Title

Sex-specific associations between plasma interleukin-6 and depression in persons with and without HIV

Authors

Petersen, Kalen J

Yu, Xiaoying

Masters, Mary Clare

et al.

Publication Date

2023-07-01

DOI

10.1016/j.bbih.2023.100644

Brain, Behavior, & Immunity - Health 30 (2023) 100644

Contents lists available at ScienceDirect

Brain, Behavior, & Immunity - Health

journal homepage: www.editorialmanager.com/bbih/default.aspx

Sex-specific associations between plasma interleukin-6 and depression in persons with and without HIV

Kalen J. Petersen [a,1], Xiaoying Yu [b,1], Mary Clare Masters [c], Judith D. Lobo [d], Tina Lu [a], Scott Letendre [d,e], Ronald J. Ellis [d], J. Allen McCutchan [e], Erin Sundermann [d,*]

[a] Department of Neurology, Washington University in St. Louis, St. Louis, Missouri, USA
[b] Department of Biostatistics & Data Science, The University of Texas Medical Branch, Galveston, TX, USA
[c] Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
[d] Department of Psychiatry, The University of California San Diego, San Diego, CA, USA
[e] Department of Medicine, The University of California San Diego, San Diego, CA, USA

ARTICLE INFO

Keywords:
Depression
HIV infection
Inflammation
Sex differences

ABSTRACT

Background: Persons with HIV (PWH) have both more frequent depression and higher levels of plasma inflammatory biomarkers compared to persons without HIV (PWoH). Inflammation and depressive symptoms are linked, including in PWH; however, it is unclear whether these associations differ by HIV serostatus and biological sex.

Methods: Six plasma inflammatory biomarkers were assessed using samples from PWH and PWoH who participated in six NIH-funded studies through the UCSD HIV Neurobehavioral Research Program (HNRP) from 2011 to 2019. Factor analysis was performed to identify intercorrelated groups of biomarkers. Factors and their components were then examined for relationships with Beck Depression Inventory-II (BDI-II) and modifying effects of sex or HIV serostatus using multivariable linear regression, adjusting for demographics, substance use diagnoses, and relevant co-morbidities.

Results: Participants included 150 PWH (age = 48.3 ± 13.1 yr; 88% biologically male) and 138 PWoH (age = 46.3 ± 15.9; 56% male). Two inflammatory factors were identified: Factor 1 loaded on interleukin-6 (IL-6), C-reactive protein (CRP), and D-dimer; Factor 2 loaded on interleukin-8, chemokine C–C ligand 2 (CCL2), and chemokine C-X-C ligand 10 (CXCL10). Sex modified the effect of Factor 1 on BDI-II, with a more positive association for men than women ($p = 0.04$). No significant association between Factor 2 and BDI-II was found. Of the biomarkers in Factor 1, only IL-6 was significantly associated with BDI-II and was modified by sex ($p = 0.003$). In sex-stratified analysis, a positive association was found for men ($\beta = 5.42$; 95% confidence interval = [1.32, 9.52]) but not women ($\beta = -3.88$; 95% C.I. = [-11.02, 3.26]). No HIV-related interactions were detected.

Interpretation: We identified a depression-associated inflammatory factor present in both PWH and PWoH, consistent with prior studies of PWH only. The association was driven by a correlation between IL-6 and depression exclusively in men, suggesting that the depression-inflammation link differs by sex. Future studies of depression etiology or treatment, including those on persons with HIV, should consider the impact of biological sex in both design and analysis.

1. Introduction

HIV and depression commonly co-occur. Depression is two to three times more common among persons with HIV (PWH) compared to the general population (Bing et al., 2001; Orlando et al., 2002). The lifetime prevalence of depression among PWH is estimated to be as high as 45% (Cruess et al., 2003; Nanni et al., 2015). Among PWH, depression has been associated with adverse health outcomes including decreases in: (a) adherence to antiretroviral therapy (ART) (Gonzalez et al., 2011), (b) HIV virologic suppression (Gokhale et al., 2019), (c) health-related quality of life (Jia et al., 2004; Tate et al., 2003), and (d) overall survival (Ironson et al., 2017). Thus, insights into underlying mechanisms

* Corresponding author. UCSD ACTRI building, office 2W517, 9452 Medical Center Dr. (MC 0875), La Jolla, CA, 92037, USA.
E-mail address: esundermann@health.ucsd.edu (E. Sundermann).
[1] These authors contributed equally to the work.

https://doi.org/10.1016/j.bbih.2023.100644
Received 9 December 2022; Received in revised form 19 April 2023; Accepted 25 May 2023
Available online 1 June 2023

and interventions to improve treatment of depression in PWH are needed.

Inflammatory processes have been implicated in the pathophysiology of depression in the general population (Haroon et al., 2018; Howren et al., 2009; Miller and Raison, 2016; Osimo et al., 2020). Observational studies have demonstrated that higher levels of systemic inflammation markers such as C-reactive protein (CRP) and interleukin-6 (IL-6) are associated with, and predict, development of depressive symptoms in otherwise healthy adults (Gimeno et al., 2009; Huang et al., 2019; Wium-Andersen et al., 2013). Experimental studies have shown that activation of inflammatory cytokines induces depressive symptoms (Cho et al., 2019; Irwin et al., 2019). In addition, treatment with anti-inflammatory agents reduces depressive symptoms in individuals with chronic inflammatory conditions (Bai et al., 2020; Kappelmann et al., 2018; Raison et al., 2013). These findings suggest that chronic inflammation plays a key role in the pathophysiology of depression and represents a potential therapeutic target.

Even with virally suppressive ART, chronic inflammation persists among PWH and is associated with non-infectious comorbidities (Deeks, 2011; Tenorio et al., 2014). Multiple studies have demonstrated that increased inflammatory biomarkers are associated with depressive symptoms in PWH (Ellis et al., 2020; Hellmuth et al., 2017; Lu et al., 2019; Musinguzi et al., 2018; Norcini Pala et al., 2016; Poudel-Tandukar et al., 2014; Rivera-Rivera et al., 2014; Saylor et al., 2019). In the limited number of studies that have included both PWH and persons without HIV (PWoH), increased inflammatory biomarkers have been linked to depression regardless of HIV serostatus (Lu et al., 2019; Stewart et al., 2020). However, such analyses did not evaluate sex differences. In a prior analysis from our group of PWH in the CNS HIV Antiretroviral Therapy Effects Research (CHARTER) cohort, higher inflammatory biomarkers (i.e., IL-6 and d-dimer) were associated with increased depressive symptoms in PWH (Ellis et al., 2020). In sex-stratified analyses, these associations were found to be specific to men.

To our knowledge, however, no studies to date have evaluated the modifying role of sex on the association between inflammation and depression in a cohort of both PWH and PWoH. The potential for sex disparities in the inflammation-depression link is an important unanswered question given sex differences in depression prevalence, symptoms, and pathophysiology (Eid et al., 2019) and the impact of biological sex and sex-specific genetic determinants of immune function (Schmiedel et al., 2018). To address this gap, we utilized plasma-based inflammatory biomarker and depressive symptom data from participants in the University of California, San Diego's HIV Neurobehavioral Research Program (HNRP) to identify the most relevant inflammatory biomarkers for depressed mood.

We tested the hypothesis that elevated inflammatory biomarkers are associated with greater depressive symptoms in PWH, and examined the role of biological sex in the link between depression and inflammation. Based on prior findings (Ellis et al., 2020), we also hypothesized a moderating role of sex such that associations between inflammatory biomarkers and depressive symptoms would be stronger in men than in women. Previous studies have also found sex-specific associations between inflammation and depression treatment. For example, change in plasma levels of interleukin-8 (IL-8) was found to predict ketamine response with opposite effect directions in male and female clinical trial participants (Kruse et al., 2021a, 2021b).

For this study, inflammatory biomarkers were selected based on both availability in the HNRP database and prior evidence of relevance to psychiatric comorbidities, particularly in PWH. For example, IL-6 levels are associated with depression and social isolation in PWH (Ellis et al., 2020, 2021). Similarly, CRP was found to be associated with depressive symptoms in PWH, with a stronger association in men than women (Poudel-Tandukar et al., 2014). Elevated d-dimer levels in the blood have been linked with greater somatic depressive symptoms in veterans with HIV even with adjustment for antidepressant use (Stewart et al., 2020). Notably, this study also found a correlation between higher IL-6 and somatic depression among PWoH. Similarly, chemokine C-X-C ligand 10 (CXCL10) was correlated with depressive symptoms in PWH (Cassol et al., 2015). Murine studies have demonstrated upregulation of CXCL10 in the hippocampus and frontal lobe with induced depressive-like behaviors (Slusarczyk et al., 2016). In humans, decreased peripheral CXCL10 was associated with responsiveness to antidepressant therapy (Wong et al., 2008). Finally, plasma chemokine C–C ligand 2 (CCL2) has been linked with brain microstructural injury in various regions, suggesting a potentially important predictor of neuropsychiatric or neurocognitive function (Ragin et al., 2006). CCL2 has been implicated in depression via its effect on neurotransmitter release and its co-localization with acetylcholine and dopamine structures in the central nervous system (Curzytek and Leskiewicz, 2021). Furthermore, its gene expression is elevated in patients with major depressive disorder (Tang et al., 2022). Thus, these six biomarkers were included in the present analysis.

