Translating the Microbiome

Revealing the Association Between Optimism and the Gut Microbiome

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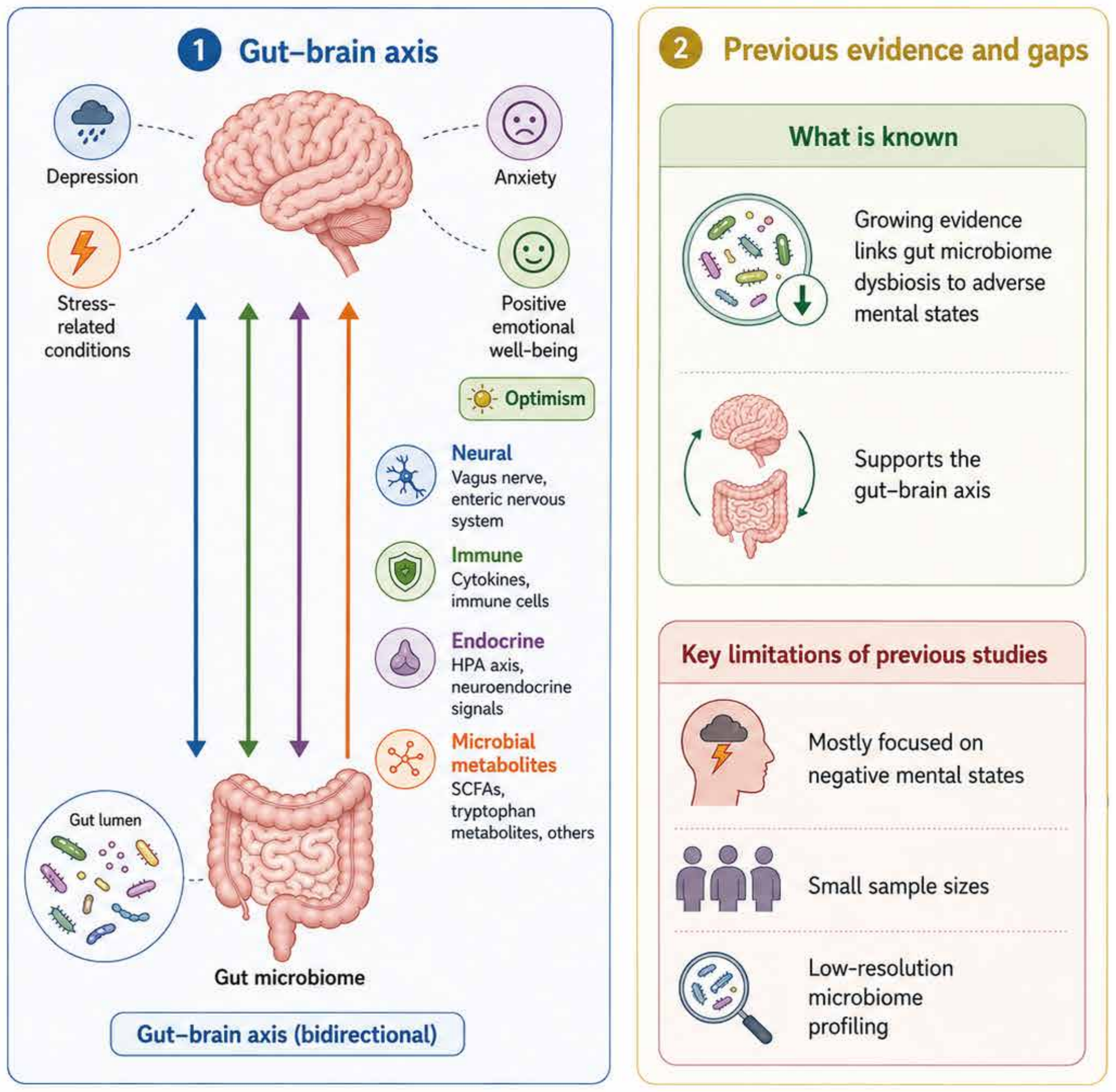
Abstract

Background: Growing evidence supports a link between gut microbiome dysbiosis and adverse mental states such as depression, anxiety, and other stress-related conditions. However, much less is known about how the gut microbiome relates to positive emotional well-being. Understanding this relationship could help explain the well-established connection between emotional well-being and health and provide further support for the gut-brain axis. Previous studies have been limited by small sample sizes and low-resolution microbiome profiling methods.

