of WMH, microbleed count, and lacunar infarcts.
- LAD based on vessel wall enhancement and pattern and presence of luminal stenosis.
- Demographics, CVD risk factors, mental health, substance use, and other variables obtained through the MWCCS.
- Elastic Net regression models used to estimate separate and interactive associations of risk factors with sex on measures of subclinical cerebrovascular disease.

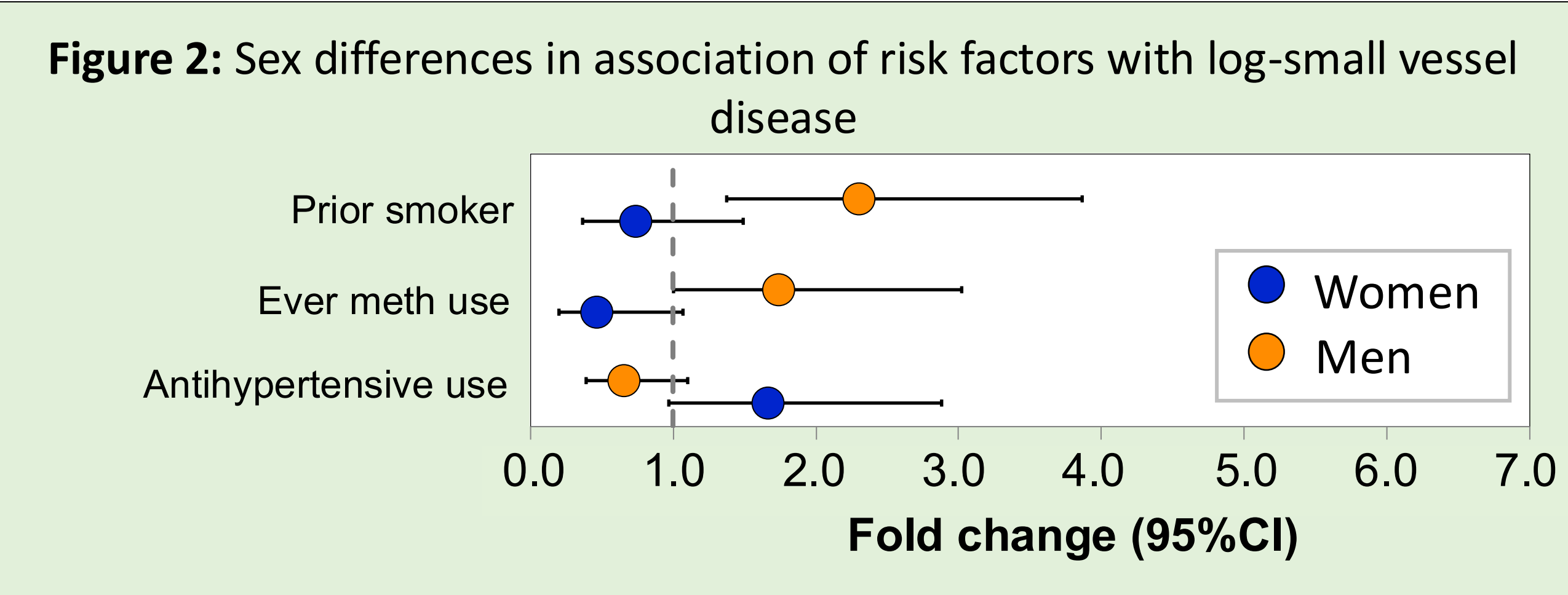
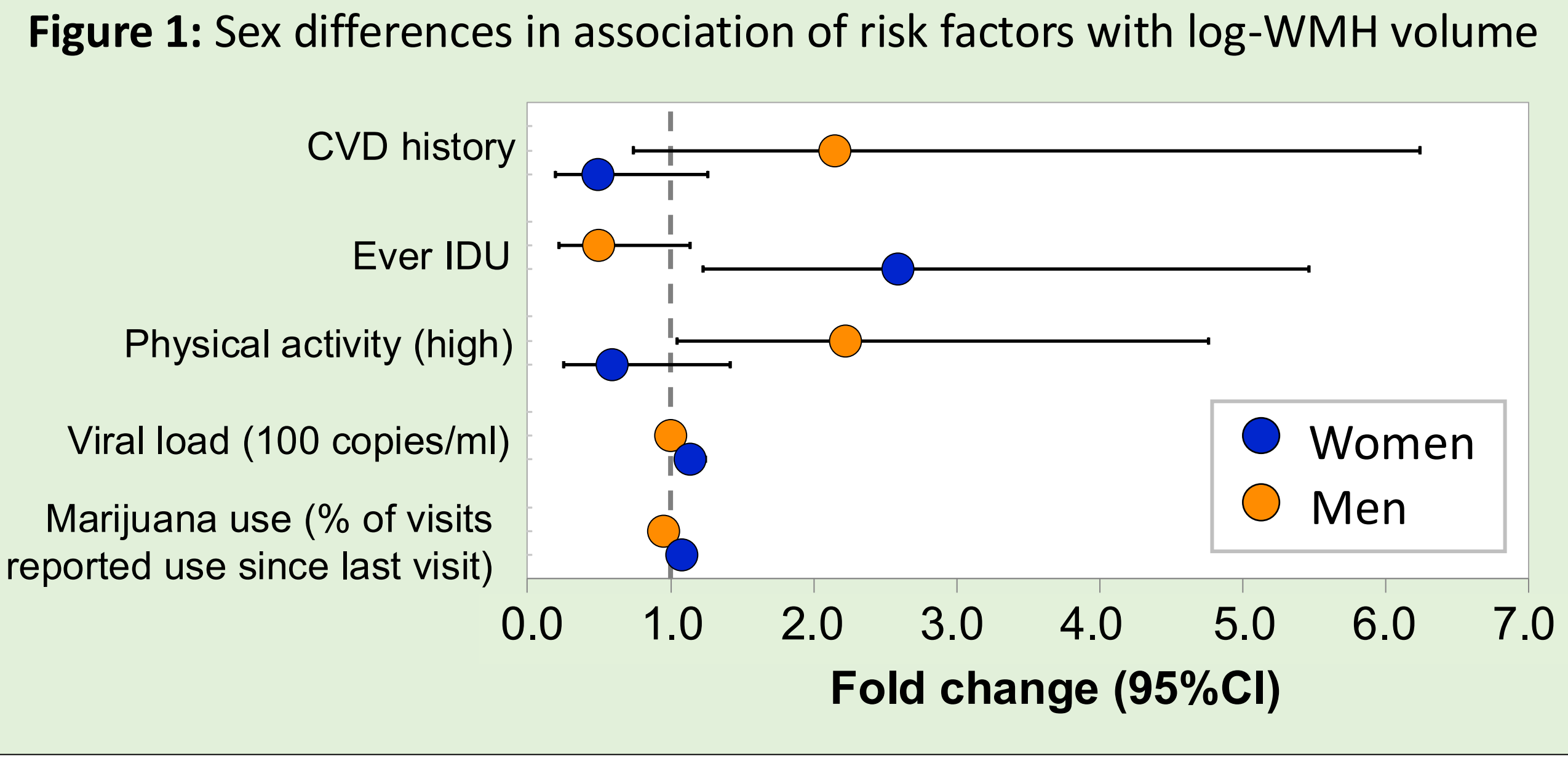
RESULTS

