

Sex differences in cytokine responses and genetic regulation thereof in people living with HIV

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BACKGROUND

- Biological sex is a key determinant for clinical outcomes in PLHIV
- Women with HIV have reduced viral loads but an increased HIV-induced risk for CVD, possibly because of increased systemic inflammation
- Here, we investigate sex differences in circulating cytokine levels and cytokine production upon PBMC stimulation as well as the genetic regulation thereof in virally suppressed PLHIV

METHODS

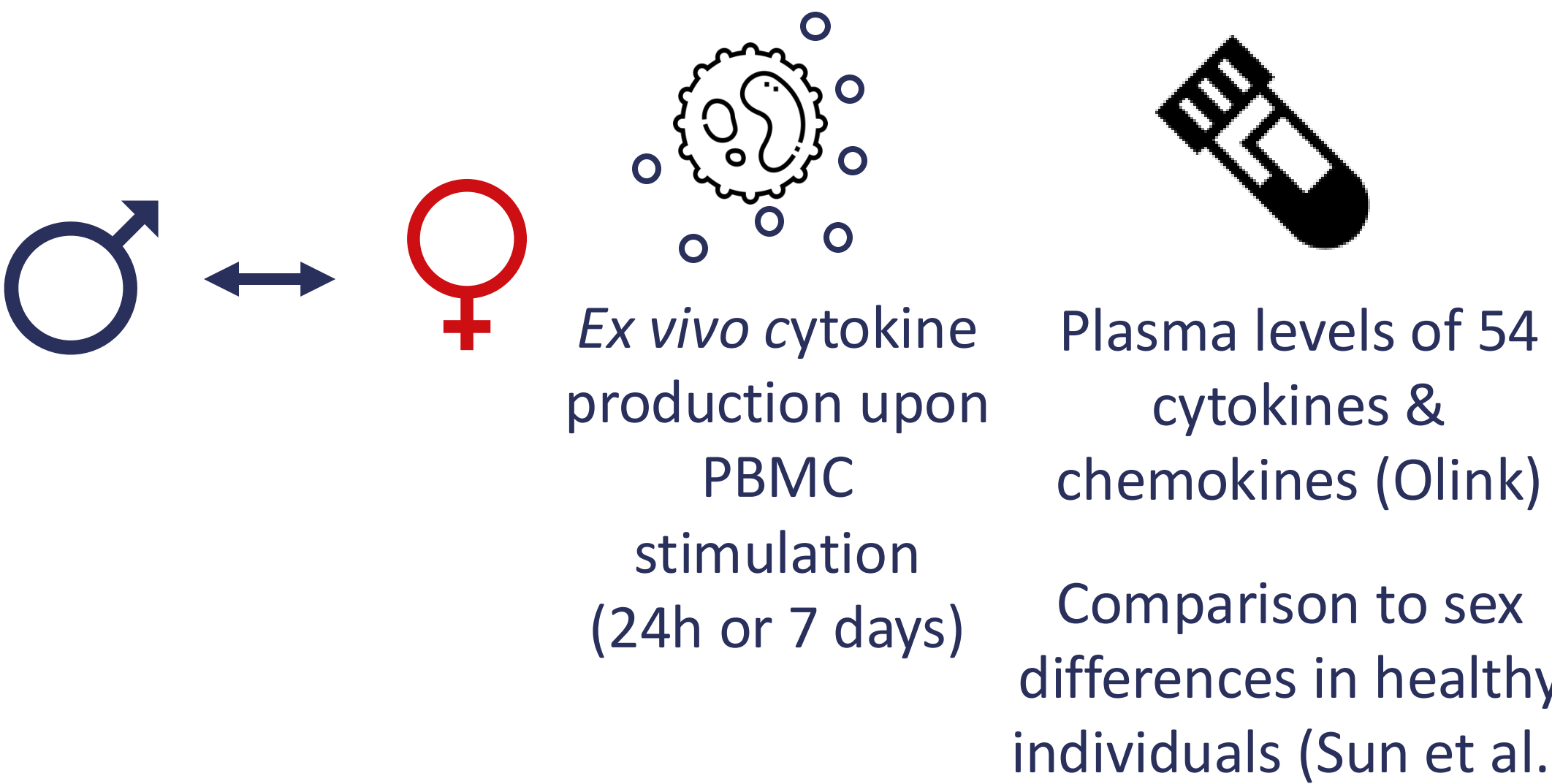
Cohort

Virally suppressed
PLHIV from the
2000HIV study



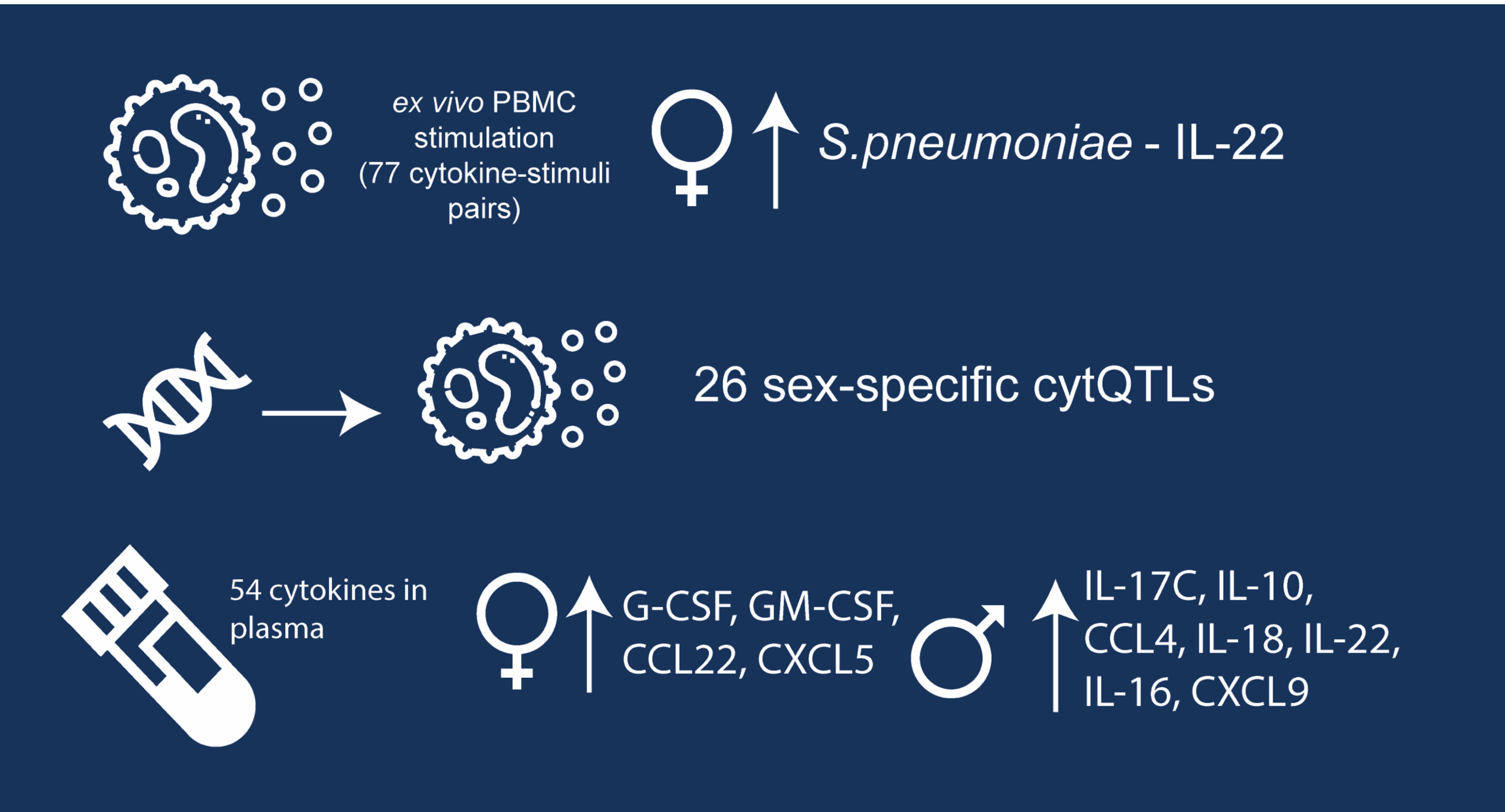
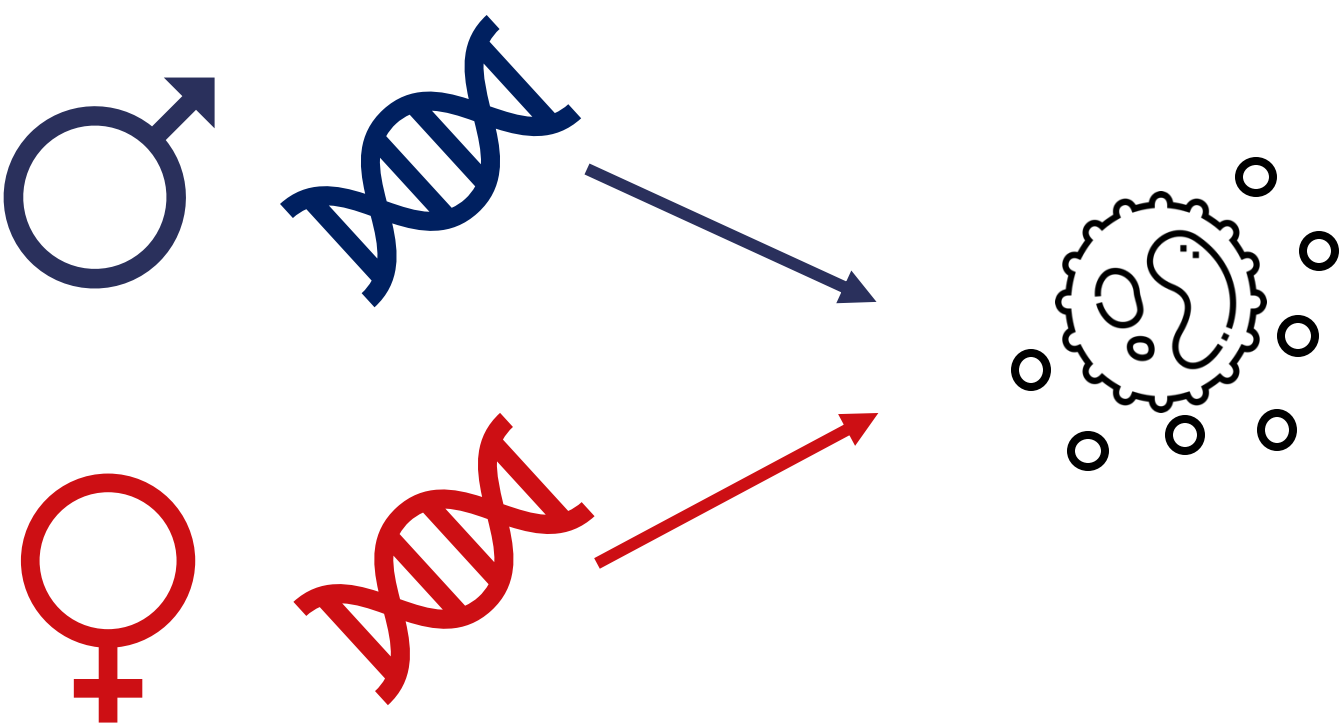
Discovery cohort N = 1309 N = 233
Validation cohort N = 281 N = 52

