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# Multi- Omics Analysis of Gut Microbiome and Atherosclerosis in Women Living with HIV


**Zheng Wang[1], David B Hanna[1], Wendy S Post[2], Alan L Landay[3], Kathleen M Weber[4], Audrey French[5] , Elizabeth T Golub[6], Jason Lazar[7], Deborah Gustafson[8], Anjali Sharma[9], Kathryn Anastos[1,9,10], Robert D Burk[1,10,11,12], Robert C Kaplan[1,13], Rob Knight[14,15,16,17], and Qibin Qi [1,18]**

[1] Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, New York, USA [2] Department of Medicine, Johns Hopkins University, Baltimore, MD, USA [3] Department of Internal Medicine, Rush University Medical Center, Chicago, IL, USA [4] Hektoen Institute of Medicine, Chicago, IL, USA [5] Department of Internal Medicine, Stroger Hospital of Cook County, Chicago, IL, USA [6] Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA [7] Department of Medicine, State University of New York Downstate Medical Center, Brooklyn , New York, USA [8] Department of Neurology, State University of New York Downstate Health Sciences University, Brooklyn, New York, USA [9] Department of Medicine, Albert Einstein College of Medicine, Bronx, New York, USA [10] Department of Obstetrics & Gynecology and Women's Health, Albert Einstein College of Medicine, Bronx, New York, USA [11] Department of Pediatrics, Albert Einstein College of Medicine, Bronx, New York, USA [12] Department of Microbiology & Immunology, Albert Einstein College of Medicine, Bronx, New York, USA [13] Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, WA, USA [14] Department of Pediatrics, University of California, San Diego, La Jolla, CA, USA [15] Department of Bioengineering, University of California, San Diego, La Jolla, CA, USA [16] Department of Computer Science and Engineering, University of California, San Diego, La Jolla, CA, USA [17] Center for Microbiome Innovation, University of California, San Diego, La Jolla, CA,USA [18] Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA, USA


## Background

Alterations in gut microbiota have been implicated in HIV infection and cardiovascular disease. However, how gut microbial alterations relate to host inflammation and metabolite profiles, and their relationships with atherosclerosis, have not been well-studied, especially in the context of HIV infection.

## Methods

- We examined associations of gut microbial species and functional components measured by shotgun metagenomics with carotid artery plaque assessed by B-mode carotid artery ultrasound in 320 women with or at high risk of HIV (65% HIV+) from the Women's Interagency HIV Study (WIHS).
- We further integrated plaque-associated microbial features with serum proteomics (74 inflammatory markers measured by the proximity extension assay) and plasma metabolomics (378 metabolites measured by liquid chromatography tandem mass spectrometry) in relation to carotid artery plaque in up to 433 WIHS women.
- Multivariable logistic/linear regression models were performed, adjusting for potential confounders such as age, race/ethnicity, study site, antibiotics use, income, education, BMI, current smoking, alcohol, HIV and ART .
- Benjamini-Hochberg FDR method was applied.

