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ORIGINAL RESEARCH

Depression and Psychosocial Stress Are Associated With Subclinical Carotid Atherosclerosis Among Women Living With HIV

Matthew E. Levy, PhD; Kathryn Anastos, MD; Steven R. Levine, MD; Michael Plankey, PhD; Amanda D. Castel, MD, MPH; Sherry Molock, PhD, MDiv; Sabyasachi Sen, MD, PhD; Federico M. Asch, MD; Joel Milam, PhD; Bradley Aouizerat, PhD; Kathleen M. Weber, RN, MS; Elizabeth T. Golub, PhD; Robert C. Kaplan, PhD; Seble Kassaye, MD, MS

BACKGROUND: To identify reasons for increased atherosclerotic risk among women living with HIV (WLWH), we evaluated the associations between psychosocial risk factors (depressive symptoms, perceived stress, and posttraumatic stress disorder symptoms) and subclinical atherosclerosis among WLWH and HIV-negative women.

METHODS AND RESULTS: Carotid artery focal plaque (localized intima-media thickness >1.5 mm) was measured using B-mode ultrasound imaging in 2004–2005 and 2010–2012 in the Women's Interagency HIV Study. We created psychosocial risk groups using latent class analysis and defined prevalent plaque at the final measurement. We also examined repeated semi-annual depression measures with respect to focal plaque formation throughout follow-up. The associations between latent class and prevalent plaque, and between depressive symptom persistence and plaque formation, were assessed separately by HIV status using multivariable logistic regression. Among 700 women (median age 47 years), 2 latent classes were identified: high (n=163) and low (n=537) psychosocial risk, with corresponding prevalence of depression (65%/13%), high stress (96%/12%), and probable posttraumatic stress disorder (46%/2%). Among WLWH, plaque prevalence was 23% and 11% in high versus low psychosocial risk classes (adjusted odds ratio [aOR], 2.12; 95% CI, 1.11–4.05) compared with 9% and 9% among HIV-negative women (aOR, 1.07; 95% CI, 0.24–4.84), respectively. New plaque formation occurred among 17% and 9% of WLWH who reported high depressive symptoms at ≥45% versus <45% of visits (aOR, 1.96; 95% CI, 1.06–3.64), compared with 9% and 7% among HIV-negative women (aOR, 0.82; 95% CI, 0.16–4.16), respectively.

CONCLUSIONS: Psychosocial factors were independent atherosclerotic risk factors among WLWH. Research is needed to determine whether interventions for depression and psychosocial stress can mitigate the increased risk of atherosclerosis for WLWH.

Key Words: atherosclerosis ■ depression ■ HIV infection ■ posttraumatic stress disorder ■ psychological stress ■ women

People living with HIV (PLWH) have an elevated risk of subclinical atherosclerosis and cardiovascular disease (CVD), attributed in large part to chronic inflammation and immune activation.[1–3] Women living with HIV (WLWH) have an ≈3 times greater CVD risk compared with HIV-negative women,[4–7] suggesting that the HIV-associated CVD risk is greater among women compared with men, the cause of which is not well understood.[8] Identification of novel pathways that explain the excess CVD risk among WLWH is needed.

Correspondence to: Matthew E. Levy, PhD, Department of Epidemiology, Milken Institute School of Public Health, The George Washington University, 950 New Hampshire Avenue NW, Suite 500, Washington, DC 20052. E-mail: mattelevy@gwu.edu

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CLINICAL PERSPECTIVE

What Is New?

- Women living with HIV (WLWH) who reported a high burden of psychosocial risk factors (ie, depressive symptoms, perceived stress, and posttraumatic stress disorder symptoms) were more likely to have prevalent subclinical atherosclerosis compared with WLWH who reported a low burden of psychosocial risk factors.
- WLWH who persistently reported high depressive symptoms over ≈7 years had a greater risk of incident subclinical atherosclerosis compared with WLWH who either rarely/never or sometimes reported high depressive symptoms.

What Are the Clinical Implications?

- WLWH with depression and/or psychosocial stress may confront a disproportionately high risk of atherosclerotic cardiovascular disease as they age compared with WLWH without such symptoms.
- Research is needed to determine whether interventions for depression and psychosocial stress can mitigate the increased risk of atherosclerosis for WLWH.

Nonstandard Abbreviations and Acronyms

aOR	adjusted odds ratio
CES-D	Center for Epidemiologic Studies Depression Scale
CHD	coronary heart disease
CVD	cardiovascular disease
IQR	interquartile range
LCA	latent class analysis
PCL-C	PTSD Checklist-Civilian Version
PLWH	people living with HIV
PSS-10	10-item Perceived Stress Scale
PTSD	posttraumatic stress disorder
VACS	Veterans Aging Cohort Study
WIHS	Women's Interagency HIV Study
WLWH	women living with HIV

One potential CVD pathway that remains understudied among WLWH, despite WLWH and particularly WLWH of color being disproportionately affected,[9,10] is depressive symptoms and psychosocial risk. In the general population, depression, stress, and trauma are known to contribute to atherosclerosis through increased inflammation and activity of the hypothalamic pituitary adrenal axis and sympathetic nervous system.[11,12] In addition, such psychosocial factors are associated with adverse health behaviors including suboptimal diet, physical inactivity, poor sleep, and nonadherence to CVD preventive medications.[13–17] Among PLWH, depression, stress, and trauma are predictors of immunosuppression, viral replication, and clinical decline,[18–20] which are associated with increased CVD risk.[21] In a predominantly male cohort of PLWH, having a diagnosis for major depressive disorder was an independent risk factor for incident CVD.[22,23] Among WLWH, persistently high depressive symptoms were associated with higher Framingham coronary risk scores.[24,25] To our knowledge, there have been no published studies examining psychosocial risk factors with respect to either subclinical CVD or CVD end points among WLWH.

