Gut Microbial Variations Associated with Proton Pump Inhibitor Use in a Hispanic Cohort

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Abstract

Proton pump inhibitors (PPI), used to treat gastrointestinal disorders, are associated with alterations in the gut microbiome. However, this is understudied in Hispanics and Latinos who have unique dietary and lifestyle characteristics. The estimated prevalence of PPI use in the US is approximately 8.6%. In the Boston-Puerto Rican Health Study (BPRHS), we observed high baseline PPI use (25%) which continued to increase over four waves of follow-up (36% PPI use at wave 4). Therefore, we examined gut microbial variations associated with PPI use in the BPRHS.

The BPRHS is a prospective cohort that enrolled 1500 participants at baseline. Data was collected across four waves over thirteen years of follow-up. Data from the fourth collection wave was used in these analyses.

At wave 4, 309 BPRHS participants self-reported PPI use and self-collected, metagenomically profiled, stool samples.

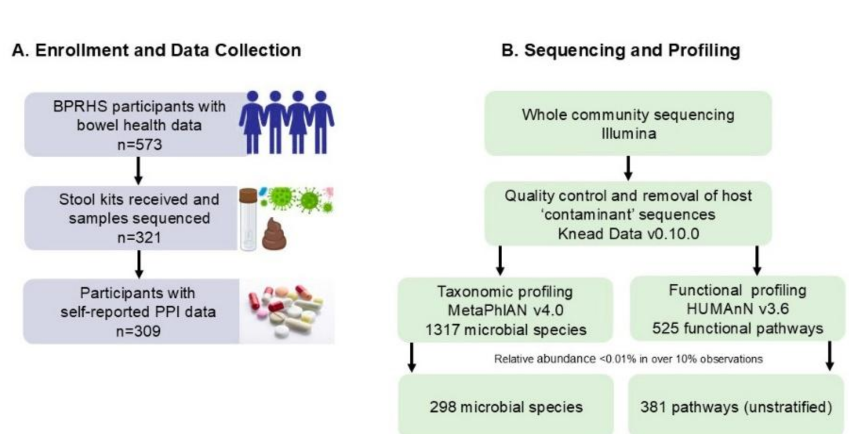
PPI use was classified as any past use.

Cross-sectional associations between gut microbial taxa, functional pathways, and PPI use were examined using omnibus tests, multivariate linear modeling in MaAsLin2, and random forest classifier in feature-wise analyses. We further compared our results with the non-Hispanic Health Professionals Follow-Up Study (HPFS) to validate key findings and examine ethnicity-related differences.

Among 309 participants (mean age 68.8y; female 74.6%), 112 (36%) self-reported PPI use. After adjusting for relevant covariates, we observed an enrichment of *Streptococcus parasanguinis* (β=3.16, FDR *P*=0.01), *S. anginosus* (β=2.89, FDR *P*<0.01), *S. salivarius* (β=2.56, FDR *P*=0.01), *S. gordonii* (β=1.98, FDR *P*=0.15), and *Rothia mucilaginosa* (β=1.54, FDR *P*=0.06), among PPI users compared to non-users. *Streptococci* and *Lactobacilli* predominantly contributed to the functional pathways associated with PPI use.

The observed enrichment of oral-typical taxa, such as *Streptococci*, among PPI users in the BPRHS, suggests the potential of PPIs to alter gut microbial composition.