2. Methods

Participants: PWH and PWoH were recruited for various research studies at the HNRP from 2011 to 2019 (hnrp.hivresearch.ucsd.edu) (Heaton et al., 1995, 2010; Morgello et al., 2001). Participants were recruited using flyers and brochures at community organizations and health fairs. Since the constituent studies were all part of the broader HNRP, recruitment and enrollment practices were identical for all participants included in the analysis. Participants provided written informed consent in accordance with Institutional Review Board-approved procedures for each study (Heaton et al., 1995). Exclusion criteria for the parent studies included major neurological disorders besides neuroHIV (e.g., epilepsy, stroke) and psychiatric conditions other than depression (e.g., psychosis, schizophrenia). Inclusion criteria for this specific study were measured depressive symptoms on the Beck Depression Inventory-II (BDI-II) and one or more systemic inflammatory biomarker assays from the same visit.

Neuromedical and clinical evaluations: Participants completed standardized neuro-medical and clinical evaluations. Demographics included self-reported age, sex, race/ethnicity, and years of formal education. Participants underwent assessment for symptoms of depression using the BDI-II, with higher scores reflecting more depressive symptoms. Current and lifetime substance use disorders (alcohol, cocaine, amphetamines, hallucinogens, sedatives, inhalants, opioids, PCP, and cannabis) were evaluated using the fully structured, computer-based Composite International Diagnostic Interview (CIDI) (Wittchen et al., 1991) using DSM-IV criteria. Participants reported medical history including head injury, type II diabetes, hypertension, chronic pulmonary disease, hyperlipidemia, and hepatitis C infection. Height and weight were measured to calculate body-mass index (BMI).

Laboratory measurements: HIV seropositivity was diagnosed by enzyme-linked immunosorbent assay (ELISA) with confirmation by Western blot or reverse transcriptase PCR (RT-PCR). HIV disease characteristics were determined via a combination of self-report (e.g., estimated duration of HIV disease) and laboratory tests (e.g., $CD4^+$ T-cell count). Plasma HIV-1 RNA level was measured by ultra-sensitive RT-PCR (Amplicor, Roche Diagnostic System) in a CLIA-certified clinical laboratory with a detectability threshold of 50 copies/mL. CD4 and CD8 T-lymphocytes counts were obtained with flow cytometry for PWH. Nadir CD4 levels were taken from medical records, study-obtained values, or self-report. Hepatitis C serostatus was measured via the Multiplo rapid test (MedMira Inc.).

Plasma levels of six inflammatory biomarkers were obtained using immunoassays: CRP, interleukin-6 (IL-6), interleukin-8 (IL-8), d-dimer, chemokine C–C ligand 2 (CCL2), and chemokine C-X-C ligand 10 (CXCL10). These markers were selected due to high coverage in HNRP studies and evidence of association with depression (Young et al., 2014). Log_{10} transformation was used to reduce the skewness of biomarker distributions for parametric analysis. To adjust for possible batch effects

due to the use of different measurement kits, concentrations of each inflammatory biomarker were regressed on plate number, and the residual values were used in all subsequent analyses (Supplemental Fig. S1).

2.1. Statistical analyses

All analyses were performed using R (2022.02.0, R Foundation, Vienna) and SAS (v9.4, SAS Inc., Cary, NC). Demographic and clinical characteristics, inflammatory biomarkers and BDI-II scores were summarized using means and standard deviations or percentages as appropriate and compared by serostatus and sex in the participants used for factor analysis. Demographics were compared among four groups (male PWH, female PWH, male PWoH, female PWoH) in larger sample used for individual biomarker analysis. Continuous variables were compared using *t*-test/analysis of variance (ANOVA), and categorical variables were compared using Chi-squared test/Fisher's exact test. If significant differences were found among the four groups, pairwise between-group comparisons were made. Kolmogorov-Smirnov tests and Q-Q plots were used to assess the normality of continuous variables.

Factor analysis was conducted on the six inflammatory biomarkers. Factor analysis was applied for three reasons. First, we sought to identify grouping patterns among the plasma inflammatory biomarkers to discover biologically related subgroups and determine which subgroups, if any, impact depression. Secondly, factor analysis reduces data dimensionality, thus enabling better control of multiple comparisons (i.e., reduction of Type I error). For example, a factor with no overall association with depression would not be broken out into individual biomarkers for regression analysis, thus reducing the number of statistical tests. Finally, we sought to determine whether previously identified biomarker factors (Ellis et al., 2020, 2021) would be recapitulated in this study.

Factor analysis was conducted only in participants with no missing values for any of the six biomarkers (n = 84 PWH; n = 117 PWoH). Specifically, we used Equamax rotation with a factor loading value of >0.4 to identify inflammatory factors (i.e., sets of inflammatory biomarkers with mutual associations). To validate the resulting factors, we calculated the Pearson correlation between the markers assigned to each factor.

Linear regression models were used to investigate the association between factors and BDI-II scores, and to test for two-way interactions among factor, sex, and serostatus, which were retained in models at $p < 0.05$. The analysis utilized the largest possible sample with complete data for the markers comprising that factor (e.g. Factor 1: n = 150 PWH; n = 138 PWoH). All models included age, education, race/ethnicity (African-American, White, Hispanic, other), and current or past substance use diagnosis as forced-in co-variates.

Additional co-variates were chosen by backward selection, i.e., iterative elimination of weakly associated variables until a final set of co-variates was reached at a pre-specified threshold of $p < 0.2$. Co-variates under selection were history of head injury, hepatitis C co-infection, type II diabetes, hypertension, hyperlipidemia, BMI, and chronic pulmonary disease. Myocardial infarction, renal disease, and liver disease were also considered, but were not modeled due to rarity in this dataset (N < 10 for each). Since antidepressant therapy might confound the relationship between inflammation and depression, we also modeled current pharmaceutical antidepressant use as a binary variable.

Given the cross-sectional nature of the analysis, antidepressant medications represented a potential collider or mediator between inflammatory biomarkers and BDI-II scores. Therefore, we opted to not include this term in our final models; however, we examined whether the results changed when antidepressant medications were modeled.

Residual analysis was used to assess model assumptions, and variance inflation factor was used to evaluate collinearity. The models were refitted using weighted least squares to remedy violations of the equal variance assumption.

Upon detection of a significant association between a factor and BDI-II, either independently or through an interactive effect with sex or HIV serostatus, the individual biomarkers comprising that factor were then examined individually in multiple linear regression models to identify which plasma biomarkers may drive factor-level association with BDI-II. To maximize the sample size, we selected the subset of participant visits with complete data for the specific biomarker under investigation. Thus, the participant sample used for individual inflammatory biomarkers was larger than that used for factor analysis, which was limited to persons with complete data for all six biomarkers. Finally, for any individual biomarker with a significant interaction term, we performed linear regression stratified by sex or serostatus.

3. Results

Participants: 201 participants with available data for all six inflammatory biomarkers at baseline were used for factor analysis, including 84 PWH (age = 43.7 ± 12.3 yr; 91% male; 81% virally suppressed) and 117 PWoH (age = 44.3 ± 16.3; 52% male). Factor analysis was performed across all participants, collapsing sex and HIV serostatus. Demographics and clinical characteristics for this set are described in Table 1. Participants were compared first by serostatus. A significantly greater proportion of PWH than PWoH were male ($p < 0.001$), but serostatus groups did not differ by race/ethnicity, age, or education. BDI-II total scores ($p < 0.001$) and prevalence of chronic pulmonary disease ($p = 0.02$) and were significantly higher in PWH than PWoH. Plasma inflammatory biomarkers differed by serostatus. CRP was greater in PWH than PWoH ($p = 0.004$), as was IL-8 ($p = 0.002$), CCL10 ($p < 0.001$) and CXCL2 ($p < 0.001$).