To address this gap in research, we investigated the role of psychosocial factors as atherosclerotic risk factors among WLWH. Our specific objective was to evaluate associations of psychosocial risk factors (ie, depressive symptoms, perceived stress, and posttraumatic stress disorder [PTSD] symptoms) with the presence and formation of carotid artery focal plaque among WLWH and HIV-negative women. Psychosocial risk factors that predict atherosclerosis could provide new targets for interventions to prevent CVD among WLWH.

METHODS

The WIHS (Women's Interagency HIV Study) has a publicly available, deidentified data set that can be accessed by researchers. Data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design

Participants were women aged 25 to 60 years in the WIHS who participated in a CVD substudy between 2004 and 2012.[26] The WIHS is a multicenter prospective observational cohort study of WLWH and demographically similar HIV-uninfected women at risk of infection.[27–29] WIHS participants were initially recruited and enrolled in 1994–1995 or 2001–2002 in Brooklyn and Bronx, NY; Chicago, IL; Washington, DC; and Los Angeles and San Francisco, CA. At semiannual visits, participants completed structured interviews and physical and laboratory assessments. Study protocols were approved by each site's institutional review board and the current analysis was approved by the George Washington University's institutional review board. All participants provided written informed consent.

Participants with a known history of coronary heart disease (CHD) (by self-report of myocardial infarction, coronary revascularization procedure, hospitalization

for congestive heart failure, hospitalization for angina, or other heart disease) were excluded from the current analysis so that the study sample would include participants who were currently at risk of CHD. This exclusion also minimized the potential for reverse causality, whereby known CHD could drive depressive symptoms or psychosocial stress. Participants with a known history of CHD were similarly excluded from other analyses of atherosclerotic outcomes in the WIHS.[26,30,31]

Carotid Examination

High-resolution B mode ultrasounds of the right carotid artery were performed at baseline in 2004–2005 and again in 2010–2012, as previously described.[26,30] A standardized protocol was used at all sites,[31] and measurements were obtained at a centralized reading center. We defined the presence of focal plaque as localized intima-media thickness >1.5 mm in at least 1 of 6 locations: the near and far walls of the common carotid artery, carotid bifurcation, and proximal internal carotid artery.[32] For cross-sectional analyses, we defined prevalent focal plaque at the time of the final carotid ultrasound measurement in 2010–2012 and excluded participants with a known history of CHD as of that time point. For prospective analyses, we defined new focal plaque formation as an increase in the number of focal plaques across the 6 locations imaged between the baseline and final carotid ultrasound measurements and excluded participants with a known history of CHD as of baseline.

Psychosocial Risk Factors

Three psychosocial risk factors (ie, high depressive symptoms, high perceived stress, and probable PTSD) were defined using self-reported data. Depressive symptoms were evaluated at each semiannual visit between the baseline and final carotid ultrasound measurements. Thus, we were able to prospectively analyze repeated measures of depressive symptoms with respect to new focal plaque formation throughout follow-up. However, perceived stress and PTSD symptoms were evaluated for the first time in 2008–2009 (≈4 years after participants' baseline carotid ultrasound measurements) and every 2 years thereafter, with most participants having had only 1 or 2 measures available before their final carotid ultrasound measurements. Because of the lack of available baseline and cumulative measures for perceived stress and PTSD symptoms, we conducted a cross-sectional analysis at the time of last carotid ultrasound measurement using the most recent available measures with respect to prevalent focal plaque. The median time between the assessment of perceived stress/PTSD symptoms and the last carotid ultrasound measurement was 398 days for WLWH (interquartile range [IQR], 204–578) and 337 days for HIV-negative women (IQR, 176–471). In addition, we used latent class analysis (LCA) to create 2 mutually exclusive psychosocial risk groups (ie, low and high psychosocial risk) based on observed patterns of the 3 psychosocial risk factors (see Statistical Analysis), similarly using the most recent measures for each psychosocial factor as of the last carotid ultrasound measurement.

High depressive symptoms were defined as a score ≥16 on the 20-item Center for Epidemiologic Studies Depression Scale (CES-D), which assesses symptoms in the past 2 weeks (α=0.92).[33] A cutoff score ≥16 is a widely used indicator for clinically meaningful depressive symptoms.[33,34] Consistent with previous WIHS studies,[35–37] high perceived stress was defined as a score in the upper tertile (≥18 in the present sample) on the 10-item Perceived Stress Scale (PSS-10), which assesses the degree to which life situations in the previous month are evaluated as unpredictable, uncontrollable, and overloaded (α=0.87).[38] Probable PTSD was defined as a score ≥45 and meeting *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition,* symptom criteria for re-experiencing (≥1 B item), avoidance (≥3 C items), and arousal (≥2 D items) on the 17-item PTSD Checklist-Civilian Version (PCL-C), which assesses symptoms in the past month (α=0.94).[39] Although the PCL-C is not a diagnostic assessment, these symptom criteria have been used to identify probable PTSD.[35,37]

Covariates

Covariates were measured at semiannual visits. For cross-sectional analyses, we defined each covariate based on the most recent measurement as of the final carotid ultrasound measurement. For prospective analyses, we used all semiannual measurements obtained between baseline and the visit before the final carotid ultrasound measurement. Sociodemographic and behavioral factors were self-reported and included age, race/ethnicity, education (upon study entry), income, current and former smoking, current alcohol use (abstainer, <3 drinks per week, 3 to 13 drinks per week, or ≥14 drinks per week), crack/cocaine use since last visit, and history of injection drug use. History of hepatitis C virus infection was based on antibody or viral RNA testing. Postmenopausal status was self-reported and defined as not having menstruated in ≥12 months, unless related to pregnancy or medication use. Cardiometabolic risk factors were based on physical and laboratory evaluations and included body mass

index, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, and history of diabetes mellitus (fasting serum glucose ≥126 mg/dL, glycated hemoglobin ≥6.5%, self-reported antidiabetic medication use, or confirmed diagnosis). Use of antihypertensive, lipid-lowering, and psychiatric medications was self-reported. HIV-related factors included history of clinical AIDS-defining illness, nadir and current CD4 cell count, HIV RNA viral load, use of highly active antiretroviral therapy, and use of specific antiretroviral drug classes (protease inhibitors, nonnucleoside reverse transcriptase inhibitors, and integrase strand transfer inhibitors).

