Sex-Specific Association Between IL-6 and Depression in Persons With and Without HIV

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BACKGROUND

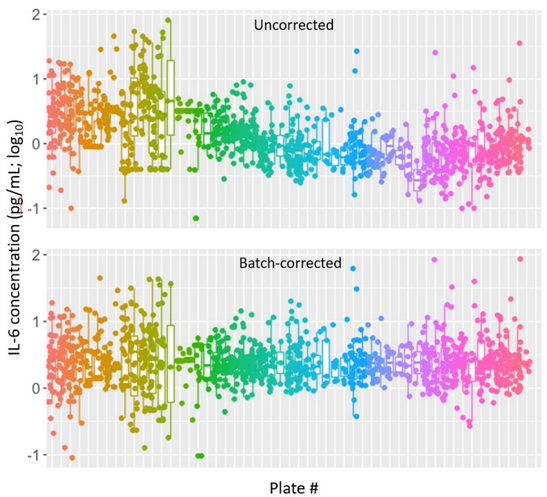
- Persons with HIV (PWH) have greater depression prevalence compared to persons without HIV (PWoH) and elevated plasma inflammatory biomarkers.
- Inflammation and depressive symptoms are known to be linked in PWH and PWoH; however, it is unclear whether associations differ by HIV serostatus and biological sex.

HYPOTHESES

- Elevated inflammatory biomarkers are associated with greater depressive symptoms in PWH.
- Sex moderates the association between inflammatory biomarkers and depressive symptoms.

METHODS

- PWH (n=150; age=48.4±13.0 yr.; 88% male) and PWoH (n=138; age=47.8±13.8; 56% male) from UCSD HIV Neurobehavioral Research Program (HNRP, 2011-2019).
- Six plasma biomarkers: interleukin-6 (IL-6), C-reactive protein (CRP), D-dimer, IL-8, chemokine C-C ligand 2 (CCL2), and chemokine C-X-C ligand 10 (CXCL10), batch corrected (as an example, see **Figure 1**).
- Factor analysis identified intercorrelated biomarker groups. Factors and their components were examined for relationships with Beck Depression Inventory-II (BDI-II).
- Tested for modifying effects of sex or HIV serostatus using multivariable linear regression, controlling for demographics, substance use, and co-morbidities.



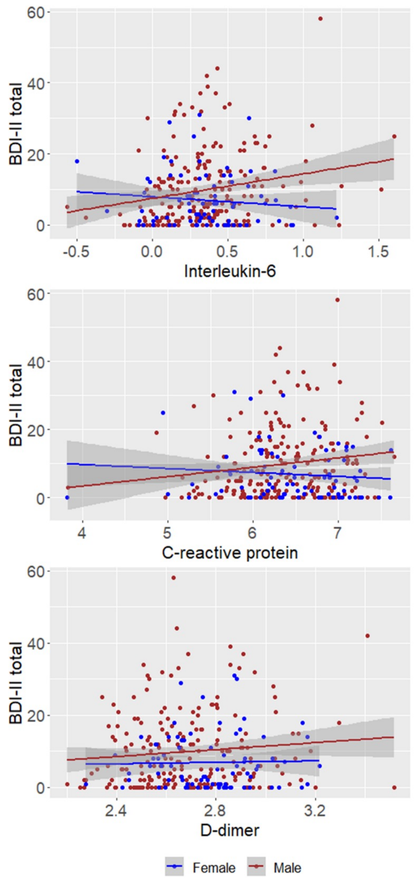
Main finding: a group of inter-correlated plasma inflammatory biomarkers is associated with depressive symptoms in male but not female PWH and PWoH. This effect did not differ by HIV serostatus. This linkage appears to be driven by pro-inflammatory cytokine interleukin-6.

RESULTS

- BDI-II scores were elevated in PWH compared to PWoH (11.7±10.8 vs. 6.2±8.0; p<0.0001).
- Two inflammatory factors were identified: Factor 1 loaded on IL-6, CRP, and D-dimer; Factor 2 loaded on IL-8, CCL2, and CXCL10.
- Sex modified the effect of Factor 1 on BDI-II, with a more positive association for men than women (p=0.041) **(Figure 2)**.
- No significant association found between Factor 2 and BDI-II.
- HIV serostatus did not moderate associations between Factors 1 or 2 and BDI-II.
- Of the biomarkers in Factor 1, only IL-6 was significantly, positively associated with BDI-II and was modified by sex (p=0.003).
- In sex-stratified analysis, a positive IL-6 vs. BDI-II association was found for men (β=5.42; 95% confidence interval=[1.32, 9.52]) **(Figure 3)**. But not for women (β=-3.88; 95% C.I.=[-11.02, 3.26])**.**
- No HIV-related interactions were detected.

Figure 1 ***(left):*** Batch corrected and uncorrected log_{10} plasma concentrations of IL-6.

Figure 3 (*right*): Factor 1 components vs. BDI-II with fitted line by sex, after batch correction.



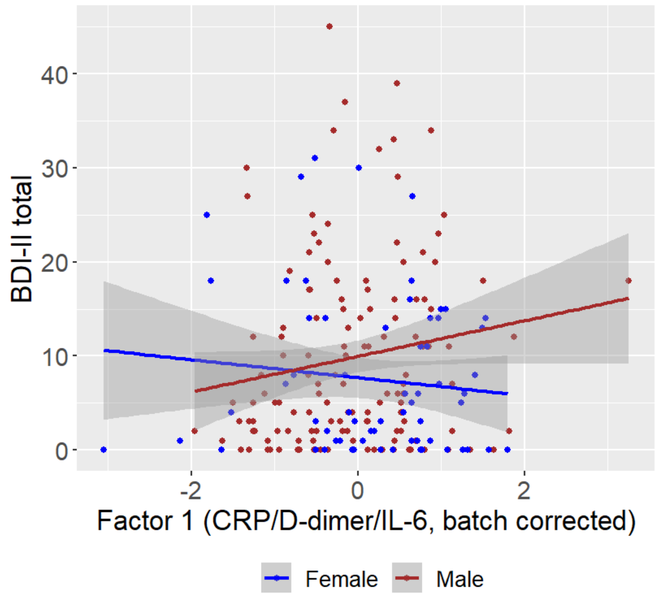


Figure 2: Factor 1 (CRP/D-dimer/IL-6) vs. BDI-II with fitted line by sex, collapsed across HIV serostatus.

CONCLUSIONS

- We identified a depression-associated inflammatory factor across HIV serostatus groups, consistent with smaller studies of PWH only.
- The association was driven by a significant correlation of IL-6 and depression in men, suggesting that the depression-inflammation link differs by sex.
- Future research studies with larger cohorts of women with HIV are needed to elucidate the role of biological sex in the inflammation-depression connection.
- Although associations did not differ by HIV serostatus, PWH may nonetheless be at greater risk for depression in part due to elevated chronic inflammation.

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