Multi-omics profiles of sex hormone-binding globulin are associated with subclinical atherosclerosis in men with HIV

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BACKGROUND

- Sex hormones and HIV infection influence cardiovascular health.
- The association between sex hormones and subclinical atherosclerosis is not fully understood, especially in the context of HIV infection.

METHODS

Study population: Multicenter AIDS Cohort Study (MACS), now part of the MACS/Women's Interagency HIV Study (WIHS) Combined Cohort Study (MWCCS), was a prospective multicenter cohort initiated in 1984. This longitudinal cohort study enrolled men with or at risk of HIV infection from four study centers and invited them to attend semiannual core visits. Sample sizes and exclusion criteria are shown in Fig. 1A.

Sex hormones measurement: Fifteen sex steroid hormones and sex hormone-binding globulin (SHBG) were quantified in serum samples, including adrenal precursors, androgens, estrogens, and progesterone.

Multi-omics profiling:

1. Gut microbiome: shotgun metagenomic sequencing in stool samples (Burk lab).
2. Plasma metabolome: untargeted LC-MS/MS (Broad Institute).
3. Plasma proteome: Olink Explore 3072 platform.

Subclinical atherosclerosis: High-resolution B-mode carotid artery ultrasound. Focal intima-media thickness >1.5 mm at any of the imaged segments in the right carotid artery.

Statistical analysis (Fig. 1B):

1. Sex hormones and plaque: *Multivariable logistic regression*
2. Sex hormones and omics signatures: *ANCOM-BC*, *Multivariable linear regression, Weighted score*
3. Interplay of sex hormones and related omics signatures in carotid artery plaque: *Multivariable logistic regression, Mediation analysis*

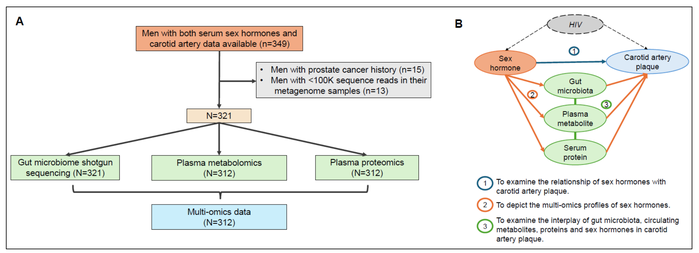


Fig. 1. Flow charts of study participants selection and analysis strategy.

Higher *sex hormone-binding globulin* (SHBG) was associated with lower odds of *carotid artery plaque* in men living with HIV, possibly explained by alterations in *lipid metabolites* and *proteins* involved in immune response and cell function regulation.

SHBG may play a protective role in subclinical atherosclerosis in men with HIV.

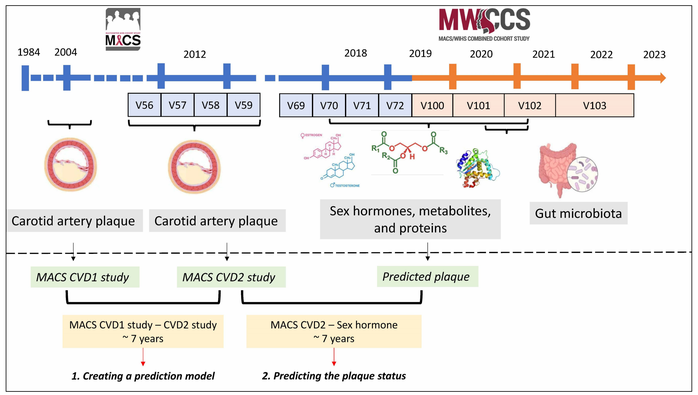


Fig. 2. Main analysis and sensitivity analysis for carotid artery plaque.

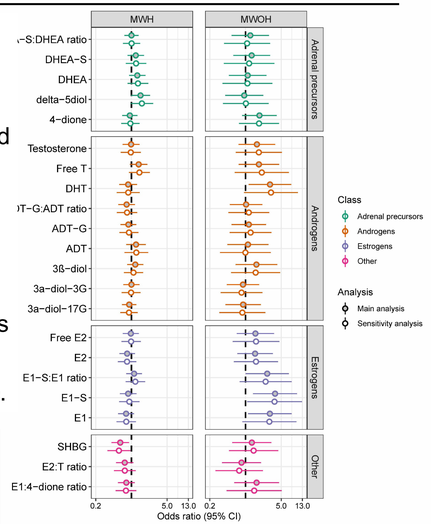
4. Since carotid artery scans were performed prior to blood sample collection, sensitivity analyses with a prediction-based approach were conducted to minimize the misclassification of plaque (Fig. 2).

$$logit(p) = \beta_0 + \sum_{i=1}^{m} \beta_i x_i$$

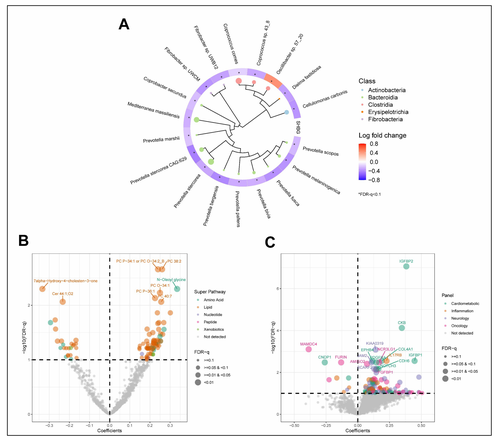
$$p = \frac{e^y}{1 + e^y}$$

RESULTS

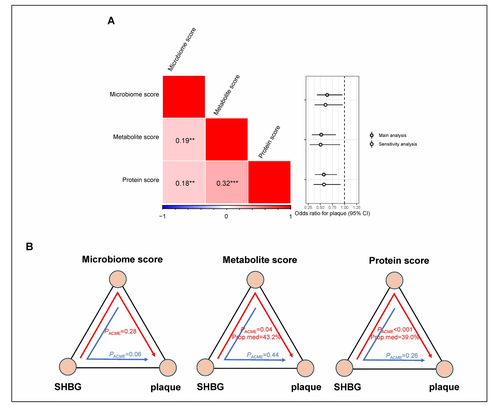
- This study included 321 men (65% living with HIV), with a median age of 62 years (interquartile range: 58, 68). Among men with HIV, 97.6% were receiving antiretroviral therapy and 75.0% had undetectable viral loads.
- Men with HIV exhibited lower levels of DHEA, DHEA-S, E1, E2, and free E2, and higher levels of delta-5diol than men without HIV.
- **Fig. 3** (right): Among men with HIV, higher level of SHBG was associated with lower odds of carotid plaque. Among men without HIV, E1-S was associated with higher odds of plaque.



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❑ **Fig. 4.** Among men with HIV, SHBG was associated with overall gut microbial composition, lower abundance of species from genera *Prevotella*, *Fibrobacter* and *Coprococcus*, higher levels of certain metabolites (primarily lipid and carnitine metabolites) and proteins enriched in the cell-cell adhesion pathway.



❑ **Fig. 5.** Among men with HIV, SHBG-related omics scores were inter-correlated and inversely associated with plaque. Metabolite and protein scores, but not the microbiome score, mediated the protective association of SHBG with plaque.

CONCLUSIONS

- Serum SHBG was associated with lower odds of carotid artery plaque, altered gut microbial species, plasma metabolites, and proteins in men with HIV.
- Future studies are warranted to substantiate these observations, establish temporality, and explore therapeutic targets within the multi-omics signatures.