Multi-omics Analysis of Gut Microbiome and Carotid Artery Atherosclerosis in Men with and without HIV

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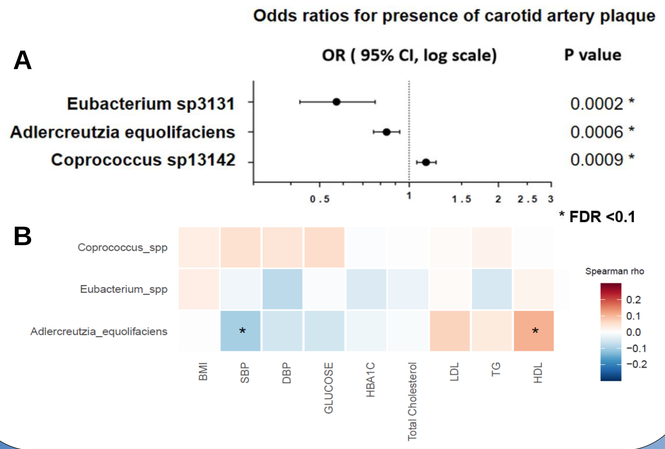
BACKGROUND

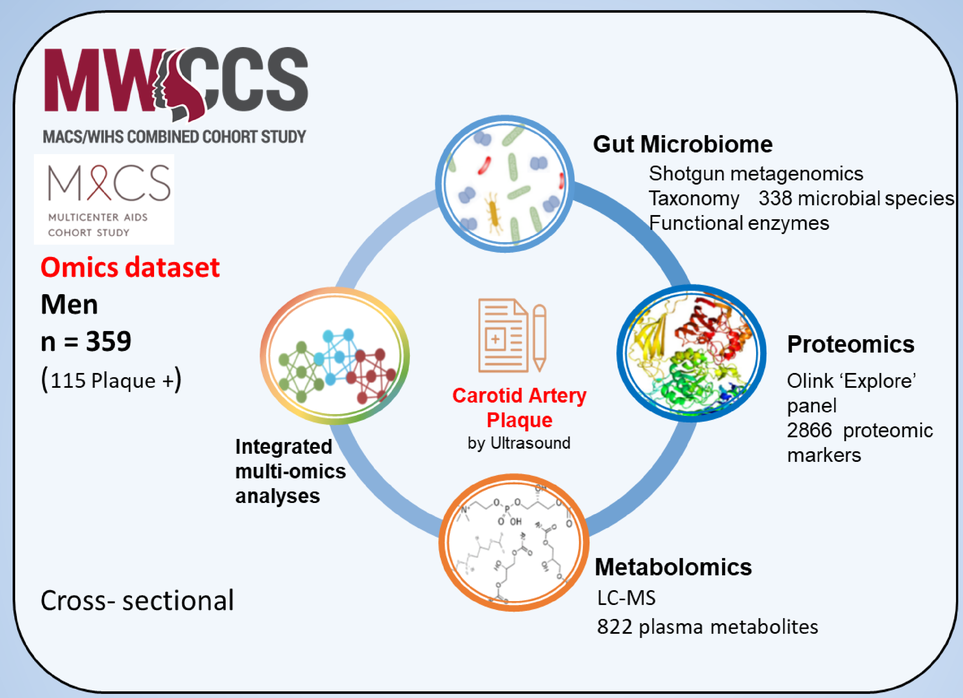
- Alterations in gut microbiota have been implicated in HIV infection and cardiovascular disease (CVD).
- How gut microbial alterations may lead to host inflammation and changes in metabolomics profiles affecting atherosclerosis is not fully elucidated, especially in the context of HIV.

METHODS

- We examined associations of gut microbial species and functional components (measured by shotgun metagenomics) with carotid artery plaque (focal intima-media thickness >1.5 mm, assessed by B-mode carotid artery ultrasound) in 359 men (65% HIV+, mean age 63) from the MACS/WIHS Combined Cohort Study.
- We measured 2866 circulating proteins by Olink platform , and 822 plasma metabolites using LC-MS.
- We further integrated plaque-associated microbial features with proteomics and metabolomics profiles
- Multivariable logistic/linear regression models were performed, adjusting for demographic, behavioral factors, and HIV status. Benjamini-Hochberg FDR method was applied.

RESULTS





- The gut microbial species *Adlercreutzia equolifaciens* and *Eubacterium sp3131* were associated with lower odds of plaque, while the potentially pathogenic bacterium *Coprococcus sp13142* was positively associated with plaque, after adjusting for demographic and behavioral factors.
- Results were consistent in both men with and without HIV.
- We examined correlations between these plaque-associated species and conventional CVD risk factors, and found that *Adlercreutzia equolifaciens* was correlated with HDL cholesterol and inversely correlated with systolic blood pressure

Figure 1. Associations of gut microbial features with carotid artery atherosclerosis.
(A) Associations between gut microbial species and carotid artery plaque. Logistic regression models were adjusted for age, race/ethnicity, study site, antibiotic use, income, education, body mass index, alcohol use, smoking, and HIV status.
(B) Partial Spearman correlations between plaque-associated microbial species and traditional CVD risk factors, adjusted for the aforementioned covariates.
Abbreviations: OR, odds ratios; CI, confidence intervals; FDR, false discovery rate. BMI, body mass index; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HbA1C, hemoglobin A1c.

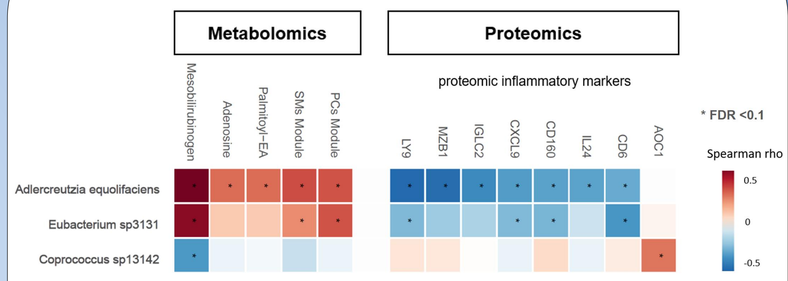


Figure 2. Associations of plaque-associated bacterial species with host circulating metabolites and proteomic inflammatory markers.
Partial Spearman correlations were performed, adjusting for age, race/ethnicity, study site, antibiotic use, income, education, body mass index, alcohol use, smoking, and HIV status.

- These plaque-associated microbial species were associated with a range of circulating metabolites and inflammatory proteins.

For example, *Adlercreutzia equolifaciens* correlated with metabolites palmitoyl-EA (known for antihypertensive and anti-inflammatory properties), and mesobilirubinogen (a metabolic product of bilirubin with antioxidant properties), and inversely correlated with the pro-inflammatory chemokines CXCL9, immune regulator CD160 and IL-24, which promotes cell apoptosis.

- Associations between bacterial species and plaque were attenuated after further adjustment for specific microbial associated circulating metabolites and proteomic inflammatory markers.

CONCLUSIONS

We identified gut microbial features associated with carotid artery atherosclerosis, with certain microbiota-related metabolites and inflammatory markers partially explaining these associations. This work, if validated, suggests potential gut microbiota-related targets for cardiovascular prevention in men with and without HIV.