Methods: Here, we analyzed whole-metagenome shotgun sequencing data from 2,019 stool samples collected from women in the Nurses' Health Study II between 2019 and 2022 to investigate associations between the gut microbiome and optimism. Optimism was measured in 2017 using the validatedself-report scale (Life Orientation Test–Revised, LOT-R).

Results: We first evaluated overall microbial diversity and community composition across optimism levels and then assessed associations of microbial species and pathways with optimism while adjusting for technical factors and relevant host covariates. We observed a weak increase in gut microbial alpha diversity with higher optimism levels. After correction for technical batch effects, overall gut microbiome composition remained significantly associated with optimism. The gut microbiome composition was also strongly influenced by host factors, including body mass index, diet, and chronic disease status. After adjustment for these host factors, 22 microbial species and 16 microbial pathways were associated with optimism at an exploratory false discovery threshold (adjusted p-values < 0.2). Several of these associations were biologically notable and supported by recent literature. For example, microbes associated with higher optimism were enriched in steroid metabolism-related functions and in pathways involved in queuosine and UMP biosynthesis.

Background

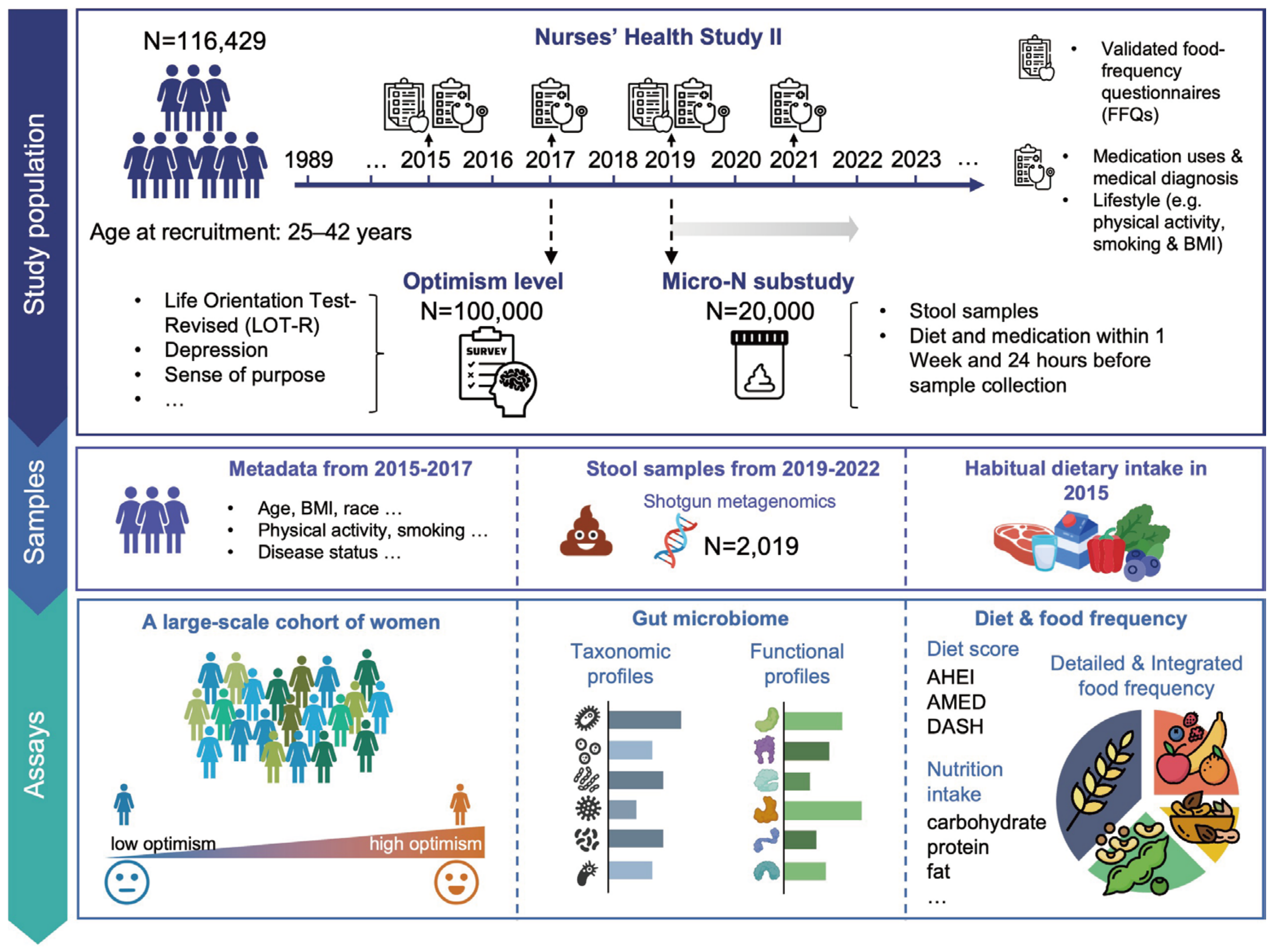


References

1. Valles-Colomer M, Falony G, Darzi Y, et al. The neuroactive potential of the human gut microbiota in quality of life and depression. Nat Microbiol. 2019;4(4):623-632. doi:10.1038/s41564-018-0337-x
2. Li L, Su Q, Xie B, et al. Gut microbes in correlation with mood: case study in a closed experimental human life support system. Neurogastroenterol Motil. 2016;28(8):1233-1240. doi:10.1111/nmo.12822
3. Ke S, Guimond AJ, Tworoger SS, et al. Gut feelings: Associations of emotions and emotion regulation with the gut microbiome in women. Psychol Med. Published online 2022:1-10.
4. Lee SH, Ku X, Oh HS, Jung Y, Chun J, Choi I. Longitudinal associations between gut microbiome diversity and emotional well-being. Health Psychol. 2024;43(5):323-327. doi:10.1037/hea0001350
5. Guimond AJ, Ke S, Tworoger SS, et al. Fulfilled Mind, Healthy Gut? Relationships of Eudaimonic Psychological Well-Being With the Gut Microbiome in Postmenopausal Women. Psychosom Med. 2024;86(5):398-409. doi:10.1097/psy.0000000000001278
6. Lee SH, Yoon SH, Jung Y, et al. Emotional well-being and gut microbiome profiles by enterotype. Sci Rep. 2020;10(1). doi:10.1038/s41598-020-77673-z