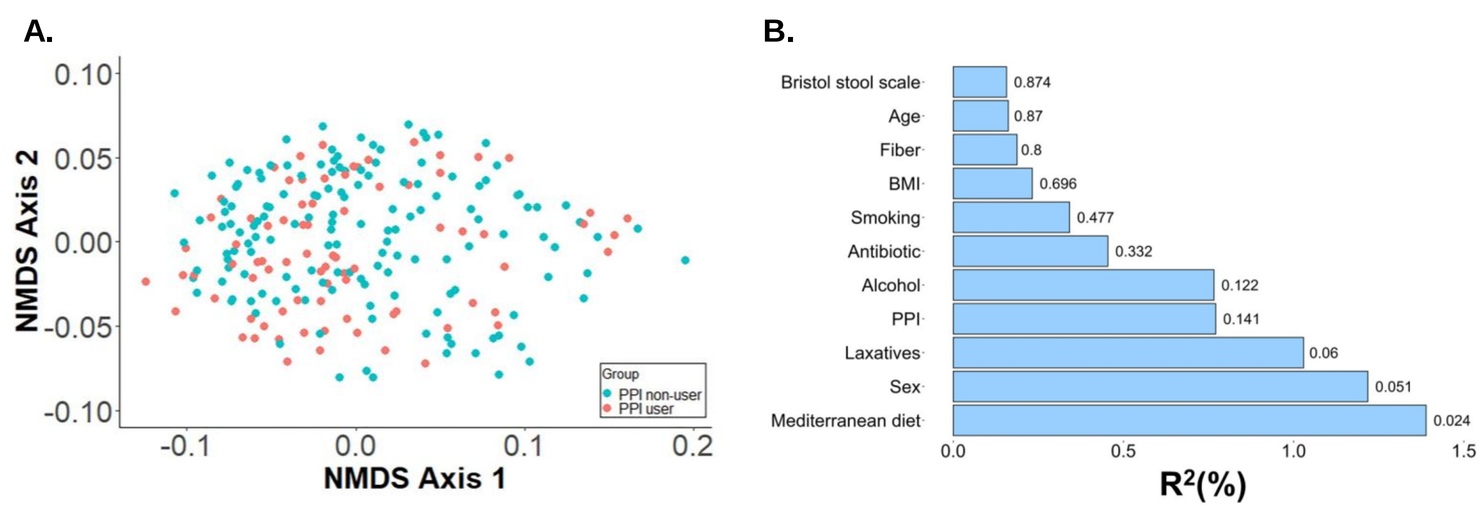
Study design



- Among 309 participants, mean age 68.8y and 74.6% female, 112 (36%) self-reported PPI use.

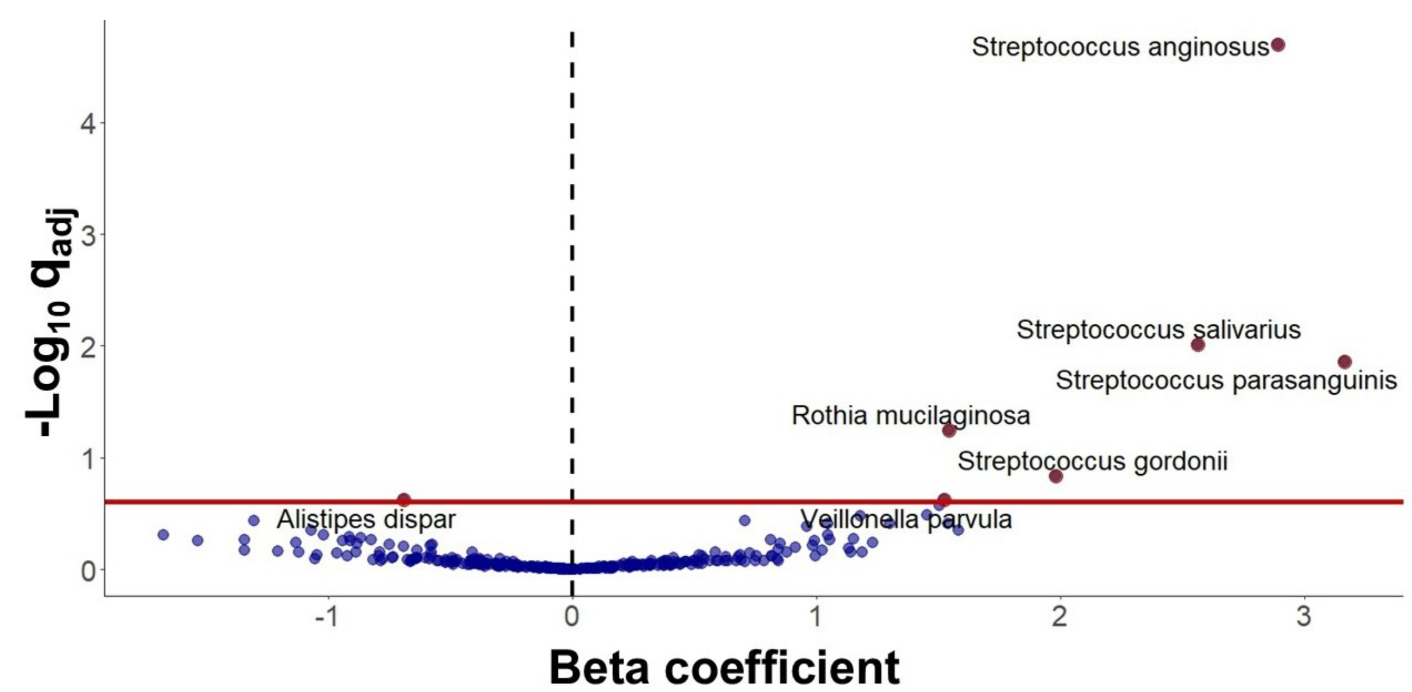
Study design figures created in Bio Render and Adobe.