Statistical Analysis

Cross-Sectional Analysis: Associations of Depressive Symptoms, Perceived Stress, and Probable PTSD With Prevalent Focal Plaque

Characteristics of participants as of their final carotid examination were summarized using frequencies and proportions or medians and IQRs and were compared by HIV serostatus using chi-square or Wilcoxon rank sum tests. Pairwise correlations among psychosocial risk factors were evaluated using Pearson correlation coefficients. We compared the prevalence of focal plaque, separately among WLWH and HIV-negative women, between participants with and without psychosocial risk factors using chi-square or Fisher exact testing. We used multivariable logistic regression to evaluate associations, stratified by HIV status, between each psychosocial risk factor and prevalent focal plaque after serially adjusting for: (1) sociodemographics, behavioral factors, history of hepatitis C virus infection, and menopausal status; (2) cardiometabolic risk factors; (3) HIV-related characteristics (WLWH only); and (4) psychiatric medication use.

We used LCA to classify participants into mutually exclusive psychosocial risk groups based on their patterns of the 3 observed psychosocial risk factors.[40] Using MPlus version 7.4, we considered LCA models with 2 to 4 classes. The best fitting model was determined by several criteria: lower Akaike information criterion, Bayesian information criterion, and sample size–adjusted Bayesian information criterion values; higher entropy values; and statistically significant *P* values for the adjusted Lo-Mendell-Rubin and bootstrapped likelihood ratio tests. A 2-class model was preferable over 3- and 4-class models based on all fit statistics evaluated (Table S1). We assigned participants to the latent class for which they had the highest posterior probability of membership. We named one class "low psychosocial risk" (77% of participants assigned), and the other class "high psychosocial risk" (23% of participants assigned), based on the conditional probabilities of high depressive symptoms, high perceived stress, and probable PTSD for each class (Table 1). Multivariable logistic regression was used to evaluate associations by HIV status between latent class membership and prevalent focal plaque.

Prospective Analysis: Association Between Persistence of Depressive Symptoms and New Focal Plaque Formation

Using all semiannual CES-D measures between baseline and the visit before the final carotid examination, we defined the proportion of visits at which participants reported high depressive symptoms and used tertiles to categorize participants as having no/low, medium, or high persistence of high depressive symptoms. Multivariable logistic regression was used to evaluate associations by HIV status between symptom persistence and new focal plaque formation. In addition to previous covariates, we adjusted for presence of baseline focal plaque and length of follow-up. Time-varying covariates were defined cumulatively as the proportion of visits with a specific value (categorical) or the mean across all visits (continuous). Unlike in cross-sectional analyses, we could not adjust for psychiatric medication use in the prospective analysis because it was not assessed at 9 visits between 2005

Table 1. Conditional Item-Response Probabilities of Individual Psychosocial Risk Factors by Latent Class Membership (2-Class Model)

	Latent Class 1: Low Psychosocial Risk (n=537), %	Latent Class 2: High Psychosocial Risk (n=163), %
Class prevalence	76.7	23.3
Conditional item-response probabilities		
High depressive symptoms*	13.3	64.9
High perceived stress†	12.0	96.4
Probable PTSD‡	1.5	46.2

PTSD indicates posttraumatic stress disorder.
*Score ≥16 on the 20-item Center for Epidemiologic Studies Depression Scale (CES-D).
†Score ≥18 (ie, in the upper tertile) on the 10-item Perceived Stress Scale (PSS-10).
‡Score ≥45 and meeting *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, symptom criteria for re-experiencing (≥1 B item), avoidance (≥3 C items), and arousal (≥2 D items) on the 17-item PTSD Checklist-Civilian Version (PCL-C).

and 2010. Statistical analyses (except LCA) were conducted using SAS version 9.4 (SAS Institute Inc).

RESULTS

Participant Characteristics

Among 700 participants, 513 (73%) were WLWH. Characteristics stratified by HIV status are provided in Table 2. Sociodemographics were similar between WLWH and HIV-negative women. Overall, the median age was 47 years (IQR, 41–53), 51% were non-Hispanic black, 30% were Hispanic, and 5% were non-Hispanic white. WLWH were less likely than HIV-negative women to currently smoke or use alcohol, have body mass index ≥30 kg/m^2, and have systolic blood pressure ≥140 mm Hg, but were more likely to have high-density lipoprotein cholesterol <40 mg/dL. Among WLWH, 86% currently used highly active antiretroviral therapy (53% protease inhibitor–based, 31% nonnucleoside reverse transcriptase inhibitor–based, and 16% integrase strand transfer inhibitor–based), 54% had CD4 cell counts >500 cells/μL, and 71% had HIV viral loads <200 copies/mL.