Participants were also compared by sex, collapsing across PWH and PWoH. Compared to women, men had a higher prevalence of substance use diagnoses ($p = 0.04$) and history of head injury ($p = 0.003$). Men with HIV had lower current CD4 cells than women with HIV ($p < 0.001$) and lower CD4/CD8 ratios ($p = 0.02$). Inflammatory biomarkers differed by sex, with higher D-dimer levels in women than men ($p = 0.005$), and higher IL-8 ($p = 0.03$) and CCL2 levels ($p < 0.001$) in men than women.

Factor analysis. Each inflammatory biomarker significantly correlated with the others, with Pearson correlation coefficients ranging from 0.19 to 0.61 (Table S1). Factor analysis on the six plasma biomarkers yielded two factors. Factor 1 loaded on CRP, IL-6 and d-dimer, while Factor 2 loaded on IL-8, CXCL10 and CCL2.

Depressive symptoms and inflammatory factors. Backward selection of co-variates across all participants resulted in a model containing BMI in addition to the forced-in co-variates age, ethnicity, education, and substance use diagnosis. BDI-II total score was the dependent variable in all regression analyses. Due to violations of the assumption of equal variance, estimates from weighted least-squares regression are reported rather than ordinary least squares. However, results for unweighted regression were similar (Table S2). Approximately one-third of participants reported using one or more antidepressant medications; however, inclusion of antidepressant use as a co-variate was found not to affect the significance or direction of modeling results.

In the combined PWH + PWoH cohort, a significant Factor 1 × sex interaction was found, such that the association between Factor 1 and BDI-II scores was significantly more positive in men than in women [interaction β coefficient = −2.74; 95% confidence interval=(−5.35, −0.13), p = 0.04] (Table 2, Fig. 1). No significant Factor 1 × HIV interaction was detected. No significant main effect or significant interactions with HIV or sex were found for Factor 2.

Depressive symptoms and single inflammatory biomarkers. We then examined whether the Factor 1 × sex interaction was driven by individual biomarkers. For this analysis, we broadened the sample to all participants with CRP, IL-6, and d-dimer levels (as opposed to participants with all six biomarker levels). This larger sample included 150 PWH (age = 48.3 ± 13.1; 88% male; 92% virally suppressed) and 138 PWoH (age = 46.3 ± 15.9; 56% male). This sample was older than the

Table 1
Demographic and clinical characteristics and inflammatory biomarkers by HIV serostatus and by sex among participants in factor analysis.

	PWH	PWoH	p-value	Male	Female	p-value
N	84	117		137	64	
Demographics						
Female	8 (9.5%)	56 (47.8%)	**<0.001**	–	–	–
Age	43.7 ± 12.3	44.3 ± 16.3	0.76	43.5 ± 13.7	45.2 ± 16.7	0.46
Race/ethnicity						
White	46 (54.8%)	57 (48.7%)	0.81	76 (55.5%)	27 (42.2%)	0.06
Hispanic/Latino	27 (32.1%)	32 (27.4%)		40 (29.2%)	19 (29.7%)	
African-American	9 (10.7%)	23 (19.7%)		19 (13.9%)	13 (20.3%)	
Other	2 (2.4%)	5 (4.3%)		2 (1.5%)	5 (7.8%)	
Education (years)	14.0 ± 2.0	14.0 ± 2.5	0.95	14.2 ± 2.2	13.8 ± 2.7	0.33
HIV Variables[a]						
HIV duration (years)	10.6 (8.9)	–	–	11.0 (9.1)	6.8 (6.3)	0.23
Viral load (log_{10})	1.6 (0.9)	–	–	1.7 (0.9)	1.1 (0.7)	0.10
Undetectable viral load (<50/mL)	66 (80.5%)	–	–	58 (78.0%)	8 (100%)	
CD4 T-cells	711 (326)	–	–	670 (295)	1087 (377)	**<0.001**
CD4 nadir	322 (261)	–	–	302 (222)	514 (485)	0.26
CD4/CD8 ratio	0.86 ± 0.48	–	–	0.79 ± 0.40	1.53 ± 0.69	**0.02**
Hepatitis C positive	1 (1.2%)	–	–	0 (0%)	1 (12.5%)	0.10
Current ART use	75 (91.5%)	–	–	68 (90.6%)	7 (100%)	1.00
Clinical variables						
BDI-II total score	12.4 ± 10.6	6.7 ± 8.2	**<0.001**	9.8 ± 10.1	7.5 ± 8.5	0.12
BMI	27.6 ± 4.9	28.2 ± 6.5	0.48	27.4 ± 5.2	29.0 ± 7.1	0.11
Substance use diagnosis (%)	8 (9.9)	15 (12.9)	0.51	20 (14.5)	3 (4.8)	**0.04**
History of head injury (%)	17 (20.7)	20 (17.1)	0.52	33 (24.3)	4 (6.4)	**0.003**
Diabetes (%)	2 (2.4)	8 (6.8)	0.20	7 (5.2)	3 (4.7)	1.00
Hypertension (%)	23 (28.1)	23 (19.7)	0.17	34 (25.0)	12 (19.1)	0.35
Chronic pulmonary disease (%)	17 (21.0)	11 (9.4)	**0.02**	21 (15.6)	7 (11.1)	0.40
Hyperlipidemia (%)	16 (19.3)	19 (16.2)	0.58	27 (19.9)	8 (12.5)	0.20
Inflammatory plasma markers (log_{10}, batch corrected)						
C-reactive protein	6.6 ± 0.53	6.4 ± 0.66	**0.004**	6.4 ± 0.57	6.5 ± 0.72	0.24
Interleukin-6	−0.14 ± 0.31	−0.22 ± 0.32	0.10	−0.19 ± 0.33	−0.17 ± 0.27	0.62
D-dimer	2.7 ± 0.22	2.7 ± 0.20	0.49	2.7 ± 0.22	2.8 ± 0.18	**0.005**
Interleukin-8	0.79 ± 0.22	0.69 ± 0.22	**0.002**	0.75 ± 0.21	0.68 ± 0.24	**0.03**
Chemokine C-X-C ligand 10	2.6 ± 0.24	2.4 ± 0.20	**<0.001**	2.5 ± 0.24	2.5 ± 0.22	0.08
Chemokine C–C ligand 2	2.0 ± 0.12	1.9 ± 0.14	**<0.001**	2.0 ± 0.14	1.9 ± 0.14	**<0.001**

Abbreviations: PWH = persons with HIV, PWoH = persons without HIV, ART = anti-retroviral therapy, BDI-II=Beck Depression Inventory-second edition, BMI = body-mass index.
[a] Statistics for this section are only relevant to PWH.

Table 2
Regression coefficients, confidence intervals, and p-values for the association between factors and BDI-II from weighted least squares models.

Variable	Coefficient (95% CI, weighted)	p-value (weighted)
Intercept	5.87 (−4.85, 16.58)	0.28
Age	−0.03 (−0.12, 0.06)	0.51
Sex (female)	0.88 (−1.88, 3.64)	0.53
HIV (positive)	4.60 (1.67, 7.54)	**0.002**
Race/ethnicity (ref = A.A.)		**0.005**
Hispanic	4.01 (0.37, 7.65)	**0.03**
White	3.55 (0.26, 6.84)	**0.04**
Other	−3.01 (−7.77, 1.75)	0.21
Education (years)	−0.54 (−1.07, −0.02)	**0.04**
Substance use diagnosis	4.48 (−0.38, 9.34)	0.07
BMI	0.23 (−0.00, 0.47)	0.06
Factor 1	0.69 (−1.26, 2.64)	0.49
Factor 2	0.58 (−1.09, 2.26)	0.49
Factor 1 × sex	−2.74 (−5.35, −0.13)	**0.04**

Factor 1 (CRP, d-dimer, IL-6); **Factor 2** (IL-8, CXCL10, CCL2**).** Abbreviations: CRP =C-reactive protein, IL-6 = interleukin-6, IL-8 = interleukin-8, CCL2 = chemokine C–C ligand 2, CXCL10 = Chemokine C-X-C ligand 10, A.A. = African-American, DX = diagnosis, BMI = body-mass index. Abbreviations: CI = confidence interval, A.A. = African-American, BMI = body-mass index.