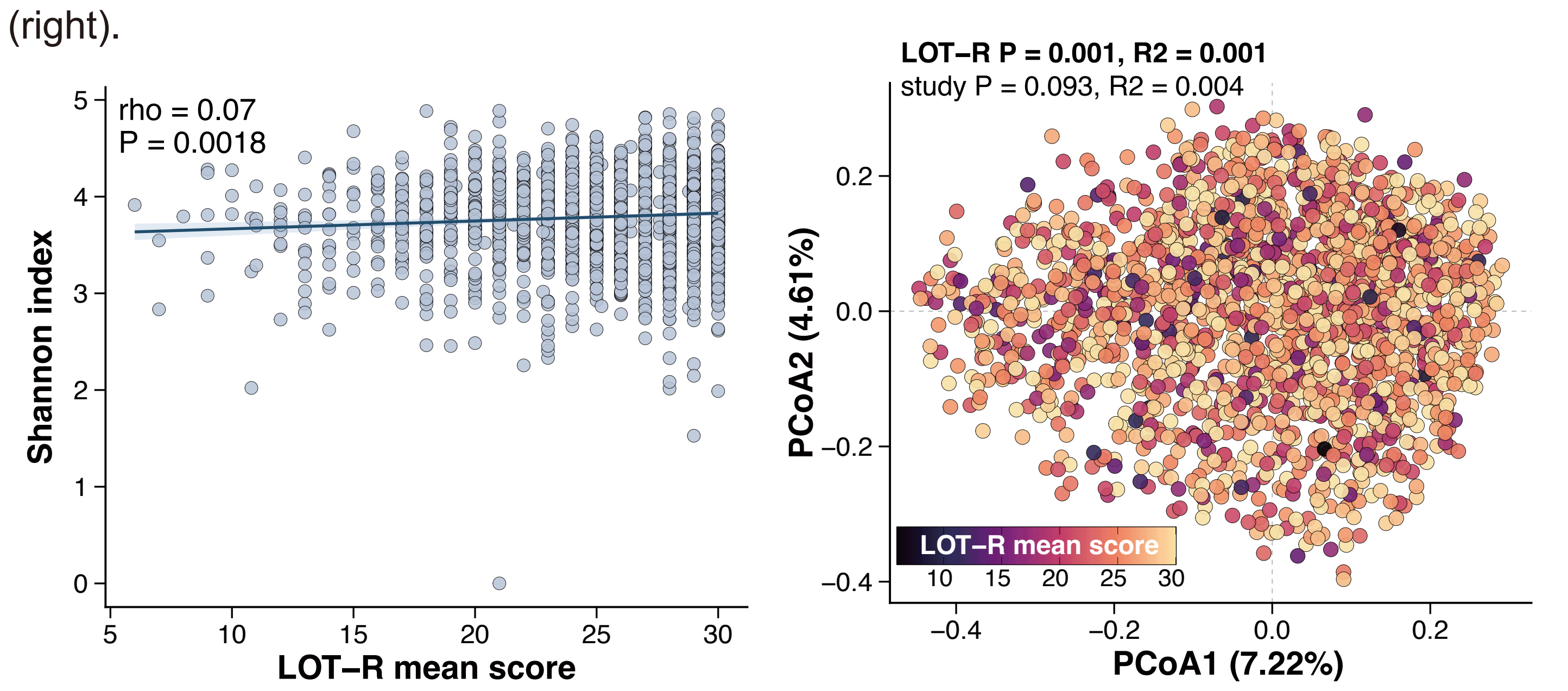
Results

Data summary



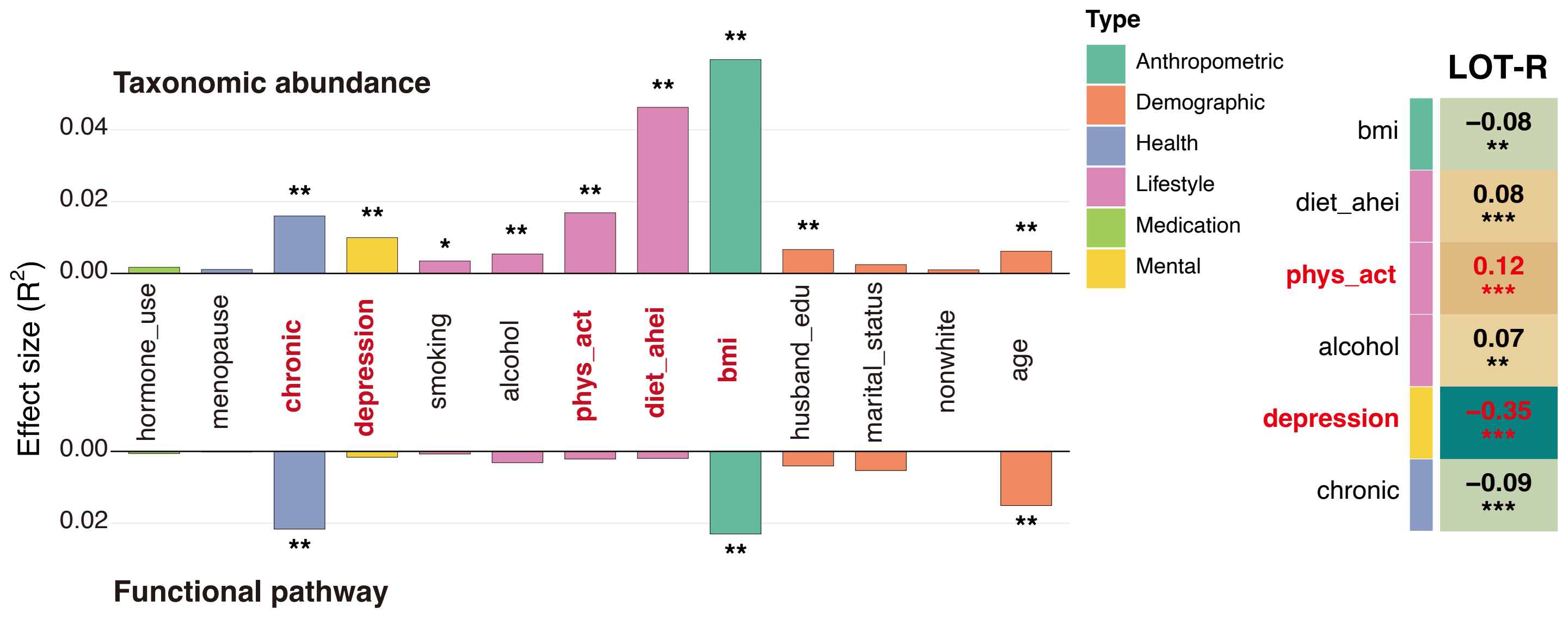
Alpha and beta diversity analyses

After batch effect correction, the gut microbial alpha diversity is weakly increased with optimism levels (left) and the overall composition (beta diversity) differs across optimism levels (right).