Bray Curtis dissimilarities



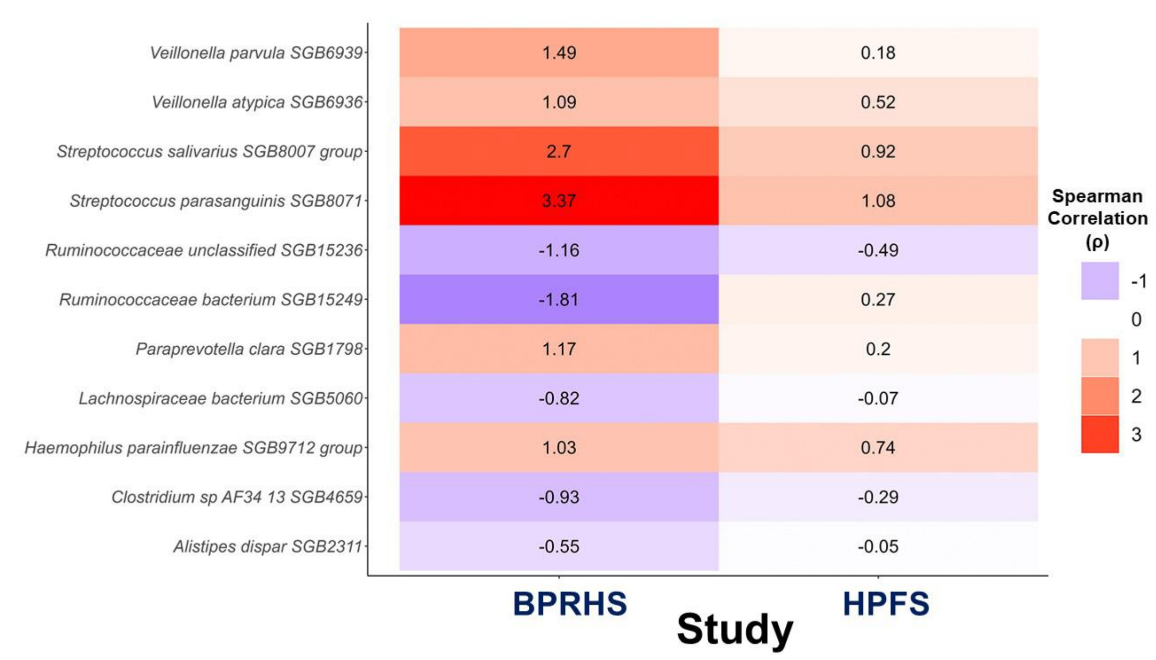
- Gut microbial composition was analyzed using Bray Curtis dissimilarities.
- **A**) Ordination was performed using non-metric multidimensional-scaling of Bray Curtis dissimilarities based on PPI use. Significance was tested using permutational multivariate analysis of variance (R^2=0.008, *P*=0.13). Analysis was adjusted for age, sex, BMI, alcohol use, smoking, Bristol stool scale, Mediterranean diet, fiber intake, laxative and antibiotic use.
- **B**) Covariates: Mediterranean diet and sex explained the most variation in the microbial composition.