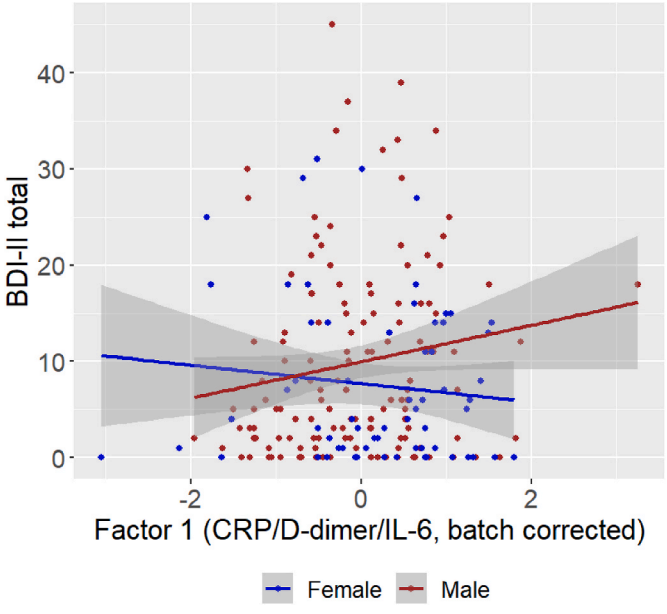

Fig. 1. Factor 1 (CRP/D-dimer/IL-6) vs. BDI-II with fitted line by sex, collapsed across HIV-serostatus.

factor analysis sample but had similar distributions of other demographic and clinical characteristics. Demographics, clinical variables, and plasma inflammatory biomarkers were compared among the four groups, i.e., by serostatus and sex (Table 3). In the larger CRP/IL-6/d-dimer sample, sex and serostatus groups differed significantly in BDI-II total score (overall $p < 0.001$), hypertension ($p = 0.04$), chronic pulmonary disease ($p = 0.02$), hyperlipidemia ($p = 0.003$), and d-dimer levels ($p = 0.002$).

No significant associations were found between BDI-II and CRP or d-

Table 3
Demographic and clinical characteristics and inflammatory biomarkers in the participant group maximizing coverage for C-reactive protein, interleukin-6, and d-dimer.

	PWH		PWoH		Overall p-value	Pairwise comparisons
	Male (a)	*Female (b)*	*Male (c)*	*Female (d)*		
N	132	18	77	61		
Demographics						
Age	48.4 ± 13.0	47.8 ± 13.8	45.1 ± 15.1	47.8 ± 16.8	0.46	–
Race/ethnicity					0.44	–
White (%)	75 (56.8)	7 (38.9)	37 (48.1)	30 (49.2)	–	–
Hispanic/Latino (%)	35 (26.5)	6 (33.3)	21 (27.3)	14 (23.0)	–	–
African-American (%)	15 (11.4)	3 (16.7)	17 (22.1)	13 (21.3)	–	–
Other (%)	7 (5.3)	2 (11.1)	2 (2.6)	4 (6.6)	–	–
Education (years)	14.6 ± 2.5	13.4 ± 2.3	14.3 ± 2.4	14.0 ± 2.6	0.15	–
HIV variables[a]						
HIV duration (years)	14.1 ± 9.7	15.0 ± 9.0	–	–	0.70	–
Viral load (log_{10})	1.6 ± 0.6	1.4 ± 0.4	–	–	0.08	–
Undetectable viral load (<50/mL; %)	122 (92)	18 (100)	–	–	0.22	–
CD4 T-cells	654 ± 296	788 ± 336	–	–	0.13	–
CD4 nadir	259 ± 196	205 ± 195	–	–	0.29	–
CD4/CD8 ratio	0.79 ± 0.49	1.12 ± 0.60	–	–	**0.03**	–
Hepatitis C positive (%)	9 (7)	4 (22)	–	–	**0.045**	–
Current ART use (%)	127 (96)	18 (100)	–	–	0.63	–
Clinical variables						
BDI-II total score	12.2 ± 11.1	7.9 ± 7.2	5.9 ± 8.2	6.5 ± 7.7	**<0.001**	a>b,a>c,a>d
BMI	27.7 ± 5.0	27.5 ± 5.7	28.0 ± 5.9	28.5 ± 7.7	0.84	–
Substance use diagnosis (%)	12 (9)	0 (0)	13 (17)	4 (7)	0.06	–
History of head injury (%)	40 (30)	4 (22)	19 (25)	7 (11)	0.06	–
Diabetes (%)	16 (12)	4 (22)	8 (10)	4 (7)	0.29	–
Hypertension (%)	48 (36)	7 (39)	17 (22)	12 (20)	**0.04**	a>c,a>d
Chronic pulmonary disease (%)	20 (15)	6 (33)	5 (6)	8 (13)	**0.02**	b > c
Hyperlipidemia (%)	49 (37)	6 (33)	17 (22)	8 (13)	**0.003**	a>c,a>d
Inflammatory plasma biomarkers (log_{10}, batch corrected)						
C-reactive protein	6.41 ± 0.56	6.41 ± 0.55	6.22 ± 0.56	6.46 ± 0.71	0.07	–
Interleukin-6	0.37 ± 0.28	0.32 ± 0.27	0.31 ± 0.34	0.36 ± 0.30	0.46	–
D-dimer	2.70 ± 0.22	2.74 ± 0.24	2.64 ± 0.21	2.78 ± 0.18	**0.002**	a>c,d>a,d > c

Abbreviations: PWH = persons with HIV, PWoH = persons without HIV, ART = anti-retroviral therapy, BDI-II=Beck Depression Inventory-second edition, BMI = body-mass index.

[a] Statistics for this section are only relevant to PWH.

dimer, either independently or through interactions with sex or serostatus. However, a significant IL-6 × sex interaction was found, such that the correlation between IL-6 and BDI-II score was higher in men than in women [interaction β = −11.04 (−17.70, −4.38), p = 0.001; Fig. 2, Table 4]. We performed a post-hoc power calculation for the sex × IL-6 interaction. With the current sample size and effect size, the power reaches 90% with a significance level of 0.05. We conclude that if the study were repeated with the current sample size, there would be a 90% chance to detect the same sex × IL-6 interaction.

IL-6 × HIV and sex × HIV interactions were not significant. Race/ethnicity was significantly associated with BDI-II (overall $p < 0.001$); Hispanic [β = 4.35 (1.58, 7.12), $p = 0.002$] and white [2.93 (0.80, 5.06), $p = 0.007$] participants had higher BDI-II scores. Diabetes (β = 3.54 (−0.10, 7.18), $p = 0.03$) was significantly associated with greater BDI-II scores.

Sex-stratified analysis: We probed the significant IL-6 × sex interaction via sex-stratified regression. IL-6 was significantly, positively associated with BDI-II score in men, [β = 5.42 (1.32, 9.52), $p = 0.01$], but not in women [β = −3.88 (−11.02, 3.26), p = 0.28].

In men, HIV-positive serostatus [β = 5.32 (2.98, 7.66), p < 0.001] and Hispanic ethnicity [β = 3.86 (0.37, 7.35), $p = 0.03$] were also associated with higher BDI-II scores. In women, Hispanic ethnicity and white race were also associated with elevated BDI-II scores [β = 5.17 (0.49, 9.84), $p = 0.03$ and 3.67 (0.09, 6.35), $p = 0.045$, respectively], as was current substance use disorder [β = 16.2 (4.05, 28.3), $p = 0.01$] and diabetes [β = 6.71 (0.56, 12.85), $p = 0.03$]. Sex-specific associations between inflammation biomarkers and BDI-II subcales (cognitive, apathy, and affective) were similar regardless of HIV serostatus (data not shown).

4. Discussion

We found that depressed mood was associated with an inflammatory factor loading on CRP, IL-6 and d-dimer in both PWH and PWoH. Investigation of individual biomarkers within this factor showed that only IL-6 was significantly associated with depressed mood. In both factor analysis and examination of individual inflammatory biomarkers, we found a moderating role of sex, whereby these relationships were driven by stronger associations in men. These findings recapitulated a factor consisting of the same three inflammatory biomarkers in a smaller sample of PWH only (Ellis et al., 2020), with similar sex-specific results despite differences in sample characteristics and the overall set of inflammatory biomarkers examined in the two studies, suggesting a robust relationship among CRP, IL-6, and d-dimer.

Our findings are also consistent with a large study in PWoH which found that men but not women with depression had elevated IL-6 (Vogelzangs et al., 2012). These results add to the evidence linking inflammation to depression in both PWH and PWoH. They also suggest sex differences in the pathophysiology of depression, and highlight the importance of examining sex as a biological variable when identifying mechanisms of or interventions for mood disorders, particularly anti-inflammatory interventions.