Table 1. Participant characteristics by sex. Several cardiometabolic risk factors were more prevalent among women, including current smoking and diabetes. Women also had a higher BMI than men. Men were more likely to report high physical activity, while women had a higher median depression score on the Center for Epidemiologic Studies Depression Scale and a higher Adverse Childhood Experience Score. Ever methamphetamine use was more prevalent among men than women.

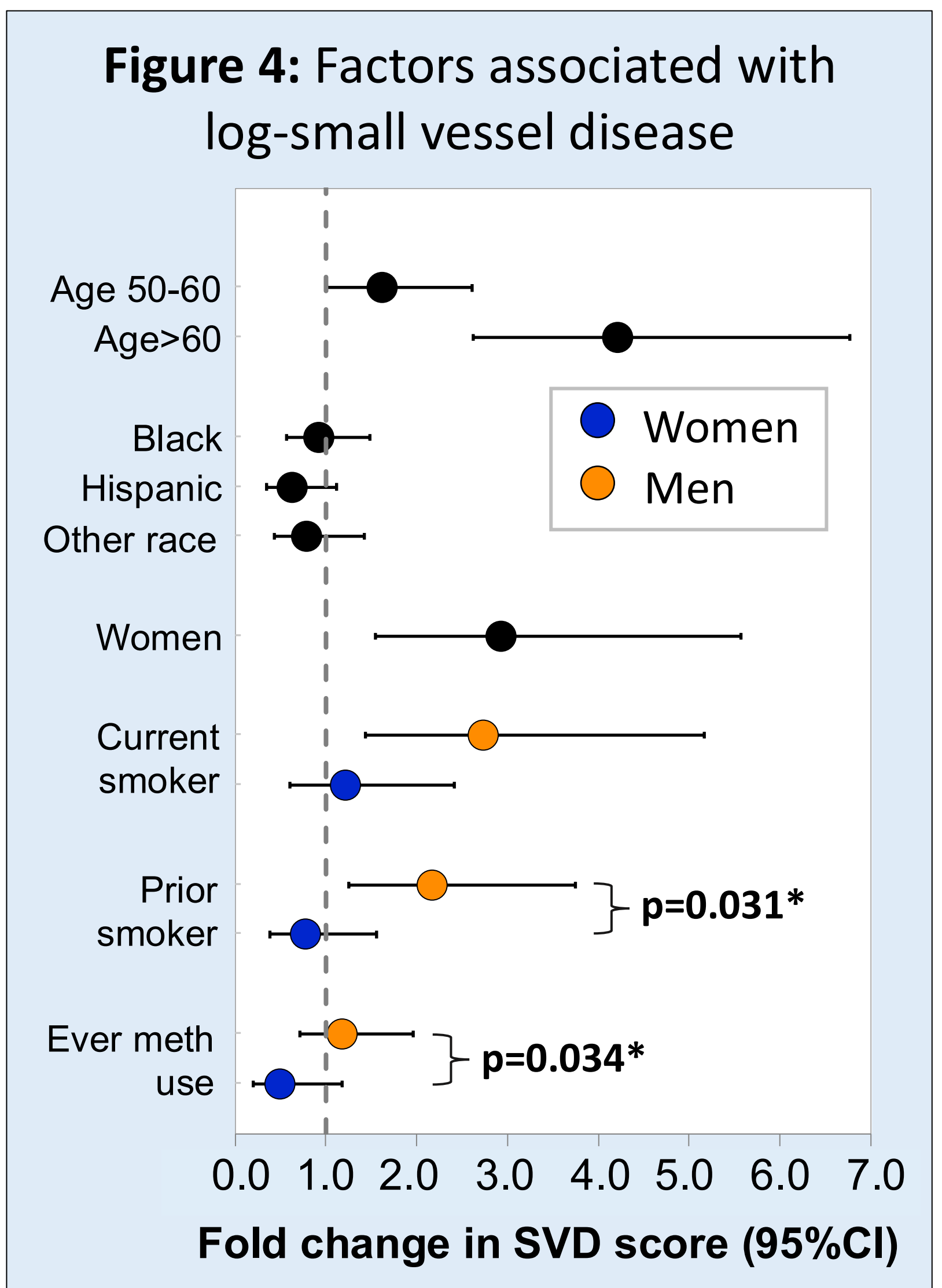
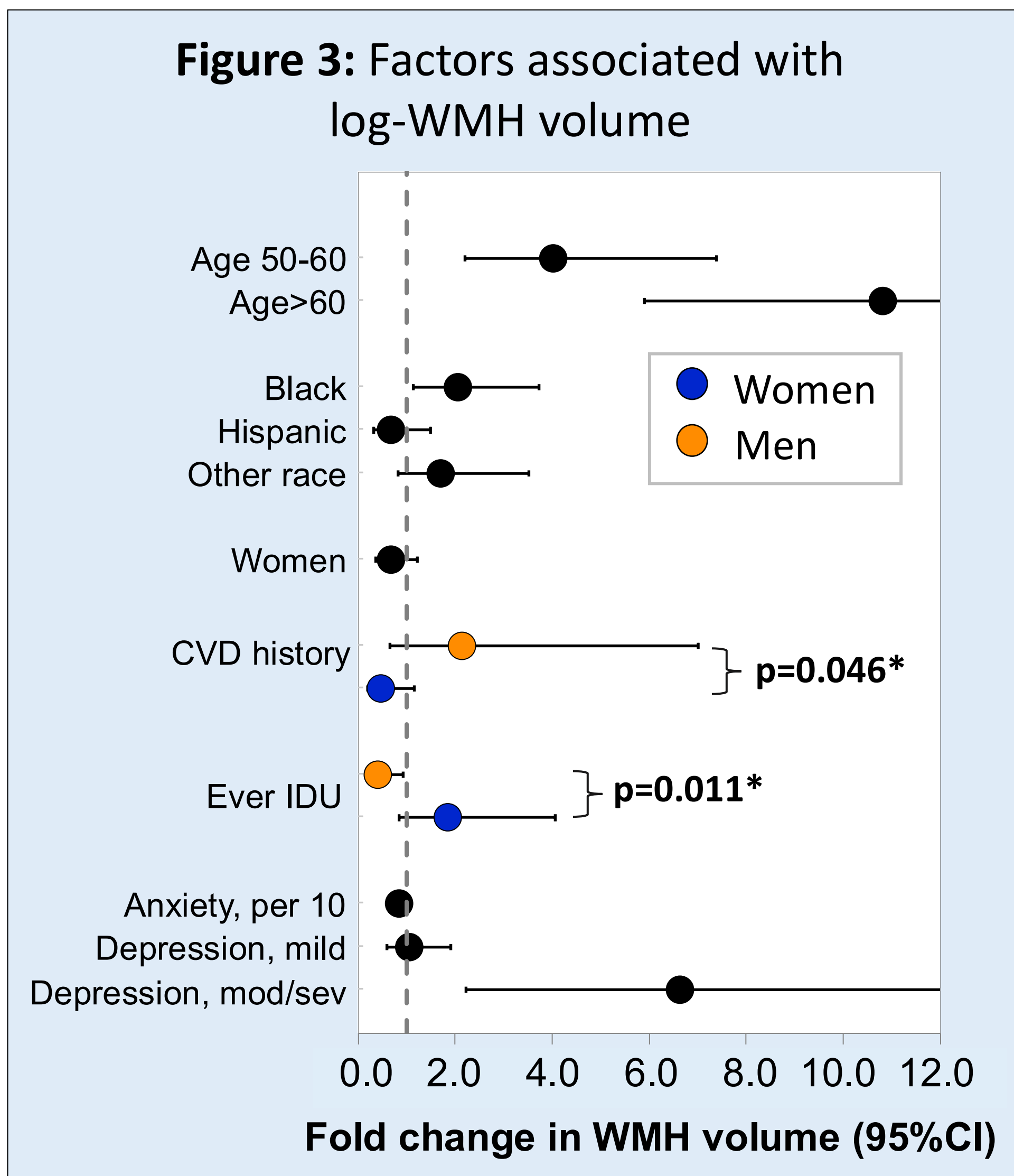
Variable	Women (N=83)	Men (N=68)	Total (N=151)	P-value	Variable (continued)	Women (N=83)	Men (N=68)	Total (N=151)	P-value
Demographics					Stress, median (Q1–Q3)				
Age (years), mean ± SD	57 ± 10	54 ± 12	56 ± 11	0.072	Adverse Childhood Experience Score	3 (1-6)	2 (1-4)	2 (1-5)	0.025
Age group, n (%)					Berger HIV Stigma Scale	76 (67-90)	73 (59-85)	75 (65-87)	0.077
≤50 years	17 (21)	28 (41)	45 (30)	0.005	Chronic Burden Scale	1 (0-3)	1 (0-3)	1 (0-3)	0.71