## Results

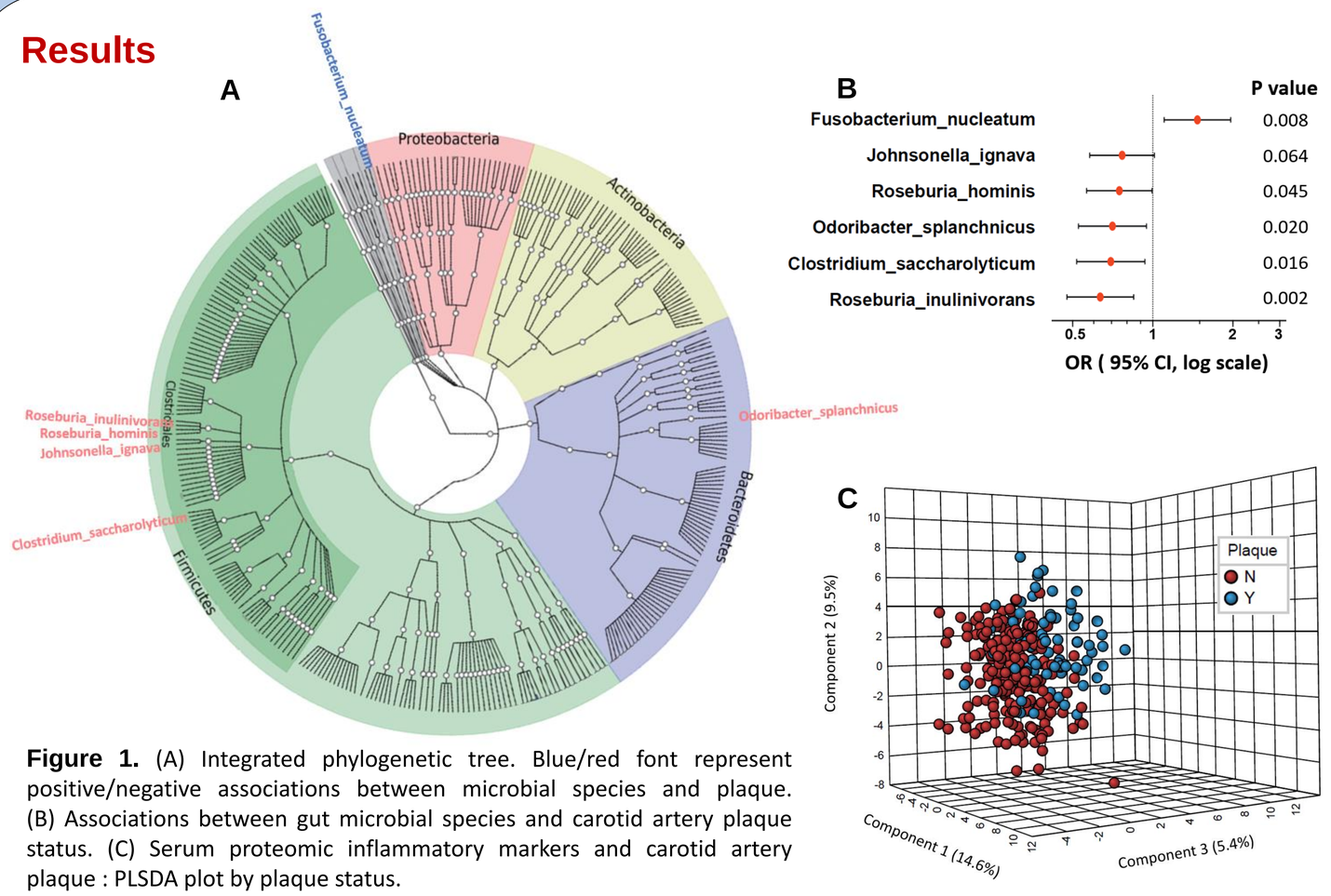


**Figure 1.** (A) Integrated phylogenetic tree. Blue/red font represent positive/negative associations between microbial species and plaque. (B) Associations between gut microbial species and carotid artery plaque status. (C) Serum proteomic inflammatory markers and carotid artery plaque : PLSDA plot by plaque status.

- Gut *F.nucleatum* was positively associated with plaque. As a potentially pathogenic bacteria, *F.nucleatum* was detected in human carotid artery plaque tissues in previous study.
- Five microbial species were inversely associated with plaque. Four of them belong to the same order *Clostridiales* in the phylum *Firmicutes*.

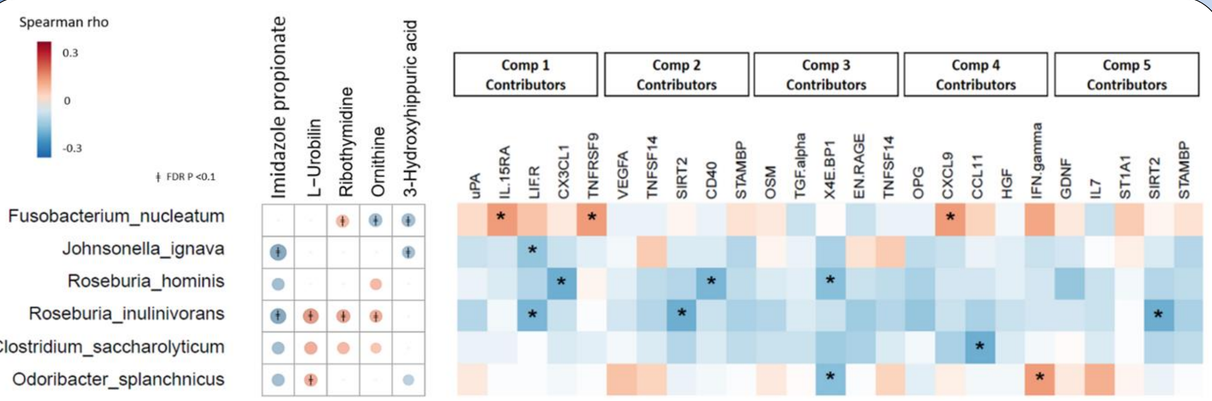


**Figure 2.** Associations of plaque-associated microbial species with circulating metabolites, and proteomic inflammatory markers.

- *F.nucleatum* was positively associated with and the other plaque-related species were inversely associated with multiple serum proteomic inflammatory markers, such as pro-inflammatory chemokines CXCL9 and CX3CL1. These proteomic inflammatory markers were also positively associated with plaque.
- Results were consistent in both women with and without HIV.

- Plaque-associated species were correlated with several plasma metabolites), including a microbial metabolite, imidazole-propionate (ImP), which was positively associated with plaque (P trend = 0.043) and several pro-inflammatory markers (eg. CXCL9 and CX3CL1, all P<0.001).
- Further functional analysis identified additional bacterial species and bacterial *hutH* gene (encoding enzyme histidine ammonia-lyase in ImP production) associated with plasma ImP levels.
- Associations between bacterial species (especially *F.nucleatum*) and plaque were attenuated after further adjustment for proteomic inflammatory markers.

## Conclusions

Among women living with or at risk of HIV, we identified several gut bacterial species and a microbial metabolite ImP associated with carotid artery atherosclerosis, which might be related to host immune activation and inflammation.