The prevalence of psychosocial risk factors was similar between WLWH and HIV-negative women. Overall, 28% reported high depressive symptoms, 35% were classified as having high perceived stress, and 14% had probable PTSD. Psychosocial risk factors were moderately correlated: r=0.41 for depression-stress, r=0.30 for depression-PTSD, and r=0.46 for stress-PTSD associations, respectively (all P<0.001). Current psychiatric medication use was reported by 27% and 16% of WLWH and HIV-negative women, respectively (P=0.0025), including 47% and 29% of those with high depressive symptoms (P=0.035), 37% and 25% with high perceived stress (P=0.063), and 48% and 29% with probable PTSD (P=0.082).

Cross-Sectional Analysis: Associations of Depressive Symptoms, Perceived Stress, Probable PTSD, and Latent Class Membership With Prevalent Focal Plaque

The prevalence of focal plaque stratified by HIV serostatus and psychosocial risk factors is provided in Table 3. Focal plaque prevalence was 14% among WLWH and 9% among HIV-negative women (P=0.094). Among WLWH, the prevalence was higher among those with (versus without) high depressive symptoms (20% versus 11%, P=0.0072) and among those with (versus without) high perceived stress (19% versus 11%, P=0.025). Similarly, among WLWH the prevalence was higher in the high (versus low) psychosocial risk latent class (23% versus 11%, P=0.0017). No difference based on the presence of probable PTSD was detected among WLWH. Among HIV-negative women, no differences in plaque prevalence were detected by the presence of psychosocial risk factors or by latent class membership.

In full multivariable models, high depressive symptoms and high perceived stress, although not significant, were positively associated with prevalent focal plaque among WLWH (adjusted odds ratio [aOR], 1.87 [95% CI, 0.99–3.55] and aOR, 1.75 [95% CI, 0.96–3.21], respectively) (Table 4). High (versus low) psychosocial risk class membership was positively and significantly associated with prevalent plaque among WLWH (aOR, 2.12; 95% CI, 1.11–4.05). No association between probable PTSD and focal plaque was found among WLWH. Among HIV-negative women, no associations were found between psychosocial risk factors or latent class membership and prevalent focal plaque. Results from full and reduced multivariable models were similar.

Prospective Analysis: Association Between Persistence of Depressive Symptoms and Focal Plaque Formation

Among 741 participants in the prospective sample, the median follow-up duration was 6.6 years (IQR, 6.5–7.0). Over a median of 13 semiannual visits (IQR, 13–14), high depressive symptoms were reported at a median proportion of 21% of visits (IQR, 0–60). Eighty participants (11%), including 12% of WLWH and 8% of HIV-negative women (P=0.11), had new focal plaque formation. Cumulative measures of covariates are provided in Table S2.

Among WLWH, 17% of those who persistently reported high depressive symptoms (upper tertile: 45–100% of visits) had new focal plaque formation, compared with 7% of those sometimes reporting high symptoms (middle tertile: 8% to <45% of visits) and 10% of those never/rarely reporting high symptoms (bottom tertile: 0% to <8% of visits) (P=0.0096). Among HIV-negative women, 9% of those who persistently reported high symptoms, compared with 7% and 8% of those sometimes and never/rarely reporting high symptoms, respectively, had new plaque formation (P=0.91).

In full multivariable models, reporting high depressive symptoms at ≥45% (versus <45%) of visits was significantly associated with greater risk of focal plaque formation among WLWH (aOR, 1.96; 95% CI, 1.06–3.64), but not among HIV-negative women (aOR, 0.82; 95% CI, 0.16–4.16) (Table 5). Results from full and reduced multivariable models were similar.

DISCUSSION

Using self-reported symptoms to measure psychosocial risk factors and carotid B-mode ultrasonography

Table 2. Characteristics by HIV Serostatus Among Women in the WIHS Cardiovascular Substudy as of the Time of the Final Carotid Ultrasound Measurement, 2010–2012 (N=700)

	WLWH (n=513)	HIV-Negative Women (n=187)	
	No. (Column %)	No. (Column %)	*P* Value
Sociodemographics			
Age, median (IQR), y	46 (41–53)	47 (41–52)	0.64
Race/ethnicity			0.28
Non-Hispanic black	265 (51.7)	94 (50.3)	
Hispanic	158 (30.8)	51 (27.3)	
Non-Hispanic white	28 (5.5)	9 (4.8)	
Other/unknown	62 (12.1)	33 (17.6)	
Education at study entry			0.057
Did not complete high school	230 (44.8)	65 (34.8)	
Completed high school	136 (26.5)	58 (31.0)	
Attended or completed college	147 (28.7)	64 (34.2)	
Income ≤$30 000/y	422 (82.3)	147 (78.6)	0.27
Behavioral characteristics			
History of smoking			0.016*
Never smoker	156 (30.4)	42 (22.5)	
Former smoker	167 (32.6)	54 (28.9)	
Current smoker	190 (37.0)	91 (48.7)	
Current alcohol use			<0.0001*
Abstainer	331 (64.5)	86 (46.0)	
Light (<3 drinks per wk)	137 (26.7)	65 (34.8)	
Moderate (3–13 drinks per wk)	12 (2.3)	17 (9.1)	
Heavier (≥14 drinks per wk)	33 (6.4)	19 (10.2)	
Recent crack/cocaine use since last visit	29 (5.7)	14 (7.5)	0.37
History of injection drug use	31 (6.0)	17 (9.1)	0.16
History of hepatitis C virus infection	145 (28.3)	40 (21.4)	0.068
Psychosocial risk factors			
High depressive symptoms†	148 (28.8)	45 (24.1)	0.21
High perceived stress‡	178 (34.7)	69 (36.9)	0.59
Probable PTSD§	69 (13.5)	28 (15.0)	0.61
Cardiometabolic risk factors			
Body mass index, kg/m^2			0.0021*
<18.5 (underweight)	7 (1.4)	2 (1.1)	
18.5 to <25 (normal)	126 (24.6)	26 (13.9)	
25 to <30 (overweight)	166 (32.4)	53 (28.3)	
≥30 (obese)	214 (41.7)	106 (56.7)	
Systolic blood pressure ≥140 mm Hg	49 (9.6)	30 (16.0)	0.016*
Current use of antihypertensive medication	153 (29.8)	56 (29.9)	0.98
Total cholesterol ≥240 mg/dL	24 (4.7)	15 (8.0)	0.088
HDL-C <40 mg/dL	104 (20.3)	21 (11.2)	0.0057*
Current use of lipid-lowering medication	72 (14.0)	17 (9.1)	0.082
History of diabetes mellitus	97 (18.9)	42 (22.5)	0.30
Postmenopausal	205 (40.0)	62 (33.2)	0.10
HIV-specific characteristics			
History of clinical AIDS	216 (42.1)	…	…
Nadir CD4 cell count, cells/μL			…