50-60 years	35 (42)	14 (21)	49 (33)		Perceived Stress Scale	15 (10-20)	13 (8-18)	14 (9-19)	0.22
>60 years	31 (37)	26 (38)	57 (38)		Mental health				
Race, n (%)					Depression screening (CAT-MDD), n (%)	28 (36)	15 (25)	43 (31)	0.17
White	14 (17)	32 (47)	46 (31)	<.0001	Depression score (CES-D), median (Q1–Q3)	11 (5-21)	5 (1-13)	9 (3-19)	0.004
Black	47 (57)	15 (22)	62 (41)		Depression severity category (CAT-DI), n (%)				
Hispanic	9 (11)	12 (18)	21 (14)		Normal	32 (42)	27 (47)	59 (44)	0.92
Other	13 (16)	9 (13)	22 (15)		Mild	37 (48)	24 (42)	61 (46)	
CVD factors					Moderate/Severe	8 (10)	6 (11)	14 (11)	
BMI (kg/m²), mean ± SD	31.8 ± 8.2	28.8 ± 5.4	30.4 ± 7.2	0.011	Anxiety severity score (CAT-ANX), median (Q1–Q3)	23 (11-40)	17 (2-40)	22 (6-40)	0.12
History of CVD¹, n (%)	9 (11)	7 (11)	16 (11)	0.95	Anxiety severity category (CAT-ANX), n (%)				
Diabetes, n (%)	15 (19)	7 (11)	22 (15)	0.19	Normal	51 (65)	41 (68)	92 (67)	0.94
Dyslipidemia, n (%)	60 (75)	38 (72)	98 (74)	0.67	Mild	15 (19)	12 (20)	27 (20)	
Hypertension, n (%)	55 (72)	34 (64)	89 (69)	0.32	Moderate/Severe	12 (16)	7 (11)	19 (14)	