Previous studies have also found relationships between depression and biomarkers of inflammation, particularly IL-6, in PWoH. Longitudinal studies in the general population have shown that inflammatory biomarkers are related to depression and that higher levels of IL-6 predict depressive symptoms (Gimeno et al., 2009; Huang et al., 2019; Valkanova et al., 2013). In a study using a large sample of UK Biobank genetic data, researchers employed a Mendelian Randomization design to support a causal role of elevated IL-6 in depression (Kelly et al., 2021),

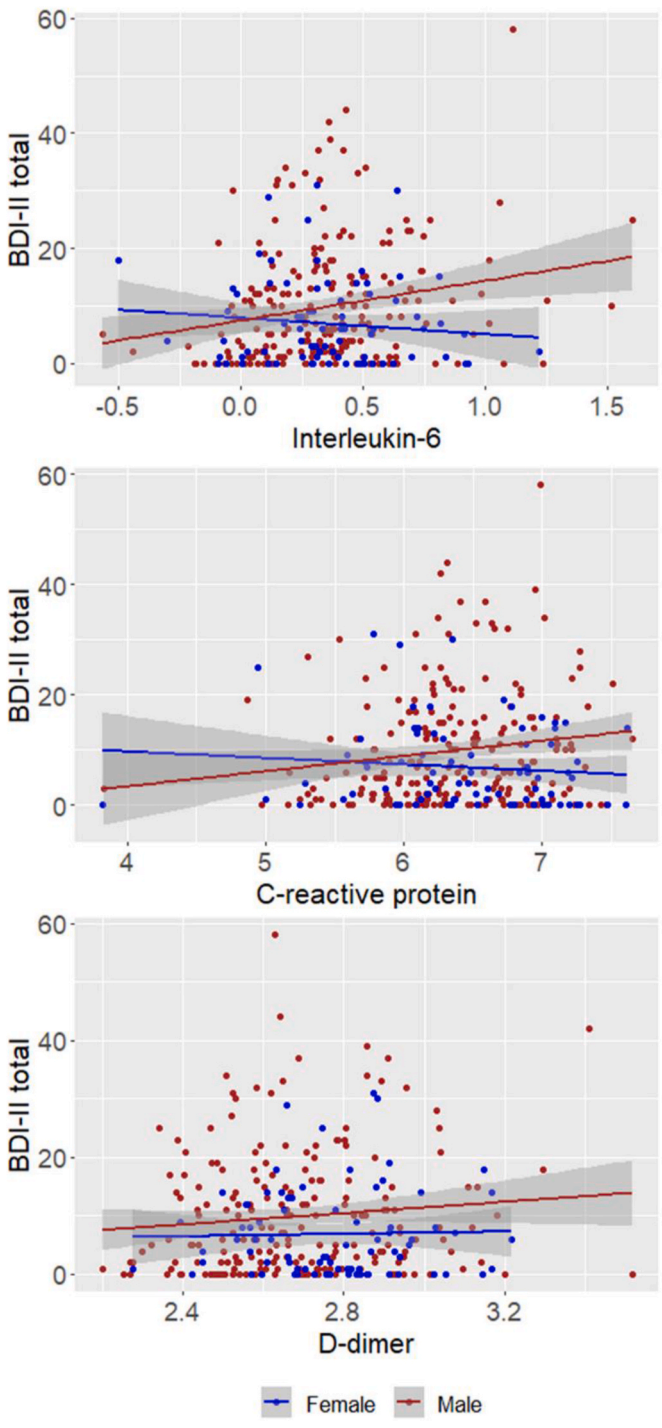

Fig. 2. Factor 1 components vs. BDI-II with fitted line by sex. Inflammatory plasma biomarkers were $\log_{10}$ transformed and batch-corrected.

likely based on interactions between inflammatory cytokines and the central nervous system. In a seminal functional MRI (fMRI) study, administration of an immunogenic stimulus to PWoH resulted in mood deterioration and greater subgenual anterior cingulate cortex brain connectivity with the ventromedial prefrontal cortex as a function of increased plasma IL-6 (Harrison et al., 2009).

Our study is also consistent with prior investigations that have identified associations between IL-6 and depressive symptoms in PWH. In a study of ART-naïve PWH in Uganda, IL-6 was found to be higher among PWH with depression as well as HIV-associated neurocognitive disorder, which was further linked with mortality (Musinguzi et al., 2018; Saylor et al., 2019). In a latent-class analysis of depressive subtypes in PWH on ART, severe somatic symptoms of depression were associated with elevated levels of IL-6 and blood monocyte counts (Pala et al., 2016). Higher levels of IL-6 were associated with greater depression and psychological distress in another study among PWH on effective ART (Fumaz et al., 2012). A related fMRI study found that elevation in IL-6 and depression were associated with altered brain activity in PWH (increased amplitude of low-frequency fluctuations) in the ventral frontal lobe, suggestive of a biological pathway by which inflammation may contribute to depression or perhaps vice versa (McIntosh et al., 2018).

While IL-6 was found to be linked with depressive symptomatology, the other two biomarkers comprising Factor 1, CRP and d-dimer, did not show a significant linkage with depression, either overall or by sex. In this respect, our results differ somewhat from other studies. For example, Ellis et al. (2020) found d-dimer levels (but not CRP levels) to be significantly correlated with depression in PWH. Conversely, Poudel-Tandukar and colleagues found a significant positive association between Beck Depression Inventory-I score and serum CRP for PWH. This concords with Memiah et al., who found that the severity of mental health symptoms was significantly elevated in PWH in the highest CRP quartile (Memiah et al., 2021). Thus, results pertaining to Factor 1 have been somewhat inconsistent. However, the linkage of these three biomarkers into a single factor has now been replicated several times, including in this study and Ellis et al. (2020, 2021).

Factor 2, comprised of CCL2, CXCL10, and IL-8, did not show a significant association with BDI-II either overall or by sex. Therefore, in keeping with the pre-specified analysis protocol, we did not test these three biomarkers separately for depression associations or sex-specific effects. However, we note that at least one prior study has linked CXCL10 levels with depression in PWH (Cassol et al., 2015), and thus we cannot rule out the psychiatric relevance of this biomarker. Other evidence also suggests that plasma CCL2 is correlated with subcortical brain injury detectable on neuroimaging and implicated in depression (Ragin et al., 2006; Curzytek and Leskiewicz, 2021; Tang et al., 2022). Finally, a previous study found that IL-8 levels predict response to anti-depressant therapy in a sex-specific manner (Kruse et al., 2021a, 2021b), an intriguing finding which is neither replicated nor contradicted here. Thus, the evidence provided here should be contextualized with existing literature, which partly supports and partly differs from our findings.

We posit that circulating estradiol and testosterone levels may mediate sex differences in the relationships between depressed mood and inflammation. Previous research is consistent with sex differences in the regulation of inflammation and immunometabolism. Females tend to have stronger immune responses to infection, with higher levels of pro-inflammatory cytokines, such as IL-6, interleukin-1β, and tumor necrosis factor-α (Ruggieri et al., 2016). Indeed, this stronger immune response may also lead to an increased risk for autoimmune diseases.

In contrast, males tend to have a higher risk of chronic inflammatory diseases, such as cardiovascular disease and type 2 diabetes, that are related to immunometabolism (Gubbels Bupp, 2015). Females tend to have a higher proportion of energy derived from fatty acids, while males rely more on glucose for energy production (Power and Schulkin, 2008). The differences in immune response, inflammation, and metabolism between males and females may be influenced by sex hormones, such as estrogen and testosterone, as well as other factors such as genetics, epigenetics, and lifestyle.

Few studies have compared the association between inflammatory biomarkers and depression in both PWH and PWoH. In the Multicenter AIDS Cohort Study, an inflammatory factor that contained soluble IL-6 receptor was found to be associated with increased depression risk both in men with and without HIV (Lu et al., 2019). Similarly, in the Veterans Aging Cohort, depression was associated with inflammatory markers in both PWH and PWoH; however, the specific associated inflammatory marker differed by HIV serostatus; depression was related to

Table 4
Regression coefficients, confidence intervals, and p-values from weighted least squares model of IL-6 and other predictors of BDI II among all participants and stratified by sex.