(*Continued*)

Table 2. Continued

	WLWH (n=513)	HIV-Negative Women (n=187)	
	No. (Column %)	No. (Column %)	*P* Value
<200	253 (49.3)	···	
200 to 500	230 (44.8)	···	
>500	30 (5.8)	···	
Current CD4 cell count, cells/μL			···
<200	65 (12.7)	···	
200 to 500	171 (33.3)	···	
>500	277 (54.0)	···	
HIV viral load <200 copies/mL	365 (71.2)	···	
History of HAART use			···
Never used HAART	27 (5.3)	···	
Previous use of HAART	46 (9.0)	···	
Current use of HAART	440 (85.8)	···	
PI-based	271 (52.8)	···	
NNRTI-based	161 (31.4)	···	
INSTI-based	82 (16.0)	···	

HAART indicates highly active antiretroviral therapy; HDL-C, high-density lipoprotein cholesterol; INSTI, integrase strand transfer inhibitor; IQR, interquartile range; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PTSD, posttraumatic stress disorder; WIHS, Women's Interagency HIV Study; and WLWH, women living with HIV.

*$P<0.05$.

†Score ≥16 on the 20-item Center for Epidemiologic Studies Depression Scale (CES-D).

‡Score ≥18 (ie, in the upper tertile) on the 10-item Perceived Stress Scale (PSS-10).

§Score ≥45 and meeting *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition,* symptom criteria for re-experiencing (≥1 B item), avoidance (≥3 C items), and arousal (≥2 D items) on the 17-item PTSD Checklist-Civilian Version (PCL-C).

to detect carotid artery focal plaque, we demonstrated that persistently high depressive symptoms over ≈7 years and a high burden of psychosocial risk factors at the end of follow-up were positively associated with incident and prevalent subclinical atherosclerosis, respectively, among WLWH, a

Table 3. Prevalence of Carotid Artery Focal Plaque Stratified by HIV Serostatus and Psychosocial Risk Factors (n=700)

	WLWH (n=513)			HIV-Negative Women (n=187)		
	No.	With Plaque, No. (%)	*P* Value	No.	With Plaque, No. (%)	*P* Value
Overall	513	71 (13.8)	···	187	17 (9.1)	···
Has high depressive symptoms*			0.0072†			0.56‡
Yes	148	30 (20.3)		45	5 (11.1)	
No	365	41 (11.2)		142	12 (8.5)	
Has high perceived stress§			0.025†			0.23
Yes	178	33 (18.5)		69	4 (5.8)	
No	335	38 (11.3)		118	13 (11.0)	
Has probable PTSD‖			0.59			1.0‡
Yes	69	11 (15.9)		28	2 (7.1)	
No	444	60 (13.5)		159	15 (9.4)	
Latent class membership			0.0017†			1.0‡
High psychosocial risk	120	27 (22.5)		43	4 (9.3)	
Low psychosocial risk	393	44 (11.2)		144	13 (9.0)	

PTSD indicates posttraumatic stress disorder; and WLWH, women living with HIV.

*Score ≥16 on the 20-item Center for Epidemiologic Studies Depression Scale (CES-D).

†$P<0.05$.

‡Calculated using Fisher exact testing.

§Score ≥18 (ie, in the upper tertile) on the 10-item Perceived Stress Scale (PSS-10).

‖Score ≥45 and meeting *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition,* symptom criteria for re-experiencing (≥1 B item), avoidance (≥3 C items), and arousal (≥2 D items) on the 17-item PTSD Checklist-Civilian Version (PCL-C).

Table 4. Adjusted Associations by HIV Serostatus Between Psychosocial Risk Factors and Prevalent Carotid Artery Focal Plaque (N=700)