Antihypertensive use, n (%)	38 (46)	28 (41)	66 (44)	0.57	Substance use, n (%)				
Statin use, n (%)	29 (35)	28 (41)	57 (38)	0.43	Ever cocaine use	37 (45)	32 (47)	69 (46)	0.76
Smoking, n (%)					Ever injection drug use	20 (24)	12 (18)	32 (21)	0.33
Never	22 (27)	28 (42)	50 (34)	0.043	Ever marijuana use	72 (87)	56 (82)	128 (85)	0.45
Current	30 (37)	13 (19)	43 (29)	0.023	Ever methamphetamine use	8 (10)	29 (43)	37 (25)	<.0001
Prior	30 (37)	26 (39)	56 (38)	0.89	HIV-related factors				
Physical activity, n (%)					CD4 nadir (cells/mm³), median (Q1–Q3)	295 (148-372)	313 (152-468)	299 (148-421)	0.45
Low	34 (44)	12 (20)	46 (34)	0.014	Viral load (copies/mL), median (Q1–Q3)	UD (UD-20)	20 (UD-25)	UD (UD-20)	0.002
Moderate	21 (27)	22 (37)	43 (32)		All variables reflect the assessment closest to MRI date unless otherwise noted. ¹ History of CVD: Prior myocardial infarction (MI), coronary artery disease, cerebrovascular accident or transient ischemic attack (CVA/TIA), peripheral arterial disease, carotid artery disease.				
High	22 (29)	25 (42)	47 (35)						

