

Exercise, the microbiome, and Parkinson's: Insights from the Fox Insight human data set.



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ABSTRACT

To date, exercise is one of the only therapeutics shown to effectively ameliorate the progression of Parkinson's disease (PD)¹ while both oral and gut microbiomes showing signs of dysbiosis². Fascinatingly, exercise has been shown to interact with the microbiome. In the gastrointestinal (GI) system, exercise has been shown to increase bacteria that help indirectly produce dopamine and motivation for exercise³, while other studies have shown increase in exercise capacity⁴. In the oral cavity, it has been shown that saliva bacteria play a role in regulating post-exercise orthostatic hypotension⁵. Given that exercise slows disease progression in those with Parkinson's, this begs the question as to whether administration of 'exercise-probiotics' can provide a targeted benefit. To answer these questions, we have performed bioinformatics analysis and AI-predictive modeling on exercise and microbiome data collected from individuals enrolled in Fox Insight PDMB sub-study (113 (saliva) and 111 (stool)), an initiative from the Michael J. Fox Foundation (MJFF) (Image 1). In the saliva microbiome, we found greater alpha-diversity (Figure 1) in Strenuous exercise participants, as well as Beta-diversity (Figure 2) differences between Light and Strenuous exercisers when controlling for covariates (Figure 3.) Using XGBoost (optimized balance accuracy 0.565) (Figure 4), we found that *Neisseria subflava*, a gram-negative Proteobacteria, is the 3rd ranking predictor of exercise behavior (Figure 5) and is more abundant in strenuously exercising participants (p<0.030, FDR = 0.174) (Figure 6.) Furthermore, *N. subflava* correlated with a lower PD motor symptom score (p<0.003, FDR 0.074), specifically with lower rigidity (p<0.0083, FDR 0.21) and slowness (p<0.0067, FDR 0.084) (Figure 7, 8) making it a top candidate to pursue in future studies.