Host phenotypes associated with overall gut microbiome structure

Gut microbiome is strongly associated with BMI, diet habitat, chronic disease history, physical activity and depression.

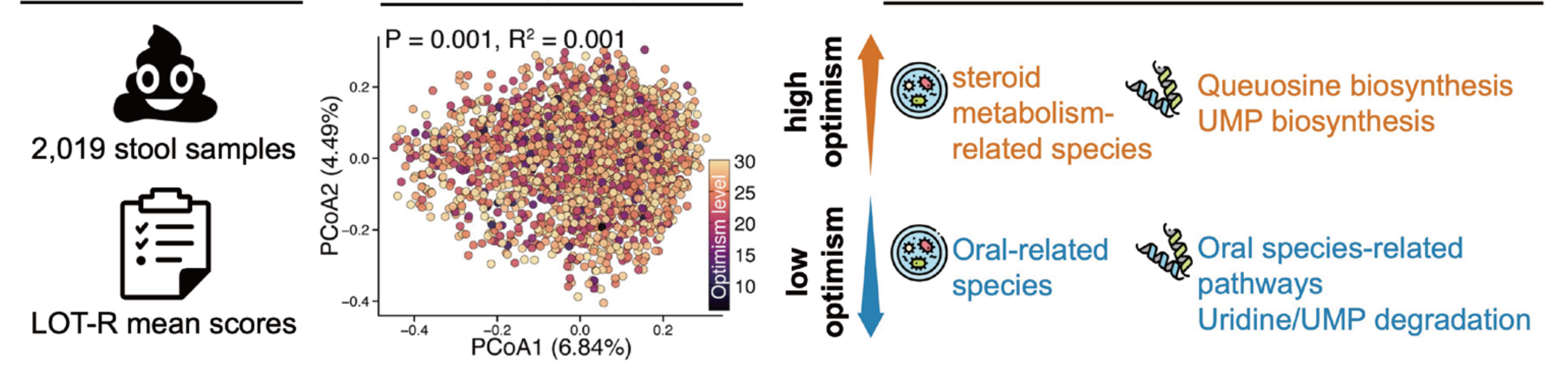


Differential abundance analysis

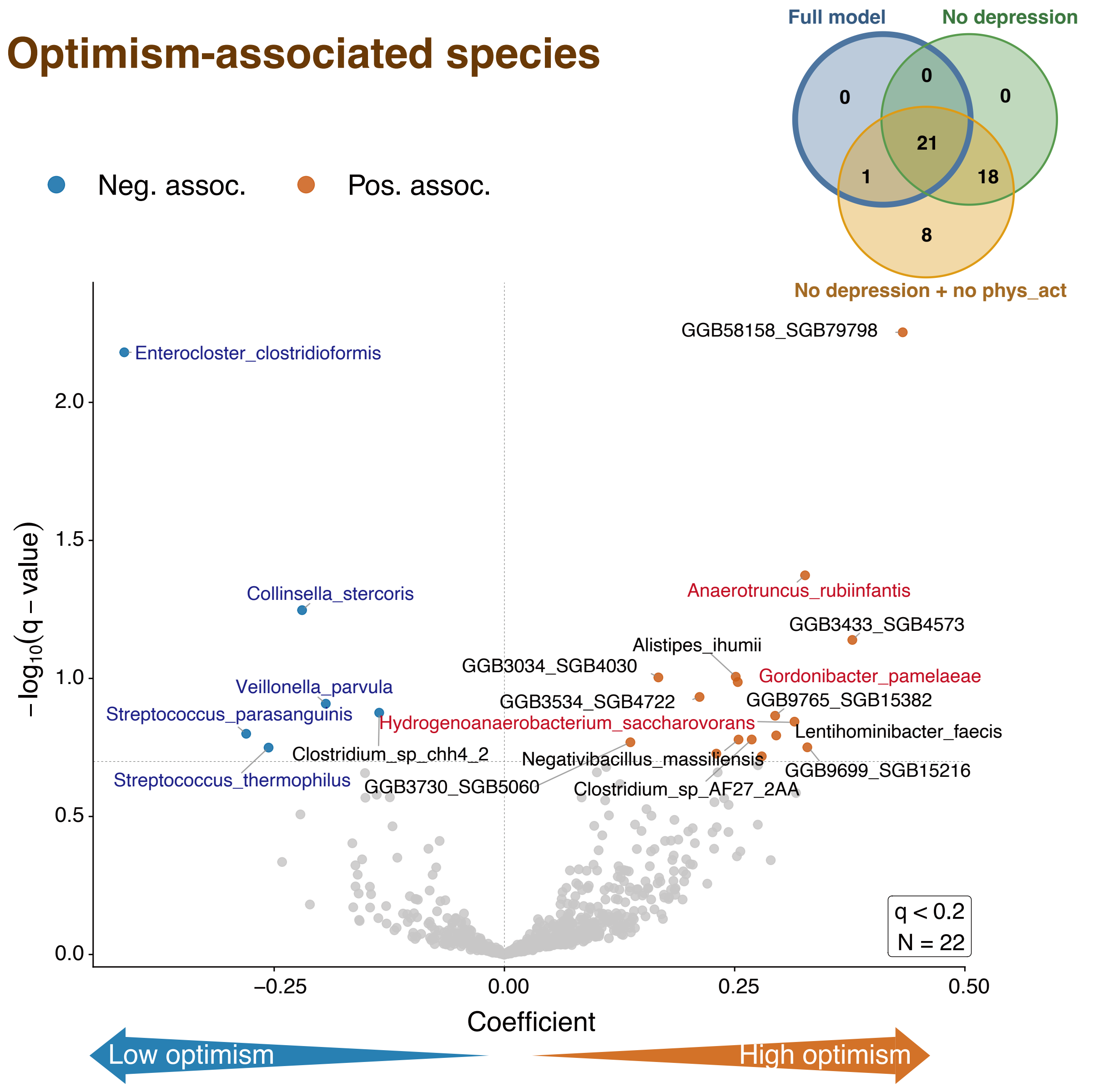
General linear model (using MaAsLin2):
optimism level ~ BMI + diet index + chronic diseases + [depression] + [physical activity] + race + age + smoking + alcohol intake + medication use + … + (1 | study)

- **Full model: all covariates**
- **No depression: excluding depression**
- **No depression + no phys_act: excluding depression & physical activity**