Predictor	All participants		Male		Female	
	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value
IL-6 (log_{10})	**5.75 (1.80, 9.71)**	**0.005**	**5.42 (1.32, 9.52)**	**0.010**	−3.88 (−11.02, 3.26)	0.28
Age	−0.05 (−0.12, 0.01)	0.11	−0.06 (−0.14, 0.02)	0.12	0 (−0.12, 0.12)	0.97
Sex (female)	**3.77 (0.97, 6.57)**	**0.009**	–	–	–	–
HIV (positive)	**4.77 (2.72, 6.82)**	**<0.001**	**5.32 (2.98, 7.66)**	**<.001**	0.73 (−2.91, 4.38)	0.69
Race/ethnicity (ref = A.A.)		**<0.001**		**0.04**		0.06
Hispanic	**4.35 (1.58, 7.12)**	**0.002**	**3.86 (0.37, 7.35)**	**0.03**	**5.17 (0.49, 9.84)**	**0.03**
White	**2.93 (0.80, 5.06)**	**0.007**	2.05 (−0.73, 4.83)	0.33	**3.67 (0.09, 6.35)**	**0.045**
Other	−1.61 (−5.09, 1.87)	0.36	−2.48 (−7.45, 2.48)	0.15	0.63 (−5.09, 0.11)	0.83
Education (years)	−0.11 (−0.50, 0.28)	0.59	0.05 (−0.46, 0.56)	0.84	−0.50 (−1.12, 7.24)	0.11
Substance DX	4.08 (−0.26, 8.42)	0.07	1.44 (−2.87, 5.75)	0.51	**16.2 (4.05, 28.3)**	**0.01**
Head Injury	2.17 (−0.24, 4.58)	0.08	1.99 (−0.89, 4.86)	0.17	2.12 (−2.09, 6.32)	0.32
BMI	**0.18 (0.002, 0.36)**	**0.048**	0.24 (−0.01, 0.48)	0.06	0.11 (−0.15, 0.37)	0.39
Diabetes	3.54 (−0.10, 7.18)	0.06	2.52 (−1.82, 6.86)	0.25	**6.71 (0.56, 12.85)**	**0.03**
IL-6 (log_{10}) × sex	**−11.04 (-17.70, -4.39)**	**0.001**	–	–	–	–

Abbreviations: PWH = persons with HIV, PWoH = persons without HIV, ART = anti-retroviral therapy, BDI-II=Beck Depression Inventory-second edition, BMI = body-mass index. Note: Terms IL-6 × HIV and Sex × HIV were not significant and removed from model.

elevated d-dimer and sCD14 among PWH and IL-6 among PWoH (Stewart et al., 2020).

Our findings suggest that targeting elevations in IL-6 and its drivers may improve mood, particularly in men (Fonseka et al., 2015). Since adherence to an effective ART regimen is associated with reductions in (but not normalization of) systemic inflammation markers including IL-6 (Castillo-Mancilla et al., 2022), interventions to sustain or improve ART adherence in PWH may improve mood. In addition, IL-6 levels may identify subtypes of depression for which antinflammatory treatment may be effective. For example, baseline IL-6 levels predict responsiveness to antidepressant therapy using ketamine (Yang et al., 2015). Future studies may target excess inflammation in PWH with treatment-resistant depression.

This study had several limitations. First, the sample of PWH was predominately male, therefore male-specific findings in sex-stratified analysis may be partly due to relatively limited power to detect effects in women with HIV. However, we note that our sample was sufficiently large to detect sex-related interactions, including sex differences in the effects of an inflammatory factor (IL-6, CRP, D-dimer) and an individual biomarker (IL-6) on depressive symptoms. Moreover, the effect size of the latter interaction was large, corresponding to an 11-point greater BDI-II increase with each log-unit of increased IL-6 for men than women, a highly significant finding ($p = 0.001$).

We acknowledge that the number of women with HIV in this study (n = 18) limits the assessment of two-way interactions of sex and serostatus on depression and three-way interactions between sex, serostatus, and inflammatory biomarkers. This limitation was a result of the need to balance sample size with the inclusion of multiple biomarkers of interest.

Second, there were some biomarkers with missing data, limiting the sample of individuals with all six biomarkers, used for factor analysis. Third, we examined plasma inflammatory biomarkers; however, biomarkers in cerebrospinal fluid (CSF) may better reflect intracerebral inflammation. In addition, the panel of soluble biomarkers was limited to those available in our database, and other pro- or anti-inflammatory biomarkers such as tumor necrosis factor-α or interleukin-10 were not examined. Finally, we measured only soluble plasma biomarkers, but not cellular markers of inflammation (i.e., activated monocytes and T lymphocytes).

The study also had several strengths. First, it was novel in examining potential modifying roles of both sex and HIV serostatus in the associations between inflammatory biomarkers and depression. Additionally, the use of factor analysis followed by targeted examination of individual biomarkers allowed the detection of correlated groupings, which informed the identification of individual depression-associated biomarkers while limiting the number of statistical tests performed.

In conclusion, this study found that higher levels of IL-6, a biomarker of systemic inflammation, were associated with greater depressive symptoms. This relationship was specific to men and did not differ by HIV serostatus. Further research is needed to determine how targeting inflammation through pharmacological or non-pharmacological treatments such as exercise may impact depression.

Funding information

This work was supported by the Sustained Training in Aging and HIV Research program [STAHR; R25MH108389]. The work was further supported by the National Institutes of Health and the National Institute of Mental Health [P30MH062512, N01 MH22005, HHSN271201000036C and HHSN271201000030C, U24 MH100928, T32 AI007384, F32 MH129151].

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Health, US Government, Department of Veterans Affairs, or any of the author's affiliated institutions or funders.

Declaration of competing interest

None.

Data availability

The authors do not have permission to share data.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2023.100644.

References

Bai, S., Guo, W., Feng, Y., Deng, H., Li, G., Nie, H., Guo, G., Yu, H., Ma, Y., Wang, J., Chen, S., Jing, J., Yang, J., Tang, Y., Tang, Z., 2020. Efficacy and safety of anti-inflammatory agents for the treatment of major depressive disorder: a systematic review and meta-analysis of randomised controlled trials. J. Neurol. Neurosurg. Psychiatry 91 (1), 21–32. https://doi.org/10.1136/jnnp-2019-320912.

Bing, E.G., Burnam, M.A., Longshore, D., Fleishman, J.A., Sherbourne, C.D., London, A. S., Turner, B.J., Eggan, F., Beckman, R., Vitiello, B., Morton, S.C., Orlando, M., Bozzette, S.A., Ortiz-Barron, L., Shapiro, M., 2001. Psychiatric disorders and drug use among human immunodeficiency virus-infected adults in the United States. Arch. Gen. Psychiatr. 58 (8), 721–728. https://doi.org/10.1001/archpsyc.58.8.721.

Cassol, E., Misra, V., Morgello, S., Kirk, G.D., Mehta, S.H., Gabuzda, D., 2015. Altered monoamine and acylcarnitine metabolites in HIV-positive and HIV-negative subjects with depression. J. Acquir. Immune Defic. Syndr. 69, 18–28.

Castillo-Mancilla, J.R., Musinguzi, N., Asiimwe, S., Siedner, M.J., Orrell, C., Bangsberg, D.R., Haberer, J.E., 2022. High residual inflammation despite HIV viral suppression: lessons learned from real-time adherence monitoring among people with HIV in Africa. HIV Med. 23 (5), 465–473.

Cho, J.H., Irwin, M.R., Eisenberger, N.I., Lamkin, D.M., Cole, S.W., 2019. Transcriptomic predictors of inflammation-induced depressed mood. Neuropsychopharmacology 44 (5), 923–929. https://doi.org/10.1038/s41386-019-0316-9.

Cruess, D.G., Evans, D.L., Repetto, M.J., Gettes, D., Douglas, S.D., Petitto, J.M., 2003. Prevalence, diagnosis, and pharmacological treatment of mood disorders in HIV disease. Biol. Psychiatr. 54 (3), 307–316. https://doi.org/10.1016/s0006-3223(03)00318-4.

Curzytek, K., Leśkiewicz, M., 2021. Targeting the CCL2-CCR2 axis in depressive disorders. Pharmacol. Rep. 73 (4), 1052–1062.

Deeks, S.G., 2011. HIV infection, inflammation, immunosenescence, and aging. Annu. Rev. Med. 62, 141–155. https://doi.org/10.1146/annurev-med-042909-093756.

Eid, R.S., Gobinath, A.R., Galea, L.A.M., 2019. Sex differences in depression: insights from clinical and preclinical studies. Prog. Neurobiol. 176, 86–102. https://doi.org/10.1016/j.pneurobio.2019.01.006.

Ellis, R.J., Iudicello, J., Sun-Suslow, N., Grelotti, D., Cherner, M., Morgan, E., Letendre, S.L., Heaton, R.K., 2021. Social isolation is linked to inflammation in aging people with HIV and uninfected individuals. J. Acquir. Immune Defic. Syndr. 86 (5), 600, 2021 Apr 4.

Ellis, R.J., Letendre, S.L., Atkinson, J.H., Clifford, D., Collier, A.C., Gelman, B.B., Marra, C., McCutchan, J.A., Morgello, S., Sacktor, N., Tang, B., Heaton, R.K., 2020. Higher levels of plasma inflammation biomarkers are associated with depressed mood and quality of life in aging, virally suppressed men, but not women, with HIV. Brain Behav. Immun. Health 7, 100121. https://doi.org/10.1016/j.bbih.2020.100121.

Fonseka, T.M., McIntyre, R.S., Soczynska, J.K., Kennedy, S.H., 2015. Novel investigational drugs targeting IL-6 signaling for the treatment of depression. Expet Opin. Invest. Drugs 24 (4), 459–475.