	WLWH (n=513)		HIV-Negative Women (n=187)	
	aOR (95% CI)	*P* Value	aOR (95% CI)	*P* Value
High depressive symptoms				
Model 1: reduced*	1.93 (1.08–3.46)	0.026†	1.50 (0.42–5.41)	0.54
Model 2: adjusted for cardiometabolic risk factors‡	1.94 (1.07–3.54)	0.030†	1.16 (0.28–4.83)	0.84
Model 3: adjusted for HIV-related factors§	1.97 (1.06–3.67)	0.032†	…	…
Model 4 (full): adjusted for use of psychotropic medications‖	1.87 (0.99–3.55)	0.055	1.27 (0.30–5.43)	0.75
High perceived stress				
Model 1: reduced*	1.73 (0.98–3.05)	0.060	0.52 (0.14–1.96)	0.33
Model 2: adjusted for cardiometabolic risk factors‡	1.78 (0.99–3.20)	0.053	0.51 (0.12–2.19)	0.37
Model 3: adjusted for HIV-related factors§	1.81 (0.99–3.30)	0.054	…	…
Model 4 (full): adjusted for use of psychotropic medications‖	1.75 (0.96–3.21)	0.070	0.53 (0.12–2.28)	0.40
Probable PTSD				
Model 1: reduced*	0.96 (0.43–2.13)	0.92	0.83 (0.16–4.50)	0.83
Model 2: adjusted for cardiometabolic risk factors‡	0.91 (0.39–2.12)	0.83	0.88 (0.14–5.49)	0.89
Model 3: adjusted for HIV-related factors§	0.87 (0.37–2.12)	0.79	…	…
Model 4 (full): adjusted for use of psychotropic medications‖	0.79 (0.32–1.95)	0.61	0.96 (0.15–6.17)	0.96
High (vs low) psychosocial risk latent class membership				
Model 1: reduced*	2.01 (1.11–3.64)	0.022†	1.21 (0.31–4.70)	0.78
Model 2: adjusted for cardiometabolic risk factors‡	2.04 (1.11–3.76)	0.022†	1.01 (0.23–4.58)	0.99
Model 3: adjusted for HIV-related factors§	2.22 (1.18–4.17)	0.014†	…	…
Model 4 (full): adjusted for use of psychotropic medications‖	2.12 (1.11–4.05)	0.023†	1.07 (0.24–4.84)	0.93

aOR indicates adjusted odds ratio; PTSD, posttraumatic stress disorder; and WLWH, women living with HIV.

*Adjusted for age (in years), race/ethnicity (non-Hispanic black, Hispanic, non-Hispanic white, or other/unknown), current income (≤$30 000 or >$30 000 per year), education at study entry (did not complete high school, completed high school, or attended/completed college), history of smoking (current, former, or never), current alcohol use (abstainer, light, moderate, or heavy), crack/cocaine use since last visit (yes or no), history of injection drug use (yes or no), history of hepatitis C virus infection (yes or no), and current self-reported menopausal status (premenopausal or postmenopausal).

†$P<0.05$.

‡Adjusted for all covariates included in model 1 as well as current body mass index (in kg/m^2), current systolic blood pressure (in mm Hg), current total cholesterol (in mg/dL), current high-density lipoprotein cholesterol (in mg/dL), current use of lipid-lowering therapy (yes or no), current use of antihypertensive medication (yes or no), and history of diabetes mellitus (yes or no).

§Adjusted for all covariates included in models 1 and 2 as well as nadir CD4 cell count (in cells/μL), history of AIDS (yes or no), current CD4 cell count (in cells/μL), current HIV viral load (<200 or ≥200 copies/mL), and current use of highly affective antiretroviral therapy (protease inhibitor–based, nonprotease inhibitor–based, or none).

‖Adjusted for all covariates included in models 1 and 2—and for WLWH, all covariates included in model 3—as well as current self-reported use of psychiatric medications (yes or no).

subpopulation disproportionately affected by depression and psychosocial stress who have experienced 3 times greater rates of CVD compared with HIV-negative women.[4–7,9,10] Associations changed little after adjustment for sociodemographic, behavioral, cardiometabolic, and HIV-related factors, providing evidence that psychosocial risk factors were independently associated with atherosclerotic risk among WLWH. Our finding that high psychosocial risk latent class membership was associated with prevalent plaque appears driven by depressive symptoms and perceived stress rather than by PTSD symptoms, which might in part be related to the smaller number of participants who reported PTSD symptoms. Given the younger age distribution of participants at the time of this substudy, the use of subclinical atherosclerosis as our outcome measure was appropriate, as subclinical carotid plaque was relatively common in this cohort compared with clinical CVD events. Findings suggest that WLWH with depression and/or psychosocial stress may confront a disproportionately high risk of atherosclerotic CVD

Table 5. Adjusted Associations by HIV Serostatus Between the Proportion of Visits With High Depressive Symptoms and Carotid Artery Focal Plaque Formation (n=741)

	WLWH (n=547)		HIV-Negative Women (n=194)	
	aOR (95% CI)	*P* Value	aOR (95% CI)	*P* Value
High depressive symptoms at ≥45% (vs <45%) of visits				
Model 1: reduced*	1.98 (1.11–3.54)	0.021†	1.09 (0.27–4.50)	0.90
Model 2: adjusted for cardiometabolic risk factors‡	2.00 (1.10–3.63)	0.023†	0.82 (0.16–4.16)	0.81
Model 3: adjusted for HIV-related factors§	1.96 (1.06–3.64)	0.033†	···	···

aOR indicates adjusted odds ratio.

*Adjusted for duration of follow-up, presence of focal plaque at baseline, age at baseline (in years), race/ethnicity (non-Hispanic black, Hispanic, non-Hispanic white, or other/unknown), education at study entry (did not complete high school, completed high school, or attended/completed college), and cumulative measures of income (≤$30 000 or >$30 000 per year), history of smoking (current, former, or never), alcohol use (abstainer, light, moderate, or heavy), crack/cocaine use since last visit (yes or no), history of injection drug use (yes or no), history of hepatitis C virus infection (yes or no), and self-reported menopausal status (premenopausal or postmenopausal).

†$P<0.05$.

‡Full model for HIV-negative women. Adjusted for all covariates included in model 1 as well as cumulative measures of body mass index (in kg/m^2), systolic blood pressure (in mm Hg), total cholesterol (in mg/dL), high-density lipoprotein cholesterol (in mg/dL), use of lipid-lowering therapy (yes or no), use of antihypertensive medication (yes or no), and history of diabetes mellitus (yes or no).