Overview

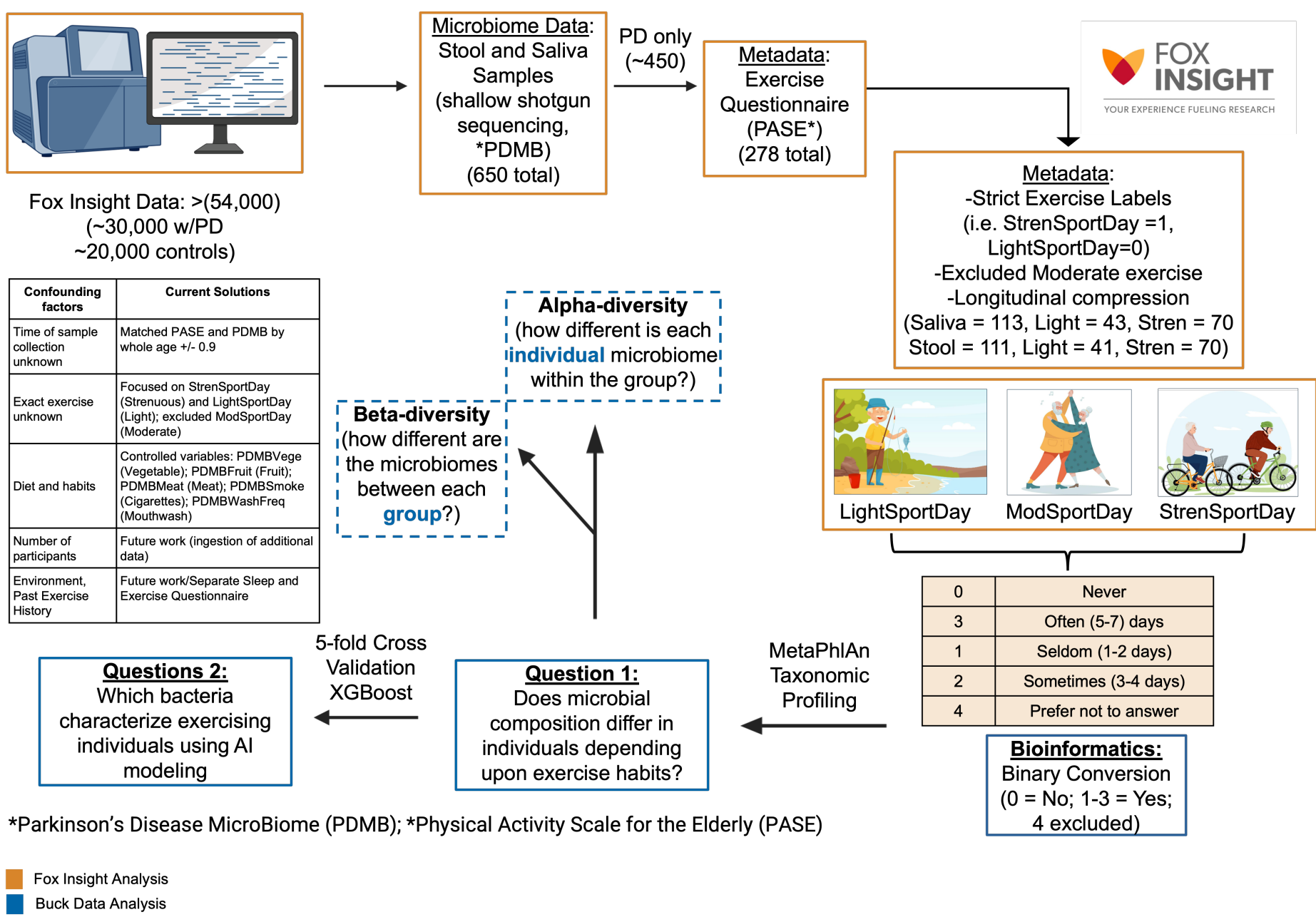


Image 1. Overview of bioinformatics and XGBoost AI modeling.