Microbial taxa associated with PPI use



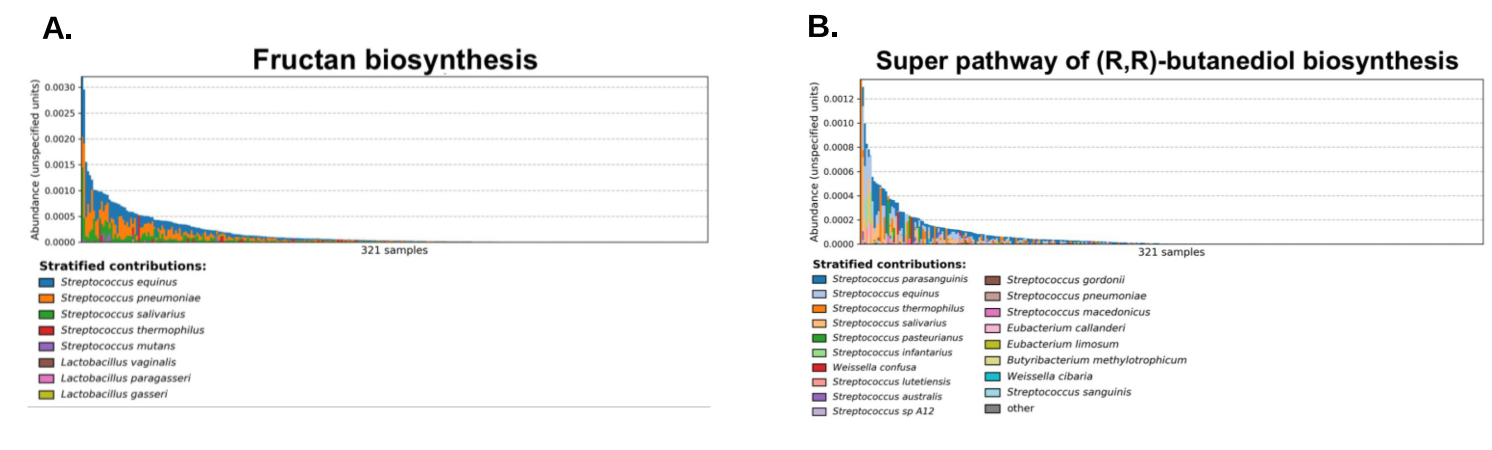
- Differential abundance of gut microbial taxa, based on PPI use, was tested using linear regression models in MaAsLin2. FDR *P*≤0.25 was considered statistically significant (red line). Analysis adjusted for age, sex, BMI, alcohol use, smoking, Bristol stool scale, Mediterranean diet, fiber intake, laxative and antibiotic use.
- Our results suggest an enrichment of *Streptococcus parasanguinis* (β=3.16, FDR *P*=0.01), *S. anginosus* (β=2.89, FDR *P*<0.01), *S. salivarius* (β=2.56, FDR *P*=0.01), *S. gordonii* (β=1.98, FDR *P*=0.15), and *Rothia mucilaginosa* (β=1.54, FDR *P*=0.06), among PPI users compared to non-users.