§Full model for women living with HIV (WLWH). Adjusted for all covariates included in models 1 and 2 as well as cumulative measures of nadir CD4 cell count (in cells/μL), history of AIDS (yes or no), CD4 cell count (in cells/μL), HIV viral load (<200 or ≥200 copies/mL), and use of highly affective antiretroviral therapy (protease inhibitor–based, nonprotease inhibitor–based, or none).

as they age compared with WLWH without such symptoms.

To our knowledge, this is the first investigation to examine psychosocial risk factors with respect to subclinical CVD among WLWH. Our findings build on prior research conducted among WLWH in the WIHS that found a positive association between persistently high depressive symptoms and higher Framingham coronary risk scores, which utilized measures for CVD risk factors (but not subclinical CVD).[24,25] To date, aside from analyses in the predominantly male VACS (Veterans Aging Cohort Study) that used diagnoses for major depressive disorder,[22,23] studies examining the HIV-associated risk of either subclinical atherosclerosis or incident CVD events have not incorporated measures for psychosocial risk factors.[4–7,41–47] While WLWH and HIV-negative women in WIHS had a similar prevalence of psychosocial risk factors (a key strength of the study design), it is possible that analyses in studies with less comparable study groups were affected by unmeasured confounding caused by differences in psychosocial risk factors between participants with and without HIV. Given the high psychosocial risk burden among WLWH, such unmeasured confounding might in part explain why the association between HIV and CVD has appeared stronger among women compared with men.

We had null findings among HIV-negative women. These results should be interpreted cautiously, as there was a smaller sample size, lower prevalence of carotid artery focal plaque, and thus less precise estimates for measures of association. Nonetheless, the associations between psychosocial risk factors and atherosclerosis were stronger among WLWH, and there was little evidence of similar associations among HIV-negative women. Additional research in large cohorts of PLWH with HIV-uninfected comparison groups is needed to further characterize differences by HIV status in the role of psychosocial factors as atherosclerotic risk factors. Depression, stress, and trauma are known to predict markers of HIV disease progression including decreases in CD4 cell count, increases in HIV viral load, and clinical decline,[18–20] which are contributors of increased CVD risk among PLWH.[21] In our analysis, we detected associations even after adjustment for HIV-related characteristics, suggesting that other unmeasured factors might explain these differences. In one study that defined a composite biomarker index incorporating stress-related neuroendocrine biomarkers (ie, urinary cortisol and catecholamines), WLWH had higher index values than HIV-negative women.[48] Our findings raise the question of whether having a chronically active physiologic stress response (ie, heightened activity of the hypothalamic pituitary adrenal axis and sympathetic nervous system) might have more adverse effects on pathways influencing atherosclerotic risk in the setting of HIV-associated chronic inflammation and immune activation.

Results should be interpreted within the context of several limitations. First, because of the aforementioned limitations regarding the smaller sample size of HIV-negative participants, there were imprecise estimates for measures of association among HIV-negative women. As such, we were limited in our ability to meaningfully compare associations between WLWH and HIV-negative women. Second, perceived stress and PTSD symptoms were not measured until the latter half of the follow-up period, and only every

2 years thereafter, precluding our ability to predict incident plaque formation using cumulative measures of perceived stress and probable PTSD. In cross-sectional analyses, there was variability in the timing of participants' most recent stress/PTSD measures with respect to their carotid ultrasound measurements. Further, since depressive symptoms were evaluated more frequently, many participants' most recent measures for depressive symptoms and stress/PTSD symptoms were on different dates. Third, because of the moderate sample size, LCA may not have identified the true number of subgroups of psychosocial risk factor patterns in this sample. Correlations among CES-D, PSS-10, and PCL-C instruments, and overlap in the symptoms assessed by each, might have also contributed to the 2-class model having been selected as preferable. Fourth, we could not adjust for psychiatric medication use in the prospective analysis, as it was not ascertained across 9 semiannual visits during follow-up. In the cross-sectional analysis, associations changed little after adjustment. Since psychosocial risk factors were defined based on self-reported symptoms, we expect that any changes in symptoms attributed to psychiatric treatment would have already been accounted for in the analysis. We also lacked data on the use of behavioral interventions such as individual or group counseling. Fifth, although we adjusted for many confounding factors, we were unable to consider behavioral factors such as diet, exercise, and sleep habits, which might have resulted in unmeasured confounding.

CONCLUSIONS

This study demonstrates that psychosocial risk factors were independent risk factors for subclinical atherosclerosis among WLWH. Future research should further characterize differences by HIV status and sex in the risk of atherosclerosis, and of incident CVD events, associated with a greater burden of psychosocial risk factors. Possible mechanisms by which psychosocial risk factors may differentially contribute to greater atherosclerotic risk among WLWH compared with HIV-negative women should also be investigated. Finally, research is needed to determine whether clinical interventions for depression and psychosocial stress can mitigate the increased risk of subclinical atherosclerosis for WLWH.

ARTICLE INFORMATION

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Affiliations

From the Department of Epidemiology, Milken Institute School of Public Health at the George Washington University, Washington, DC (M.E.L., A.D.C.); Departments of Medicine (K.A.) and Epidemiology & Population Health (K.A., R.C.K.), Albert Einstein College of Medicine, Bronx, NY; Departments of Neurology and Emergency Medicine, State University of New York Downstate Health Sciences University, Brooklyn, NY (S.R.L.); Department of Neurology, Kings County Hospital Center, Brooklyn, NY (S.R.L.); Department of Medicine, Georgetown University Medical Center, Washington, DC (M.P., S.K.); Department of Psychology, The George Washington University, Washington, DC (S.M.); Division of Endocrinology, George Washington University School of Medicine and Health Sciences, Washington, DC (S.S.); Cardiovascular Core Laboratories and Cardiac Imaging Research, MedStar Health Research Institute, MedStar Heart and Vascular Institute, Washington, DC (F.M.A.); Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA (J.M.); New York University School of Dentistry and Bluestone Center for Clinical Research, New York, NY (B.A.); Cook County Health/Hektoen Institute of Medicine, Chicago, IL (K.M.W.); Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD (E.T.G.).