Alpha- and Beta- Diversity

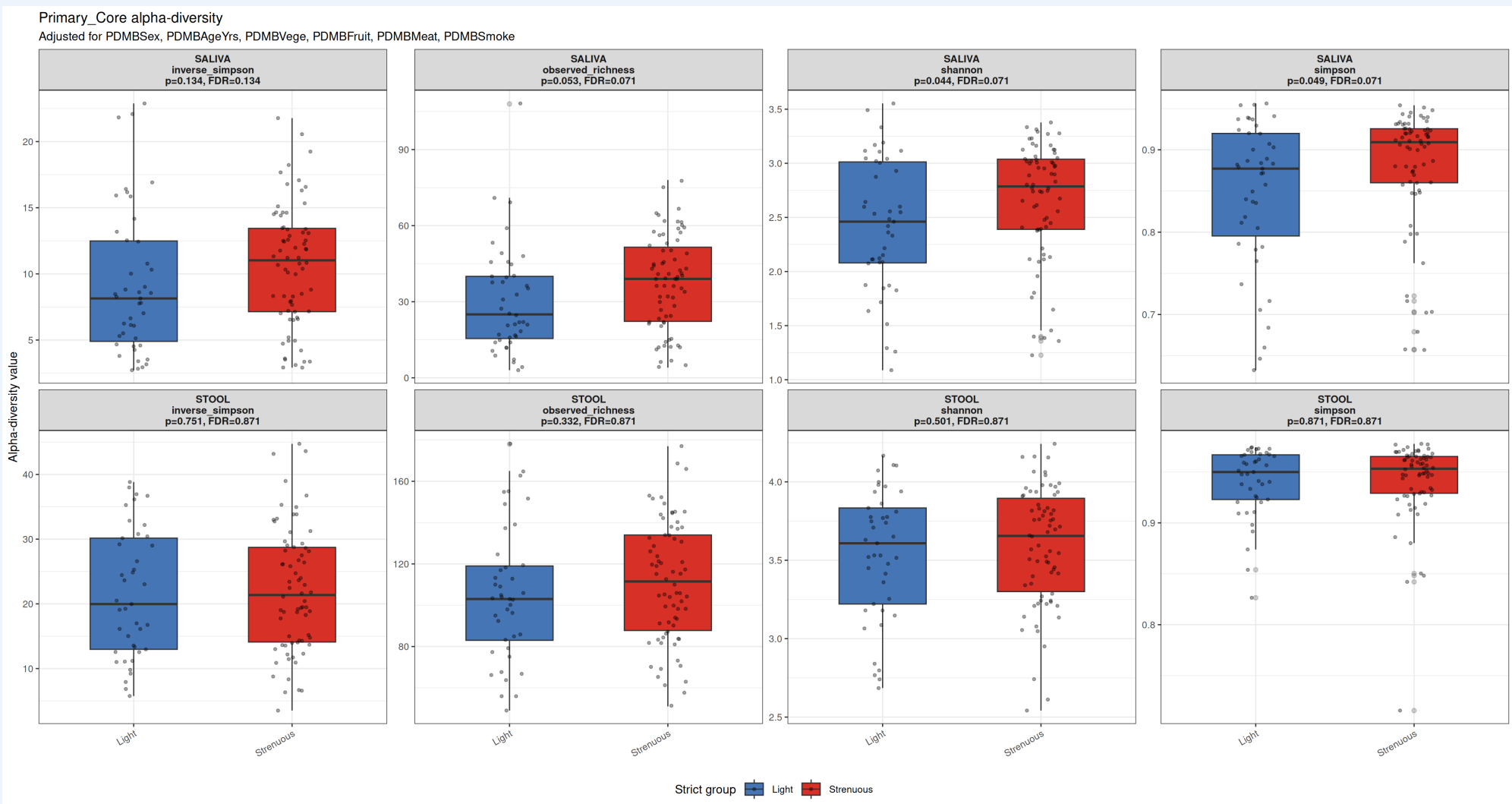


Figure 1. Alpha diversity for saliva (top) and stool (bottom).