Fumaz, C.R., Gonzalez-Garcia, M., Borras, X., Muñoz-Moreno, J.A., Perez-Alvarez, N., Mothe, B., Brander, C., Ferrer, M.J., Puig, J., Llano, A., 2012. Psychological stress is associated with high levels of IL-6 in HIV-1 infected individuals on effective combined antiretroviral treatment. Brain Behav. Immun. 26 (4), 568–572.

Gimeno, D., Kivimäki, M., Brunner, E.J., Elovainio, M., De Vogli, R., Steptoe, A., Kumari, M., Lowe, G.D., Rumley, A., Marmot, M.G., Ferrie, J.E., 2009. Associations of C-reactive protein and interleukin-6 with cognitive symptoms of depression: 12-year follow-up of the Whitehall II study. Psychol. Med. 39 (3), 413–423. https://doi.org/10.1017/s0033291708003723.

Gokhale, R.H., Weiser, J., Sullivan, P.S., Luo, Q., Shu, F., Bradley, H., 2019. Depression prevalence, antidepressant treatment status, and association with sustained HIV viral suppression among adults living with HIV in care in the United States, 2009-2014. AIDS Behav. 23 (12), 3452–3459. https://doi.org/10.1007/s10461-019-02613-6.

Gonzalez, J.S., Batchelder, A.W., Psaros, C., Safren, S.A., 2011. Depression and HIV/AIDS treatment nonadherence: a review and meta-analysis. J. Acquir. Immune Defic. Syndr. 58 (2), 181–187. https://doi.org/10.1097/QAI.0b013e31822d490a.

Gubbels Bupp, M.R., 2015. Sex, the aging immune system, and chronic disease. Cell. Immunol. 294, 102–110.

Haroon, E., Daguanno, A.W., Woolwine, B.J., Goldsmith, D.R., Baer, W.M., Wommack, E.C., Felger, J.C., Miller, A.H., 2018. Antidepressant treatment resistance is associated with increased inflammatory markers in patients with major depressive disorder. Psychoneuroendocrinology 95, 43–49. https://doi.org/10.1016/j.psyneuen.2018.05.026.

Harrison, N.A., Brydon, L., Walker, C., Gray, M.A., Steptoe, A., Critchley, H.D., 2009. Inflammation causes mood changes through alterations in subgenual cingulate activity and mesolimbic connectivity. Biol. Psychiatr. 66 (5), 407–414. https://doi.org/10.1016/j.biopsych.2009.03.015.

Heaton, R.K., Clifford, D.B., Franklin Jr., D.R., Woods, S.P., Ake, C., Vaida, F., Ellis, R.J., Letendre, S.L., Marcotte, T.D., Atkinson, J.H., Rivera-Mindt, M., Vigil, O.R., Taylor, M.J., Collier, A.C., Marra, C.M., Gelman, B.B., McArthur, J.C., Morgello, S., Simpson, D.M., Group, C., 2010. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. Neurology 75 (23), 2087–2096. https://doi.org/10.1212/WNL.0b013e318200d727.

Heaton, R.K., Grant, I., Butters, N., White, D.A., Kirson, D., Atkinson, J.H., McCutchan, J.A., Taylor, M.J., Kelly, M.D., Ellis, R.J., et al., 1995. The HNRC 500–neuropsychology of HIV infection at different disease stages. HIV Neurobehavioral Research Center. J. Int. Neuropsychol. Soc. 1 (3), 231–251. https://doi.org/10.1017/s1355617700000230.

Hellmuth, J., Colby, D., Valcour, V., Suttichom, D., Spudich, S., Ananworanich, J., Prueksakaew, P., Sailasuta, N., Allen, I., Jagodzinski, L.L., Slike, B., Ochi, D., Paul, R., Group, R.S.S., 2017. Depression and anxiety are common in acute HIV infection and associate with plasma immune activation. AIDS Behav. 21 (11), 3238–3246. https://doi.org/10.1007/s10461-017-1788-4.

Howren, M.B., Lamkin, D.M., Suls, J., 2009. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. Psychosom. Med. 71 (2), 171–186. https://doi.org/10.1097/PSY.0b013e3181907c1b.

Huang, M., Su, S., Goldberg, J., Miller, A.H., Levantsevych, O.M., Shallenberger, L., Pimple, P., Pearce, B., Bremner, J.D., Vaccarino, V., 2019. Longitudinal association of inflammation with depressive symptoms: a 7-year cross-lagged twin difference study. Brain Behav. Immun. 75, 200–207. https://doi.org/10.1016/j.bbi.2018.10.007.

Ironson, G., Fitch, C., Stuetzle, R., 2017. Depression and survival in a 17-year longitudinal study of people with HIV: moderating effects of race and education. Psychosom. Med. 79 (7), 749–756. https://doi.org/10.1097/PSY.0000000000000488.

Irwin, M.R., Cole, S., Olmstead, R., Breen, E.C., Cho, J.J., Moieni, M., Eisenberger, N.I., 2019. Moderators for depressed mood and systemic and transcriptional inflammatory responses: a randomized controlled trial of endotoxin. Neuropsychopharmacology 44 (3), 635–641. https://doi.org/10.1038/s41386-018-0259-6.

Jia, H., Uphold, C.R., Wu, S., Reid, K., Findley, K., Duncan, P.W., 2004. Health-related quality of life among men with HIV infection: effects of social support, coping, and depression. AIDS Patient Care STDS 18 (10), 594–603. https://doi.org/10.1089/apc.2004.18.594.

Kappelmann, N., Lewis, G., Dantzer, R., Jones, P.B., Khandaker, G.M., 2018. Antidepressant activity of anti-cytokine treatment: a systematic review and meta-analysis of clinical trials of chronic inflammatory conditions. Mol. Psychiatr. 23 (2), 335–343. https://doi.org/10.1038/mp.2016.167.

Kelly, K.M., Smith, J.A., Mezuk, B., 2021. Depression and interleukin-6 signaling: a mendelian randomization study. Brain Behav. Immun. 95, 106–114.

Kruse, J.L., Olmstead, R., Hellemann, G., Breen, E.C., Tye, S.J., Brooks 3rd, J.O., Wade, B., Congdon, E., Espinoza, R., Narr, K.L., Irwin, M.R., 2021a. Interleukin-8 and lower severity of depression in females, but not males, with treatment-resistant depression. J. Psychiatr. Res. 140, 350–356.

Kruse, J.L., Vasavada, M.M., Olmstead, R., Hellemann, G., Wade, B., Breen, E.C., Brooks, J.O., Congdon, E., Espinoza, R., Narr, K.L., Irwin, M.R., 2021b. Depression treatment response to ketamine: sex-specific role of interleukin-8, but not other inflammatory markers. Transl. Psychiatry 11, 167.

Lu, H., Surkan, P.J., Irwin, M.R., Treisman, G.J., Breen, E.C., Sacktor, N., Stall, R., Wolinsky, S.M., Jacobson, L.P., Abraham, A.G., 2019. Inflammation and risk of depression in HIV: prospective findings from the multicenter AIDS cohort study. Am. J. Epidemiol. 188 (11), 1994–2003. https://doi.org/10.1093/aje/kwz190.

McIntosh, R.C., Paul, R., Ndhlovu, L.C., Hidalgo, M., Lobo, J.D., Walker, M., Shikuma, C.M., Kallianpur, K.J., 2018. Resting-state connectivity and spontaneous activity of ventromedial prefrontal cortex predict depressive symptomology and peripheral inflammation in HIV. J. Neurovirol. 24 (5), 616–628.

Memiah, P., Nkinda, L., Majigo, M., Humwa, F., Haile, Z.T., Muthoka, K., Zuheri, A., Kamau, A., Ochola, L., Buluku, G., 2021. Mental health symptoms and inflammatory markers among HIV infected patients in Tanzania. BMC Publ. Health 21, 1113.

Miller, A.H., Raison, C.L., 2016. The role of inflammation in depression: from evolutionary imperative to modern treatment target. Nat. Rev. Immunol. 16 (1), 22–34. https://doi.org/10.1038/nri.2015.5.

Morgello, S., Gelman, B.B., Kozlowski, P.B., Vinters, H.V., Masliah, E., Cornford, M., Cavert, W., Marra, C., Grant, I., Singer, E.J., 2001. The National NeuroAIDS Tissue Consortium: a new paradigm in brain banking with an emphasis on infectious disease. Neuropathol. Appl. Neurobiol. 27 (4), 326–335. https://doi.org/10.1046/j.0305-1846.2001.00334.x.

