TRYPTOPHAN METABOLISM, THE GUT MICROBIOME, AND CAROTID ARTERY PLAQUE IN WIHS WOMEN

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BACKGROUND

- The perturbation of tryptophan (TRP)-kynurenine (KYN) metabolism has been linked with HIV infection and cardiovascular disease (CVD), but the relationship of other TRP metabolites with the gut microbiome and atherosclerosis is not fully understood within the context of HIV infection.

METHODS

- Ten TRP metabolites, including microbial indole derivatives, were quantified in plasma among women (*N* = 251) from 3 sites of the Women's Interagency HIV Study between 2018-2019.
- The gut microbiome was profiled through 16S ribosomal RNA sequencing and shotgun metagenomics in fecal samples that were collected close to the visits of blood collection for TRP metabolites measurements.
- Carotid artery ultrasound was used to assess the presence of plaque.
- The Analysis of Compositions of Microbiomes with Bias Correction (ANCOMBC) was performed to select gut microbial features associated with TRP metabolites.
- Logistic regression was used to examine cross-sectional associations of plasma metabolites and selected gut microbial features with carotid artery plaque.
- Associations analyses were adjusted for sociodemographic factors, study sites and HIV serostatus.

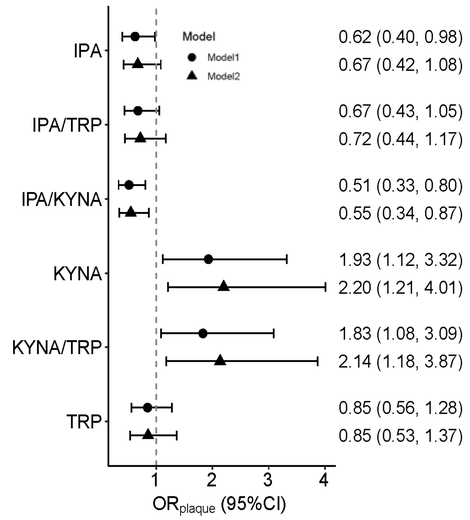


Fig 1. Associations of selected tryptophan (TRP) metabolites and derived ratios with prevalent carotid artery plaque (N=188).

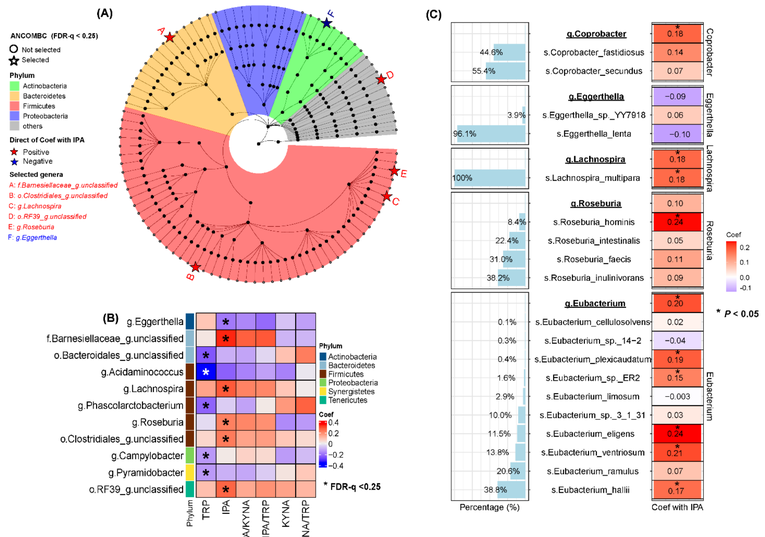


Fig 2. Taxonomic features associated with selected plasma tryptophan (TRP) metabolites.

Table Population characteristics among all participants and by presence of carotid artery plaque