XGBoost/AI Model

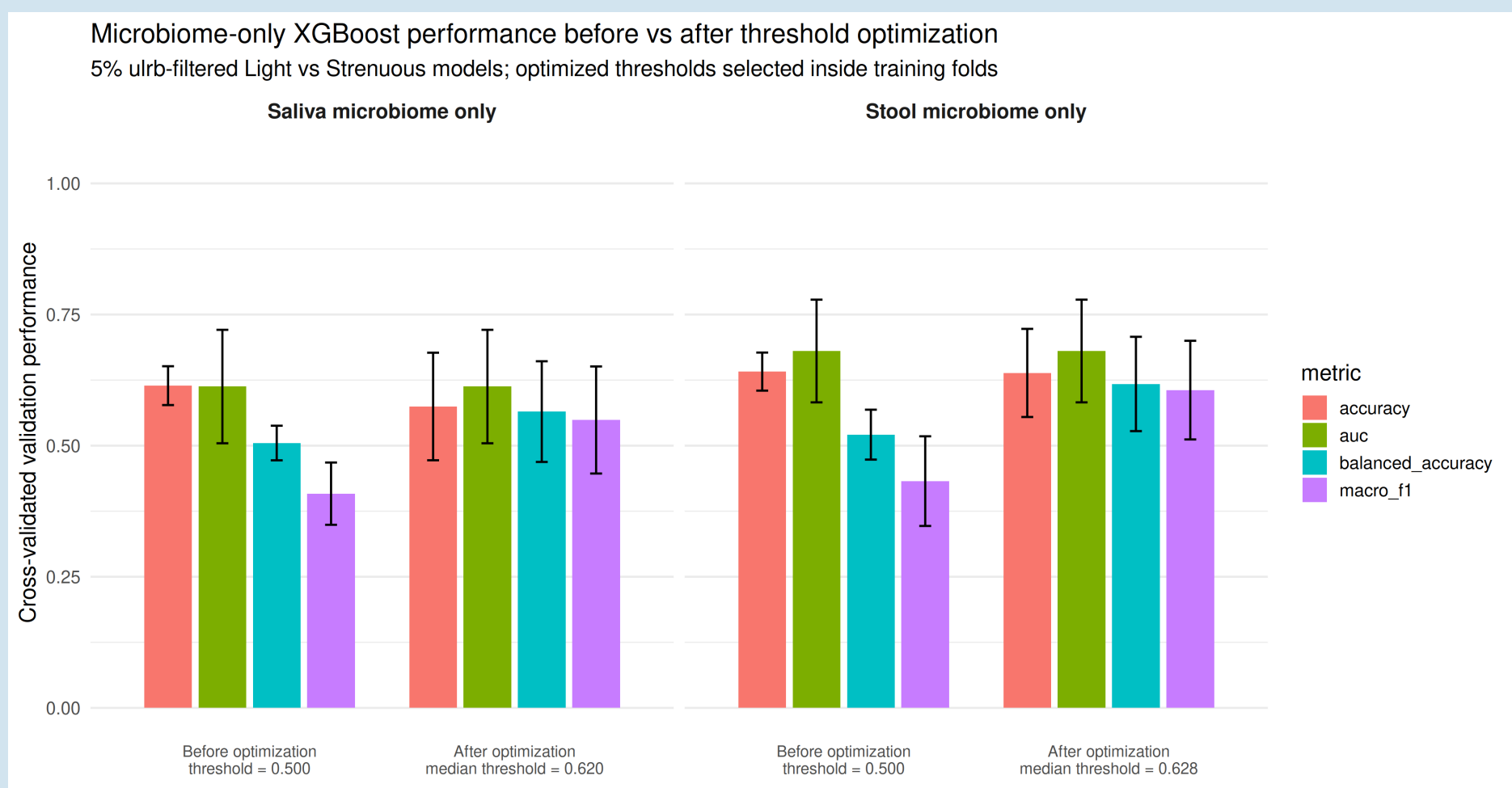


Figure 4. XGBoost 5-fold cross validation with optimized threshold analysis.

Figure 5. SHAP and beeswarm plots of saliva (top) and stool (bottom).



Figure 6. Abundance graphs of top 25 predictive saliva bacteria.