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Disclosures

None.

Supplementary Materials

Tables S1–S2

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SUPPLEMENTAL MATERIAL

Table S1. Fit statistics for latent class models of psychosocial risk factors among women in the Women's Interagency HIV Study cardiovascular sub-study, 2010-2012 (n=700).

Fit statistics	2 classes	3 classes	4 classes
AIC	**2040.628**	2048.628	2056.628
BIC	**2072.486**	2098.690	2124.895
ABIC	**2050.260**	2063.763	2077.267
Adj. LMR-LRT *(p)*	**260.035 (<0.0001)**	0 (0.50)	0 (0.71)
BLRT *(p)*	**269.958 (<0.0001)**	0 (1.00)	0 (1.00)
Entropy	**0.768**	0.659	0.691

AIC, Akaike information criterion; BIC, Bayesian information criterion; ABIC, sample size adjusted Bayesian information criterion; adj. LMR-LRT, adjusted Lo-Mendell-Rubin likelihood ratio test; BLRT bootstrap likelihood ratio test; *p*, p-value.

Boldface indicates optimal fit (i.e., lowest for AIC, BIC, and ABIC; $p<0.05$ for adj. LMR-LRT and BLRT; highest for entropy).

Table S2. Cumulative measures of characteristics during follow-up by HIV serostatus among women in the Women's Interagency HIV Study cardiovascular sub-study, 2004-2012 (n=741).

	WLWH (n=547)	**HIV-negative women (n=194)**	
Static covariates	**n (col %)**	**n (col %)**	**p**
Age at baseline (years), median (IQR)	40 (35-46)	40 (34-46)	0.44
Race/ethnicity			0.26
Non-Hispanic Black	281 (51.4)	100 (51.6)	
Hispanic	165 (30.2)	50 (25.8)	
Non-Hispanic white	31 (5.7)	9 (4.5)	
Other/unknown	70 (12.8)	35 (18.0)	
Education at study entry			0.11
Did not complete high school	242 (44.2)	69 (35.6)	
Completed high school	149 (27.2)	60 (30.9)	
Attended or completed college	156 (28.5)	65 (33.5)	
Duration of follow-up (years), median (IQR)	6.6 (6.4-7.0)	6.6 (6.5-7.0)	0.29
Presence of focal plaque at baseline	39 (7.1)	15 (7.7)	0.78
Time-updated covariates*	**n (%) at end of follow-up**	**n (%) at end of follow-up**	**p**
History of injection drug use	36 (6.6)	18 (9.3)	0.21
History of hepatitis C infection	160 (29.3)	41 (21.1)	**0.029**
History of diabetes	109 (19.9)	46 (23.7)	0.27
Postmenopausal (self-reported)	218 (39.9)	61 (31.4)	**0.038**
History of clinical AIDS	230 (42.1)	---	---
Nadir CD4 count (cells/μL), median (IQR)	206 (87-313)	---	---
Time-varying categorical covariates	**mean % of visits (SD)**	**mean % of visits (SD)**	**p**
Income ≤$30,000 per year	83% (31)	80% (31)	0.065
History of smoking			
Never smoked	31% (46)	22% (41)	**0.013**
Former smoker	29% (40)	26% (38)	0.61
Current smoker	39% (44)	52% (45)	**0.0009**
Current alcohol use			
Abstainer	62% (37)	44% (37)	**<0.0001**
Light (<3 drinks/week)	30% (31)	38% (32)	**0.0003**
Moderate (3-13 drinks/week)	3% (8)	5% (9)	**<0.0001**
Heavier (≥14 drinks/week)	5% (14)	12% (21)	**<0.0001**
Recent crack/cocaine use since last visit	6% (18)	12% (24)	**<0.0001**
Current use of anti-hypertensive medication	22% (38)	18% (35)	0.32
Current use of lipid-lowering medication	8% (24)	4% (16)	**0.013**
HIV viral load <200 copies/mL	61% (35)	---	---
Current use of HAART			
PI-based use of HAART	48% (41)	---	---
Non-PI-based	28% (37)	---	---
None	25% (35)	---	---

Time-varying continuous covariates	mean of means across visits (SD)	mean of means across visits (SD)	p
Body mass index (kg/m^2)	29.4 (7.0)	32.8 (8.7)	**<0.0001**
Systolic blood pressure (mm Hg)	119 (13)	123 (15)	**0.0004**
Total cholesterol (mg/dL)	176 (32)	178 (33)	0.63
HDL-C (mg/dL)	50 (14)	55 (14)	**<0.0001**
Current CD4 count (cells/μL)	530 (265)	---	---

HAART, highly active antiretroviral therapy; HDL-C, high-density lipoprotein cholesterol; INSTI, integrase strand transfer inhibitor; IQR, interquartile range; PI, protease inhibitor; SD, standard deviation; WLWH, women living with HIV.

Boldface indicates p<0.05.

* During study follow-up, 6 participants reported injection drug use for the first time (0.8%), 6 participants were newly infected with hepatitis C virus (0.8%), 49 participants were newly classified as having diabetes (6.6%), 268 participants reported post-menopausal status for the first time (36.2%), 40 participants with HIV had newly identified clinical AIDS (7.3%), and 248 participants with HIV had a new nadir CD4 count (45.3%).