Characteristics	Participants with tryptophan (TRP) metabolites measured (N=251)	Participants with TRP metabolites and plaque information (N=188)		
		Without plaque (N=147)	With plaque (N=41)	*P*
Age (years)	52.4 (7.8)	51.8 (7.5)	57.7 (5.4)	<0.001
BMI (kg/m^2)	31.9 (7.6)	32.1 (8.0)	32.0 (7.5)	0.83
Race/ethnicty (n,%)				0.77
African American	180 (71.7%)	107 (72.8%)	28 (68.3%)	
Hispanic	61 (24.3%)	33 (22.4%)	11 (26.8%)	
White/others	10 (3.98%)	7 (4.76%)	2 (4.88%)	
Education levels (n, %)				0.75
Before Highschool	102 (40.6%)	65 (44.2%)	18 (43.9%)	
Highschool	73 (29.1%)	43 (29.3%)	10 (24.4%)	
College and above	76 (30.3%)	39 (26.5%)	13 (31.7%)	
Family annual income (n, %)				0.41
<12,000$	126 (50.2%)	82 (55.8%)	22 (53.7%)	
12,000~24,000$	71 (28.3%)	35 (23.8%)	7 (17.1%)	
>24,000$	54 (21.5%)	30 (20.4%)	12 (29.3%)	
Smoking status (n,%)				0.20
Never smoker	50 (19.9%)	30 (20.4%)	4 (9.8%)	
Current smoker	96 (38.2%	58 (39.5%)	16 (39.0%)	
Former smoker	105 (41.8)	59 (40.1%)	21 (51.2%)	
Total cholesterol (mg/dL)	191.7 (42.4)	191.1 (43.8)	191.0 (39.2)	0.90
HDL cholesterol (mg/dL)	60.2 (18.2)	60.8 (18.8)	58.3 (19.2)	0.44
Systolic blood pressure (mmHg)	130.6 (19.8)	129.5 (19.0)	135.4 (21.7)	0.19
Fasting glucose (mg/dL)	99.7 (28.7)	96.0 (25.2)	113.4 (40.3)	0.00
Took lipids lowering medication (n,%)	59 (23.5%)	31 (21.1%)	18 (43.9%)	0.01
Took antihypertensive medication (n, %)	115 (45.8%)	59 (40.1%)	28 (68.3%)	0.00
Took antidiabetic medication (n,%)	46 (18.3%)	26 (17.7%)	12 (29.3%)	0.16
HIV positive (n,%)	138 (55.0%)	80 (54.4%)	23 (56.1%)	0.99
Highly active ART use in past 6 months among HIV+ *	129 (93.5%)	74 (50.3%)	23 (56.1%)	0.518
CD4 positive cells (per mm^3) *	846 (613, 1146)	805 (608,1145)	868 (631,1171)	0.551
Detectable HIV RNA (n,%)	27 (19.6%)	18 (22.5%)	2 (8.7%)	0.230
HIV RNA viral load (cp/mL) *	75.00 (32.50, 333.00)	66.0 (31.3,1038.0)	125.0 (80.0,170.0)	0.960
Antibiotics use (n,%)	7 (3.3%)	6 (4.6%)	0 (0.00%)	0.397

Notes: *P* values were generated according to student Student's t-test (for normally distributed variables), Kruskal–Wallis test for (for highly skewed variables), and Chisq-Test (for categorical variables); * only available among HIV+ women, while for HIV RNA virus load, only detectable values were presented. Continuous variables were presented as mean (standard deviation [SD]), except for CD4 positive cells and HIV RNA virus load, which were presented as median (interquartile

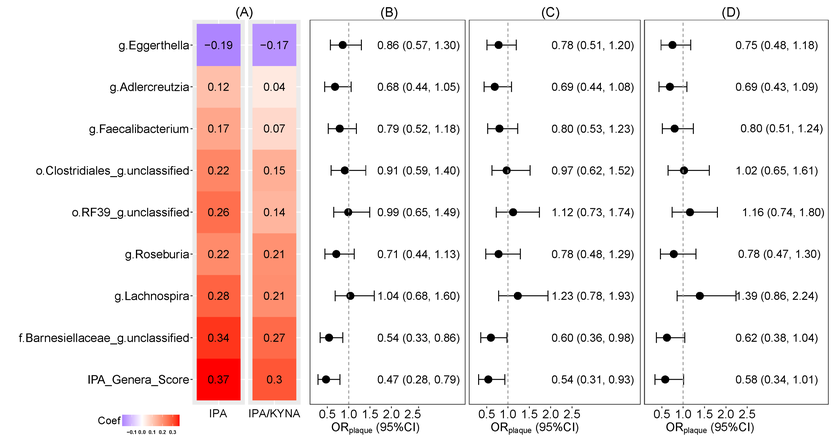


Fig 3. Associations of indole-3-propionate (IPA) associated-genera with prevalent carotid artery plaque.

RESULTS

- 251 women (median age: 52.4 yrs, 71.7% Black; among 138 HIV+ women, 93.5% on ART, 80.4% with undetectable viral load) in the main analysis.
- After multivariate adjustment, carotid artery plaque was positively associated with kynurenic acid (KYNA) (odds ratio [OR] = 1.93, 95% confidence interval [CI]: 1.12, 3.32, per one Z-score increase) and KYNA/TRP (OR=1.83, 95%CI: 1.08, 3.09), and inversely associated with indole-3-propionate (IPA) (OR = 0.62, 95% CI: 0.4, 0.98) and IPA/KYNA (OR= 0.51, 95%CI: 0.33, 0.8).
- We identified six gut bacterial genera associated with IPA levels (FDR-q<0.25), five of which and multiple species within them were positively with IPA, most especially *Roseburia sp.*, *Eubacterium sp*. *Lachnospira sp.*, and *Coprobacter sp*.
- a constructed IPA-associated-bacteria score was inversely associated with plaque (OR=0.47, *P*=0.004), and the association was attenuated after further adjustment for IPA levels (OR=0.54, *P*=0.02) or IPA/KYNA (OR=0.58, *P*=0.05).
- No gut bacteria were associated with KYNA levels and the effect modification by HIV serostatus was generally non-significant

CONCLUSIONS

- Plasma IPA levels and related gut bacteria were inversely associated with carotid artery plaque, suggesting a potential beneficial role of IPA and its gut bacterial producers in atherosclerosis and CVD.

ADDITIONAL KEY INFORMATION

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- **Reproducible work**: Data and analysis codes will be available on reasonable request to co-responding author.
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MWCCS MACS/WIHS COMBINED COHORT STUDY

EINSTEIN Albert Einstein College of Medicine