Concordant associations BPRHS and HPFS cohorts



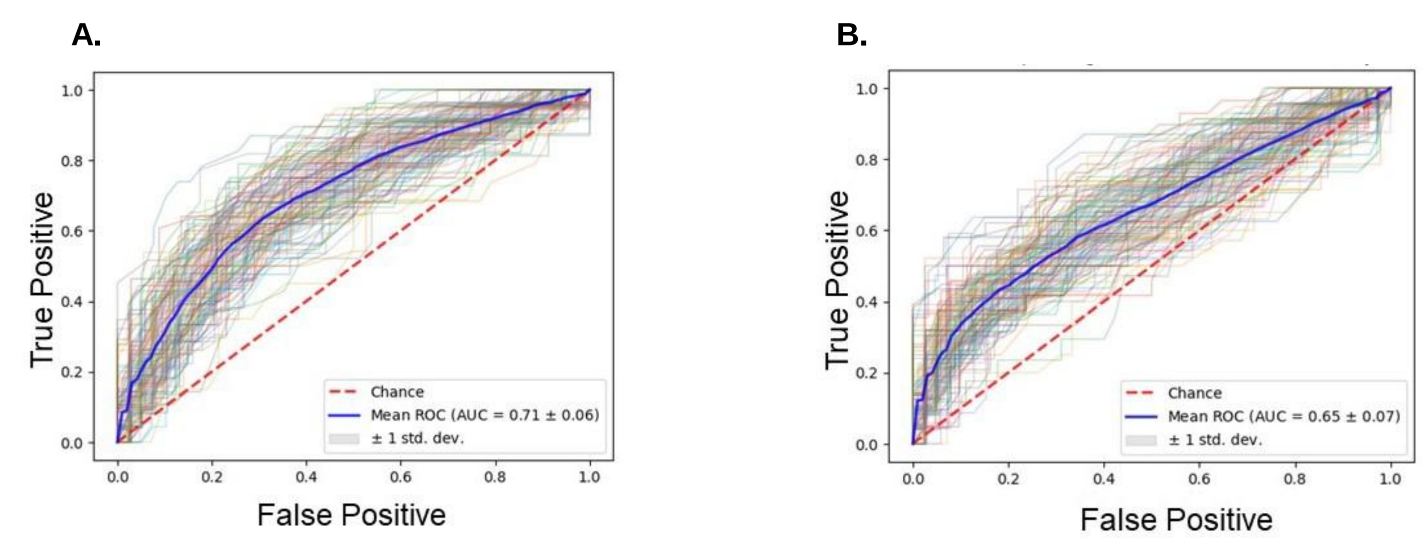
- Comparison of beta coefficients from adjusted MaAsLin2 for gut microbial taxa in BPRHS (taxa n=20; FDR P≤0.25) and gut microbial taxa in HPFS (all taxa i.e., n=497).
- BPRHS analysis adjusted for age, sex, and BMI and HPFS analysis adjusted for age and BMI.
- Concordant associations between microbial taxa and PPI use was observed in both cohorts.

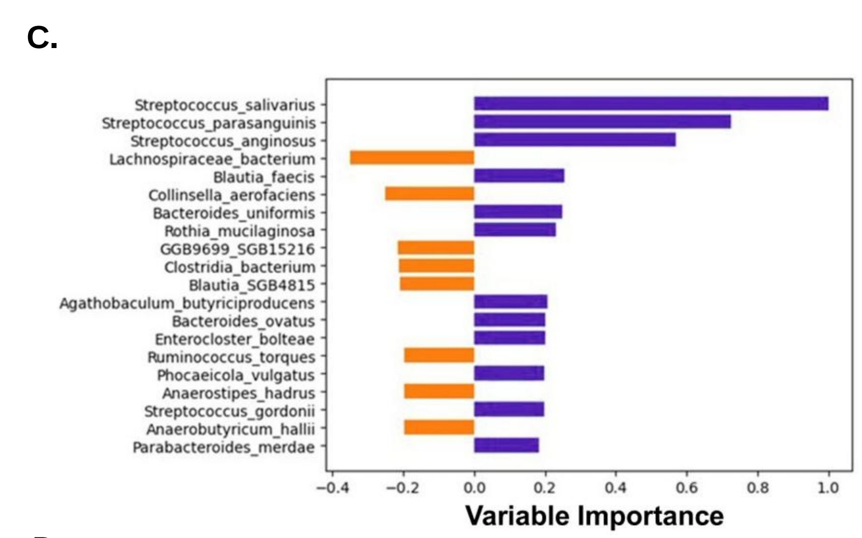
Functional pathways associated with PPI use