Table 2: Imaging markers of subclinical cerebrovascular disease.

Cerebrovascular imaging outcomes	Women (N=83)	Men (N=68)	Total (N=151)	P-value
Small vessel disease (SVD) score, median (Q1–Q3)	1 (0-2)	0 (0-1)	1 (0-1)	0.026
WMH volume (mL), median (Q1–Q3)	0.54 (0.20-2.62)	0.53 (0.22-1.33)	0.53 (0.21-1.56)	0.63
Large artery disease (LAD) score, median (Q1-Q3)	1 (0-2)	1 (0-1)	1 (0-1)	0.61



Figures 1 and 2: Sex differences in factors associated with imaging markers of cerebral small vessel disease. To identify sex-specific risk factors, we tested for sex-by-risk factor interactions. Figures 1 and 2 display factors for which the association with WMH volume and SVD differed significantly by sex, with effect estimates shown separately for women and men. Injection drug use, marijuana use, and higher viral load were associated with greater WMH volume in women but not men, while high level of physical activity and prior smoking were associated with lower WMH volume or SVD for women. Other factors, including hypertension, statin use, dyslipidemia, depression, anxiety, cocaine use, and alcohol use, did not show a statistically significant interaction with sex.



Women had a higher median SVD score (1, IQR 0-2) than men (0, IQR 0-1; p=0.026), whereas median LAD score was 1 for both women (IQR 0-2) and men (IQR 0-1; p=0.61). In age- and race-adjusted multivariable models with Elastic Net-selected covariates, women had a higher burden of SVD than men (2.93-fold higher SVD, 95% CI 1.54 to 5.57-fold higher, p=0.001). LAD, however, was not significantly different between women and men (1.16-fold higher LAD for women, 95% CI 0.56-fold lower to 2.41-fold higher LAD, p=0.69).

Figures 3 and 4: Factors associated with imaging markers of cerebral small vessel disease. We used Elastic Net regression to identify factors significantly associated with WMH volume and SVD. Variables selected by elastic net were then entered into multivariable linear regression models, as shown in Figures 3 and 4. Older age and moderate to severe depression, were associated with greater WMH volume, while older age, female sex, and smoking among men were associated with SVD.
*p-value for sex-by-risk factor interaction

CONCLUSIONS

The effect of modifiable factors on cerebrovascular injury in PWH differed by sex. Targeting these modifiable factors could narrow the cerebrovascular risk gap observed in female participants with HIV.

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