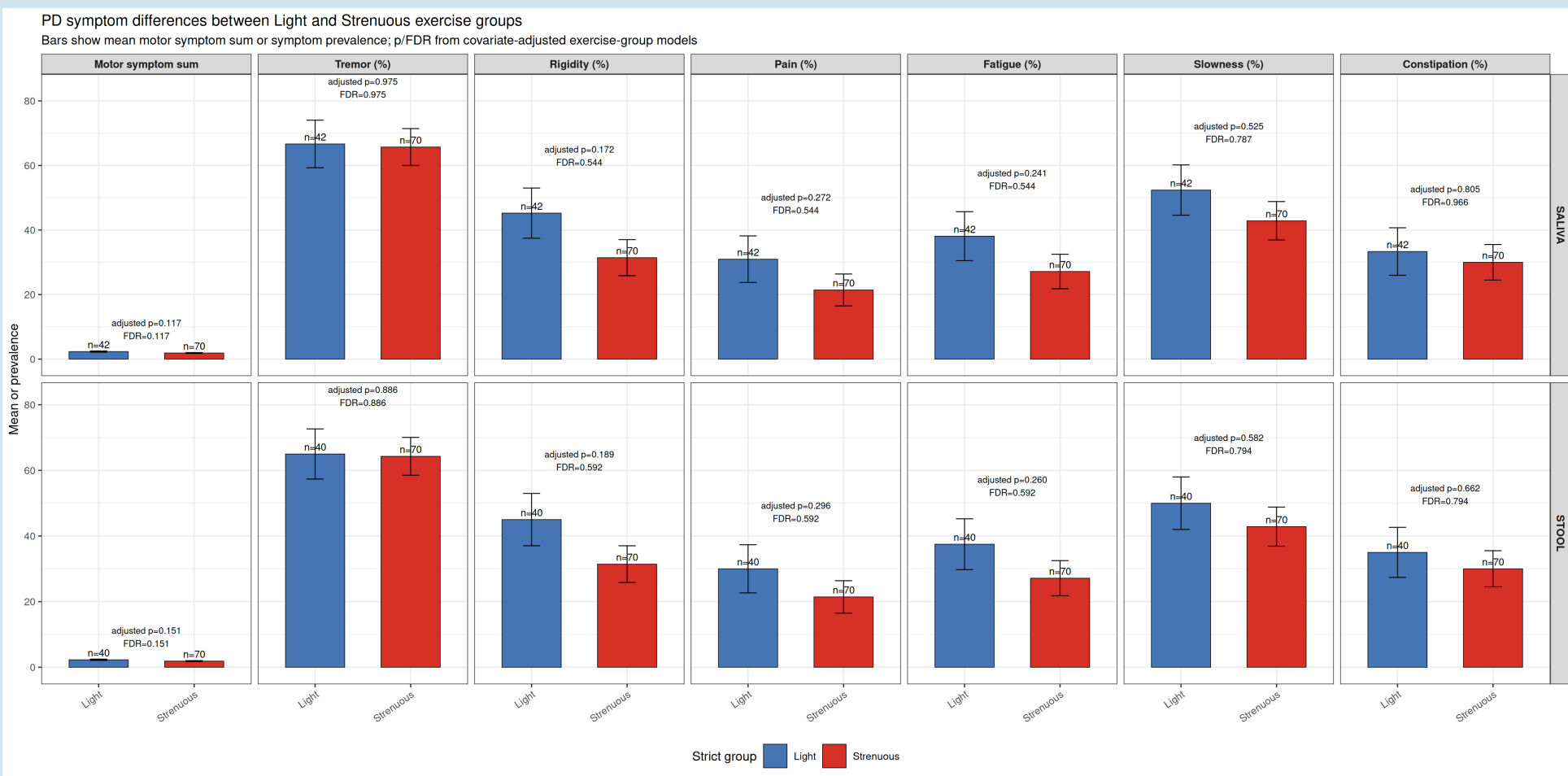


Figure 7. Motor and non-motor symptom differences between Light and Strenuous exercisers (saliva (top), stool (bottom)).