Comparison between males and females



Sex-stratified cytQTL mapping

Genetic regulation of *ex vivo* cytokine production

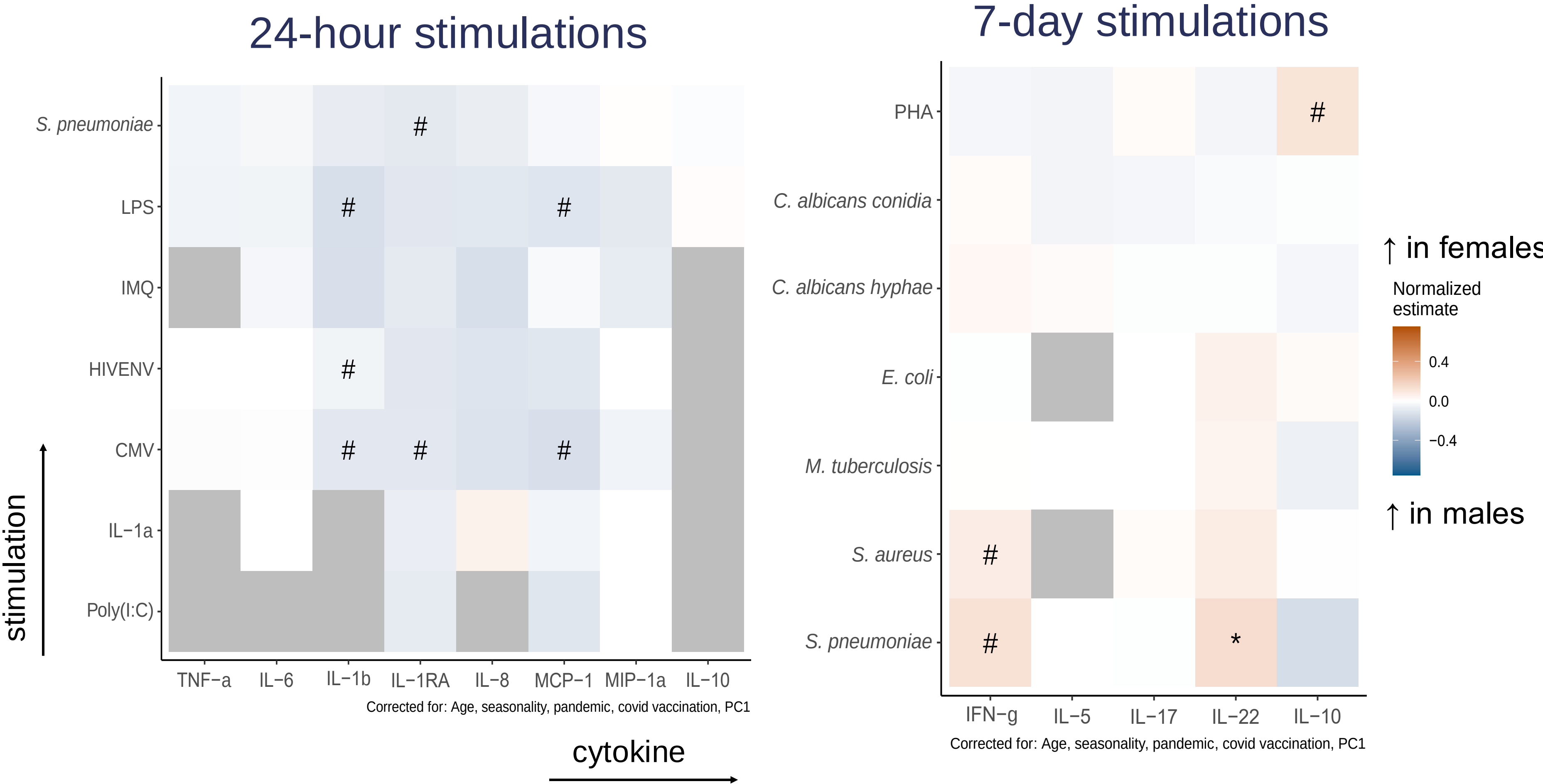


CONCLUSIONS

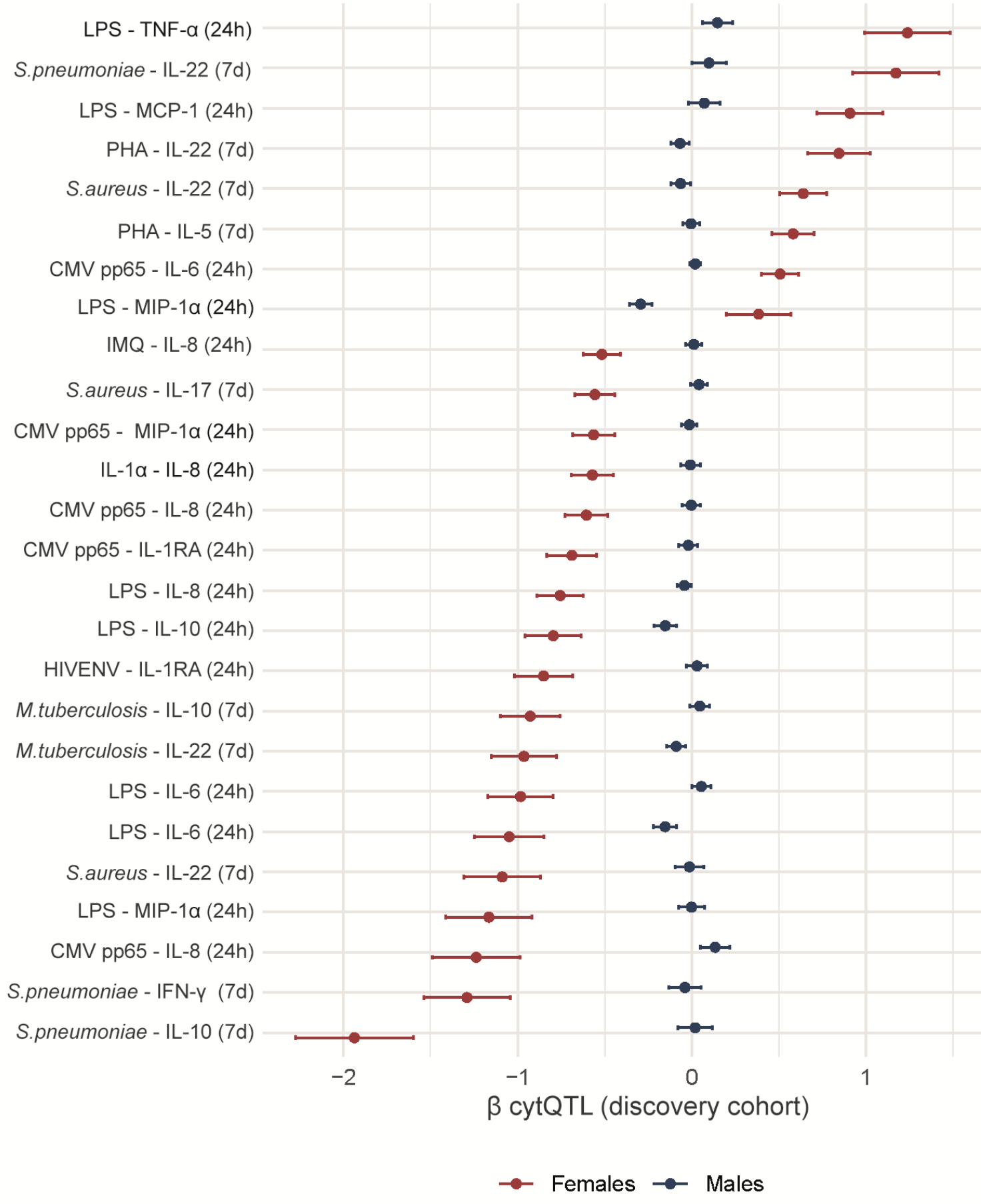
- Sex differences in cytokine responses between virally suppressed PLHIV are limited. There is a trend towards lower 24 hour cytokine responses in females, which might be related to lower monocyte percentages in females, but could not be validated.
- After 7 day stimulations, only IL-22 production to *S. pneumoniae* was significantly increased in females.
- We identified genetic regulation of *ex vivo* cytokine production at 26 independent loci in a sex-specific manner, including one locus regulating IL-22 response to *S. pneumoniae*.
- Sex differences in 10 cytokines in plasma, including HIV-specific downregulation of IL-10 and CXCL9 in females.
- No difference in pro-inflammatory cytokines associated with systemic inflammation (IL-6, TNF- α , and IL-1 β)
- Understanding this sex-specific regulation of cytokine responses can aid in the development of immunological interventions.