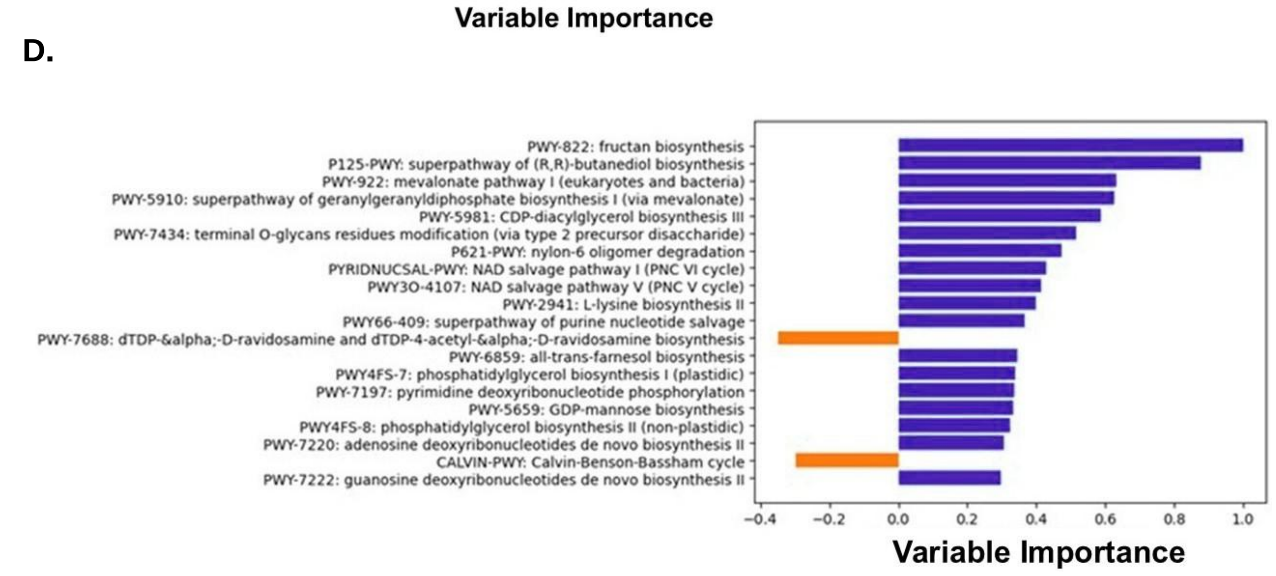
- PPI use was associated with enrichment of fructan (β=2.22 , FDR *P*<0.01) and butanediol biosynthesis (β=2.06, FDR *P*<0.01) based on MaAsLin2 analysis. Stratified analysis of fructan (**A**) and butanediol biosynthesis (**B**) suggest *Streptococci* and *Lactobacilli* predominantly contribute to the functional pathways associated with PPI use.

Random Forest classifier





- Random forest classifier was used to evaluate if gut microbial taxa (**A**) and pathways (**B**) predict PPI use.
- Based on performance, by area under the curve (AUC) of receiver operating characteristic: microbial taxa AUC=0.71±0.06 and pathways AUC=0.65±0.07.
- We analyzed mean importance to identify microbial taxa (**C**) and pathways (**D**) that influenced the model's predictions.



Future directions

- Our results suggest that PPIs may alter gut microbial composition.
- More studies are needed to understand the impact of PPI use on the gut microbiome in different ethnicities.

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