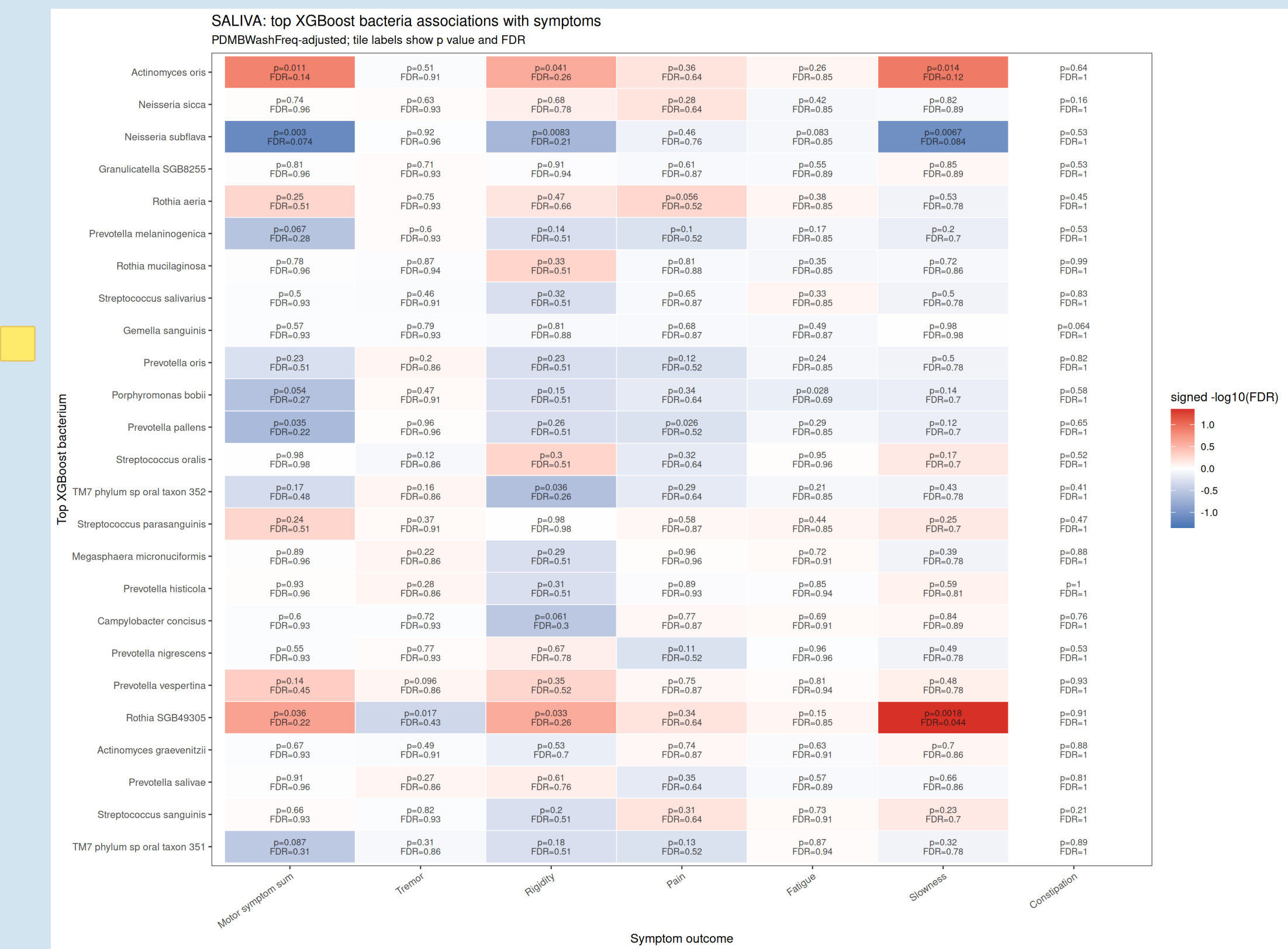


Figure 8. Top XGBoost saliva bacteria associations with motor and non-motor symptoms.

Conclusion

In this study of **Fox Insight PDMB-exercise** participants, we found that stronger microbiome differences (**alpha-** and **beta-** diversity) are present in the **saliva** microbiomes of **Light** and **Strenuous exercisers** as compared to **stool**. We modeled microbiome-based prediction of exercise behavior with **XGBoost** and found that the saliva model predicted exercise activity at **0.565 balanced accuracy**. Within this model, ***N. subflava*** appeared as a strong exercise predicting bacteria (**ranking 3rd**) with **higher abundance in Strenuous exercise** participants and significant correlation to **improvement in motor symptoms**, specifically rigidity and slowness. In **parallel work** uncovering microbiome differences between Parkinson's subtypes (previously defined as **body-first** and **brain-first**)⁶, *N. subflava* also appeared as a top predictor (validated in 3 different models.) Here, **lower abundance** levels appeared in **body-first** participants while near control levels were present in brain-first participants. In other studies, it has been shown that *N. subflava* is reduced in those with Parkinson's as compared to control⁷. **Altogether, our data suggests that reduced *N. subflava* abundance correlates with less activity and worsened symptoms.** Future work with aim to determine *N. subflava*'s capacity as an 'exercise-probiotic' i.e. a bacteria which mimics exercise related benefits as a possible treatment for Parkinson's.

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