RESULTS

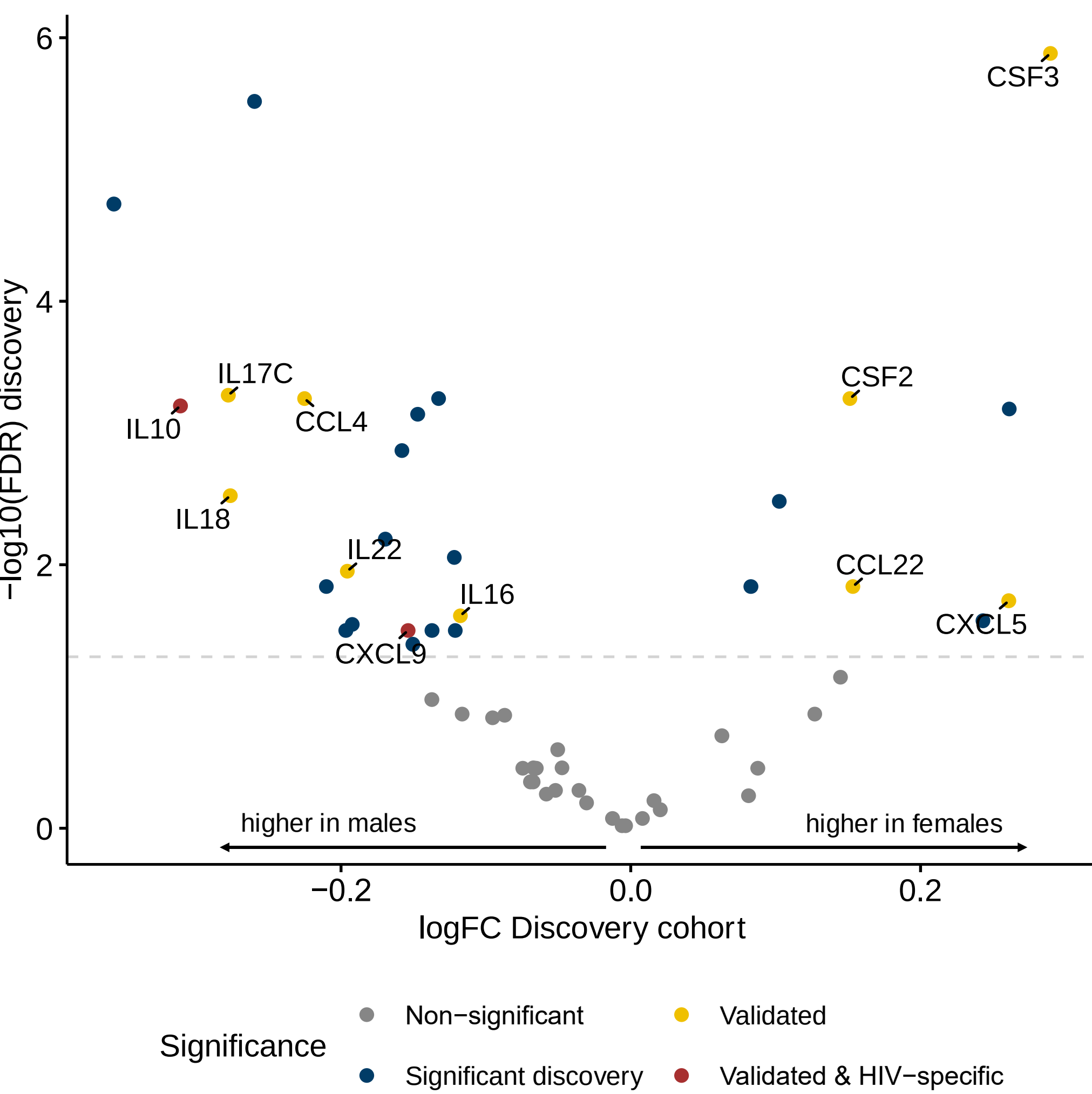
Ex vivo cytokine production in females vs males
* $FDR_{discovery} < 0.05$ & $P_{validation} < 0.05$; #: $FDR_{discovery} < 0.05$, similar direction validation cohort



Sex-specific cytQTLs



Plasma cytokines in females vs males



ADDITIONAL KEY INFORMATION

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Sun, B.B., Chiou, J., Traylor, M. et al. Plasma proteomic associations with genetics and health in the UK Biobank. Nature 622, 329–338 (2023)