Musinguzi, K., Obuku, A., Nakasujja, N., Birabwa, H., Nakku, J., Levin, J., Kinyanda, E., 2018. Association between major depressive disorder and pro-inflammatory cytokines and acute phase proteins among HIV-1 positive patients in Uganda. BMC Immunol. 19 (1), 1. https://doi.org/10.1186/s12865-017-0239-3.

Nanni, M.G., Caruso, R., Mitchell, A.J., Meggiolaro, E., Grassi, L., 2015. Depression in HIV infected patients: a review. Curr. Psychiatr. Rep. 17 (1), 530. https://doi.org/10.1007/s11920-014-0530-4.

Norcini Pala, A., Steca, P., Bagrodia, R., Helpman, L., Colangeli, V., Viale, P., Wainberg, M.L., 2016. Subtypes of depressive symptoms and inflammatory biomarkers: an exploratory study on a sample of HIV-positive patients. Brain Behav. Immun. 56, 105–113. https://doi.org/10.1016/j.bbi.2016.02.013.

Orlando, M., Burnam, M.A., Beckman, R., Morton, S.C., London, A.S., Bing, E.G., Fleishman, J.A., 2002. Re-estimating the prevalence of psychiatric disorders in a nationally representative sample of persons receiving care for HIV: results from the HIV Cost and Services Utilization Study. Int. J. Methods Psychiatr. Res. 11 (2), 75–82. https://doi.org/10.1002/mpr.125.

Osimo, E.F., Pillinger, T., Rodriguez, I.M., Khandaker, G.M., Pariante, C.M., Howes, O.D., 2020. Inflammatory markers in depression: a meta-analysis of mean differences and variability in 5,166 patients and 5,083 controls. Brain Behav. Immun. 87, 901–909. https://doi.org/10.1016/j.bbi.2020.02.010.

Pala, A.N., Steca, P., Bagrodia, R., Helpman, L., Colangeli, V., Viale, P., Wainberg, M.L., 2016. Subtypes of depressive symptoms and inflammatory biomarkers: an exploratory study on a sample of HIV-positive patients. Brain Behav. Immun. 56, 105–113.

Poudel-Tandukar, K., Bertone-Johnson, E.R., Palmer, P.H., Poudel, K.C., 2014. C-Reactive protein and depression in persons with human immunodeficiency virus infection: the positive living with HIV (POLH) study. Brain Behav. Immun. 42, 89–95. https://doi.org/10.1016/j.bbi.2014.06.004.

Power, M.L., Schulkin, J., 2008. Sex differences in fat storage, fat metabolism, and the health risks from obesity: possible evolutionary origins. Br. J. Nutr. 99, 931–940.

Ragin, A.B., Wu, Y., Storey, P., Cohen, B.A., Edelman, R.R., Epstein, L.G., 2006. Monocyte chemoattractant protein-1 correlates with subcortical brain injury in HIV infection. Neurology 66, 1255–1257.

Raison, C.L., Rutherford, R.E., Woolwine, B.J., Shuo, C., Schettler, P., Drake, D.F., Haroon, E., Miller, A.H., 2013. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. JAMA Psychiatr. 70 (1), 31–41. https://doi.org/10.1001/2013.jamapsychiatry.4.

Rivera-Rivera, Y., Garcia, Y., Toro, V., Cappas, N., Lopez, P., Yamamura, Y., Rivera-Amill, V., 2014. Depression correlates with increased plasma levels of inflammatory

cytokines and a dysregulated oxidant/antioxidant balance in HIV-1-Infected subjects undergoing antiretroviral therapy. J. Clin. Cell. Immunol. 5 (6) https://doi.org/10.4172/2155-9899.1000276.

Ruggieri, A., Anticoli, S., D'Ambrosio, A., Giordani, L., Viora, M., 2016. The influence of sex and gender on immunity, infection and vaccination. Annali dell'Istituto superiore di sanita 52 (2), 198–204.

Saylor, D., Kumar, A., Nakigozi, G., Anok, A., Batte, J., Kisakye, A., Mayanja, R., Nakasujja, N., Robertson, K.R., Gray, R.H., Wawer, M.J., Pardo, C.A., Sacktor, N., 2019. Interleukin-6 is associated with mortality and neuropsychiatric outcomes in antiretroviral-naive adults in Rakai, Uganda. J. Neurovirol. 25 (6), 735–740. https://doi.org/10.1007/s13365-019-00759-6.

Schmiedel, B.J., Singh, D., Madrigal, A., Valdovino-Gonzalez, A.G., White, B.M., Zapardiel-Gonzalo, J., Ha, B., Altay, G., Greenbaum, J.A., McVicker, G., Seumois, G., Rao, A., Kronenberg, M., Peters, B., Vijayanand, P., 2018. Impact of genetic polymorphisms on human immune cell gene expression. Cell 175 (6), 1701–1715 e1716. https://doi.org/10.1016/j.cell.2018.10.022.

Slusarczyk, J., Trojan, E., Chwastek, J., Basta-Kaim, A., 2016. A potential contribution of chemokine network dysfunction to the depressive disorders. Curr. Neuropharmacol. 14 (7), 705–720.

Stewart, J.C., Polanka, B.M., So-Armah, K.A., White, J.R., Gupta, S.K., Kundu, S., Chang, C.H., Freiberg, M.S., 2020. Associations of total, cognitive/affective, and somatic depressive symptoms and antidepressant use with cardiovascular disease-relevant biomarkers in HIV: veterans aging cohort study. Psychosom. Med. 82 (5), 461–470. https://doi.org/10.1097/PSY.0000000000000808.

Tang, R., Vargas-Medrano, J., Ramos, E., Thompson, P., Gadad, B., 2022. Gene expression analysis of CCL2, MOBP and OPALIN in major depressive disorder and suicidality. Neurology 98 (18 Supplement), 3266.

Tate, D., Paul, R.H., Flanigan, T.P., Tashima, K., Nash, J., Adair, C., Boland, R., Cohen, R. A., 2003. The impact of apathy and depression on quality of life in patients infected with HIV. AIDS Patient Care STDS 17 (3), 115–120. https://doi.org/10.1089/10872910376380793 6.

Tenorio, A.R., Zheng, Y., Bosch, R.J., Krishnan, S., Rodriguez, B., Hunt, P.W., Plants, J., Seth, A., Wilson, C.C., Deeks, S.G., Lederman, M.M., Landay, A.L., 2014. Soluble markers of inflammation and coagulation but not T-cell activation predict non-AIDS-defining morbid events during suppressive antiretroviral treatment. J. Infect. Dis. 210 (8), 1248–1259. https://doi.org/10.1093/infdis/jiu254.

Valkanova, V., Ebmeier, K.P., Allan, C.L., 2013. CRP, IL-6 and depression: a systematic review and meta-analysis of longitudinal studies. J. Affect. Disord. 150 (3), 736–744. https://doi.org/10.1016/j.jad.2013.06.004.

Vogelzangs, N., Duivis, H.E., Beekman, A.T., Kluft, C., Neuteboom, J., Hoogendijk, W., Smit, J.H., de Jonge, P., Penninx, B.W., 2012. Association of depressive disorders, depression characteristics and antidepressant medication with inflammation. Transl. Psychiatry 2, e79. https://doi.org/10.1038/tp.2012.8.

Wittchen, H.U., Robins, L.N., Cottler, L.B., Sartorius, N., Burke, J.D., Regier, D., 1991. Cross-cultural feasibility, reliability and sources of variance of the composite international diagnostic Interview (CIDI). The multicentre WHO/ADAMHA field trials. Br. J. Psychiatry 159, 645–653. https://doi.org/10.1192/bjp.159.5.645, 658.

Wium-Andersen, M.K., Orsted, D.D., Nielsen, S.F., Nordestgaard, B.G., 2013. Elevated C-reactive protein levels, psychological distress, and depression in 73, 131 individuals. JAMA Psychiatr. 70 (2), 176–184. https://doi.org/10.1001/2013.jamapsychiatry.102.

Wong, M.L., Dong, C., Maestre-Mesa, J., Licinio, J., 2008. Polymorphisms in inflammation-related genes are associated with susceptibility to major depression and antidepressant response. Mol. Psychiatr. 13 (8), 800–812.

Yang, J.-j., Wang, N., Yang, C., Shi, J.-y., Yu, H.-y., Hashimoto, K., 2015. Serum interleukin-6 is a predictive biomarker for ketamine's antidepressant effect in treatment-resistant patients with major depression. Biol. Psychiatr. 77 (3), e19–e20.

Young, J.J., Bruno, D., Pomara, N., 2014. A review of the relationship between proinflammatory cytokines and major depressive disorder. J. Affect. Disord. 169, 15–20.