ORIGINAL RESEARCH

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

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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 semiannual 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. Women living with HIV (WLWH) have an ∼3 times greater CVD risk compared with HIV-negative women, suggesting that the HIV-associated CVD risk is greater among women compared with men, the cause of which is not well understood. Identification of novel pathways that explain the excess CVD risk among WLWH is needed.
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

Nonstandard Abbreviations and Acronyms

| Acronym | Description |
|---------|-------------|
| 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 |
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 sites31 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 (≥16 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 over-loaded (α=0.87).35 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 | Latent Class 2: High Psychosocial Risk |
|--------------------------------------|---------------------------------------|
| (n=537), %                           | (n=163), %                             |
| Class prevalence                     | 76.7                                  |
| 23.3                                 |                                       |
| Conditional item-response probabilities|                                      |
| High depressive symptoms*            | 13.3                                  |
| High perceived stress†               | 12.0                                  |
| Probable PTSD‡                       | 1.5                                   |

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/m², 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) | P Value |
| No. (Column %) | No. (Column %) | |
|  **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** | | 0.016* |
| History of smoking | | |
| 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** | | 0.21 |
| High depressive symptoms† | 148 (28.8) | 45 (24.1) | |
| High perceived stress‡ | 178 (34.7) | 69 (36.9) | 0.59 |
| Probable PTSD§ | 69 (13.5) | 28 (15.0) | 0.61 |
|  **Cardiometabolic risk factors** | | 0.0021* |
| Body mass index, kg/m² | | |
| <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 (9.8) | 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)
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. (Column %) | No. (Column %) | P Value |
| Overall              | 513          | 71 (13.8)                 | ... |
| Has high depressive symptoms* | 148          | 30 (20.3)                 | ... |
| Yes                  | 148          | 30 (20.3)                 | 0.0072† |
| No                   | 365          | 41 (11.2)                 | ... |
| Has high perceived stress§ | 178          | 33 (18.5)                 | ... |
| Yes                  | 178          | 33 (18.5)                 | 0.025§ |
| No                   | 335          | 38 (11.3)                 | ... |
| Has probable PTSD∥   | 335          | 38 (11.3)                 | ... |
| Yes                  | 69           | 11 (15.9)                 | 0.59  |
| No                   | 444          | 60 (13.5)                 | ... |
| Latent class membership | 444          | 60 (13.5)                 | ... |
| High psychosocial risk | 120          | 27 (22.5)                 | 0.0017† |
| Low psychosocial risk | 393          | 44 (11.2)                 | ... |

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).
subpopulation disproportionately affected by depression and psychosocial stress who have experienced 3 times greater rates of CVD compared with HIV-negative women.\textsuperscript{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 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\textsuperscript{*} | 1.93 (1.08–3.46) | 0.026\textsuperscript{†} | 1.50 (0.42–5.41) | 0.54 |
| Model 2: adjusted for cardiometabolic risk factors\textsuperscript{4} | 1.94 (1.07–3.54) | 0.030\textsuperscript{†} | 1.16 (0.28–4.83) | 0.84 |
| Model 3: adjusted for HIV-related factors\textsuperscript{5} | 1.97 (1.06–3.67) | 0.032\textsuperscript{†} | ... | ... |
| Model 4 (full): adjusted for use of psychotropic medications\textsuperscript{6} | 1.87 (0.99–3.55) | 0.055 | 1.27 (0.30–5.43) | 0.75 |
| **High perceived stress** | | | | |
| Model 1: reduced\textsuperscript{*} | 1.73 (0.98–3.05) | 0.060 | 0.52 (0.14–1.96) | 0.33 |
| Model 2: adjusted for cardiometabolic risk factors\textsuperscript{4} | 1.78 (0.99–3.20) | 0.053 | 0.51 (0.12–2.19) | 0.37 |
| Model 3: adjusted for HIV-related factors\textsuperscript{5} | 1.81 (0.99–3.30) | 0.054 | ... | ... |
| Model 4 (full): adjusted for use of psychotropic medications\textsuperscript{6} | 1.75 (0.96–3.21) | 0.070 | 0.53 (0.12–2.28) | 0.40 |
| **Probable PTSD** | | | | |
| Model 1: reduced\textsuperscript{*} | 0.96 (0.43–2.13) | 0.92 | 0.83 (0.16–4.50) | 0.83 |
| Model 2: adjusted for cardiometabolic risk factors\textsuperscript{4} | 0.91 (0.39–2.12) | 0.83 | 0.88 (0.14–5.49) | 0.89 |
| Model 3: adjusted for HIV-related factors\textsuperscript{5} | 0.87 (0.37–2.12) | 0.79 | ... | ... |
| Model 4 (full): adjusted for use of psychotropic medications\textsuperscript{6} | 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\textsuperscript{*} | 2.01 (1.11–3.64) | 0.022\textsuperscript{†} | 1.21 (0.31–4.70) | 0.78 |
| Model 2: adjusted for cardiometabolic risk factors\textsuperscript{4} | 2.04 (1.11–3.76) | 0.022\textsuperscript{†} | 1.01 (0.23–4.58) | 0.99 |
| Model 3: adjusted for HIV-related factors\textsuperscript{5} | 2.22 (1.18–4.17) | 0.014\textsuperscript{†} | ... | ... |
| Model 4 (full): adjusted for use of psychotropic medications\textsuperscript{6} | 2.12 (1.11–4.05) | 0.023\textsuperscript{†} | 1.07 (0.24–4.84) | 0.93 |

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

\textsuperscript{*}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).

\textsuperscript{†}P<0.05.

\textsuperscript{*}Adjusted for all covariates included in model 1 as well as current body mass index (in kg/m\textsuperscript{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).

\textsuperscript{4}Adjusted for all covariates included in models 1 and 2 as well as nadir CD4 cell count (in cells/\mu L), history of AIDS (yes or no), current CD4 cell count (in cells/\mu L), current HIV viral load (<200 or ≥200 copies/mL), and current use of highly active antiretroviral therapy (protease inhibitor–based, nonprotease inhibitor–based, or none).

\textsuperscript{5}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).
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 WHS 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 WHS 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

| 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).

†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/m²), 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 HIV-negative women. 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 effective antiretroviral therapy (protease inhibitor–based, nonprotease inhibitor–based, or none).
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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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).

| Static covariates                              | WLWH (n=547) | HIV-negative women (n=194) | p    |
|------------------------------------------------|--------------|---------------------------|------|
| Age at baseline (years), median (IQR)          | 40 (35-46)   | 40 (34-46)                | 0.44 |
| Race/ethnicity                                 |              |                           |      |
| Non-Hispanic Black                             | 281 (51.4)   | 100 (51.6)                | 0.26 |
| 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                                           | 23% (35)                  | ---                       |      |
| Time-varying continuous covariates                  | mean of means across visits (SD) | mean of means across visits (SD) | P         |
|---------------------------------------------------|-----------------------------------|-----------------------------------|-----------|
| Body mass index (kg/m²)                           | 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.

* 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%).

Boldface indicates p<0.05.