Conclusion

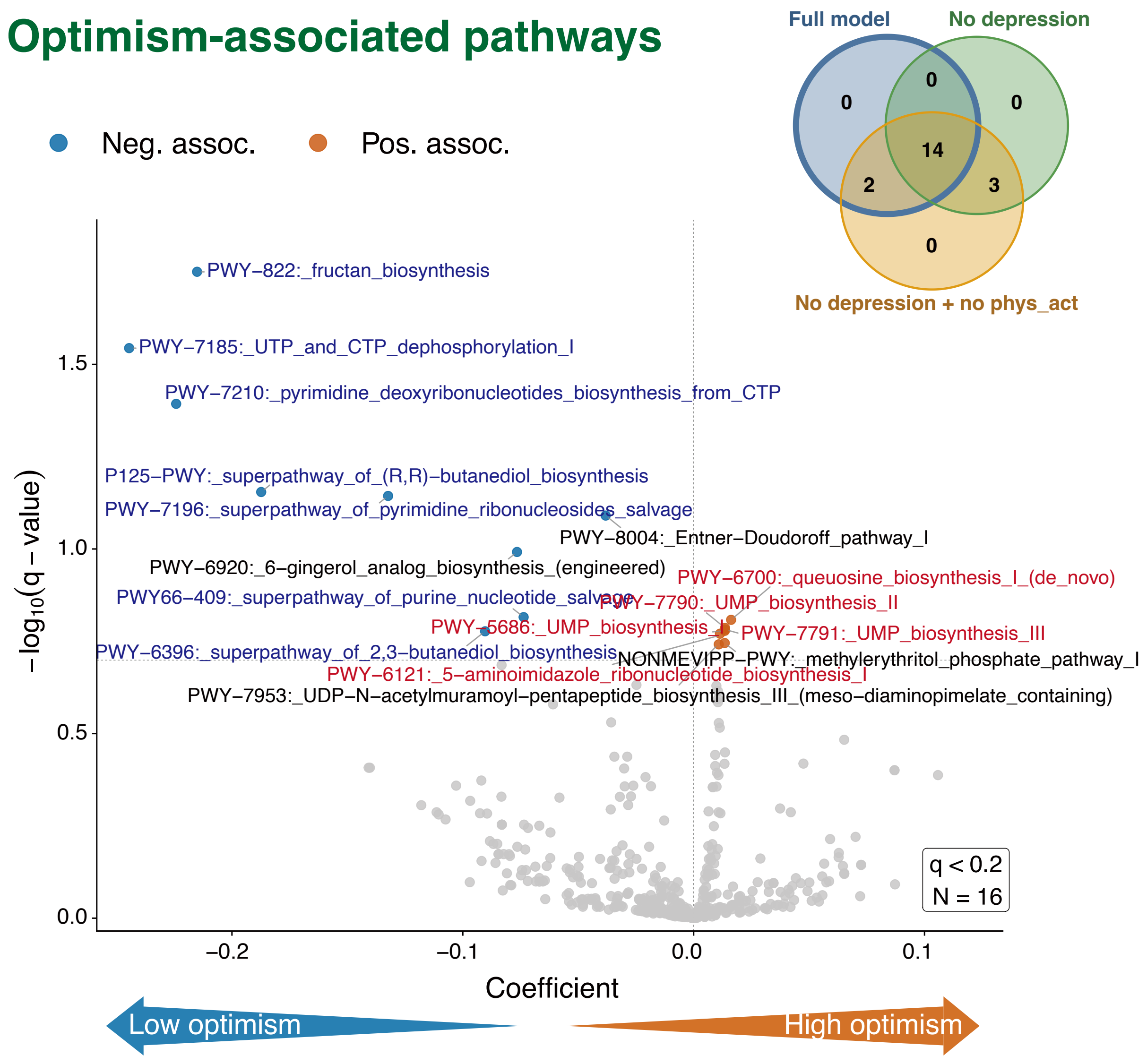


Optimism-associated species



Species	Prior evidence / reported association	Reference
Anaerotruncus rubiinfantis	Negatively associated with mild cognitive impairment (MCI)	Fan et al., *Alzheimer's Research & Therapy* (2025)
Gordonibacter pamelaeae	This species can 21-dehydroxylate host-derived biliary corticoids to produce tetrahydroprogesterones, including allopregnanolone-related metabolites, suggesting that gut microbial steroid metabolism may be relevant to pregnancy and women's health	McCurry et al., *Cell* (2024)
Hydrogenoanaerobacterium saccharovorans	Capable of producing H_2; Hydrogen gas was shown to be necessary for robust bacterial 21-dehydroxylation activity	McCurry et al., *Cell* (2024)
Enterocloster clostridioformis	Reported to be associated with the depression group	Park et al., *International Journal of Molecular Sciences* (2023)
Streptococcus parasanguinis (oral-related)	Higher abundance in women with depressive symptoms during early pregnancy and later anxiety symptoms postpartum	Hieta et al., *Brain, Behavior, & Immunity - Health* (2025)
Streptococcus thermophilus (oral-related)	Associated with the depression group	Park et al., *International Journal of Molecular Sciences* (2023)
Collinsella stercoris	The genus *Collinsella* has been associated with moderate and severe major depressive disorder, as well as depressive symptoms	Zhong et al., *Frontiers in Cellular and Infection Microbiology* (2022); Taylor et al., *Nutritional Neuroscience* (2020)
Veillonella parvula (oral-related)	Enriched in schizophrenia and linked to altered GABA- and tryptophan-related metabolite networks	Zhu et al., *Nature Communications* (2020); Wang et al., *Schizophrenia Bulletin* (2024)

Optimism-associated pathways



Pathway	Prior evidence / biological context	Reference
PWY-6700: queuosine biosynthesis I / de novo	Queuosine is a gut bacteria- and food-derived micronutrient implicated in brain health, stress regulation, and cognitive function, with potential relevance to depression mitigation	Cirzi et al., *The EMBO Journal* (2023)
PWY-5686: UMP biosynthesis I; PWY-7790: UMP biosynthesis II; PWY-7791: UMP biosynthesis III	Dietary or oral UMP supplementation, particularly together with DHA, has been linked in animal models to enhanced dopaminergic activity, neurite outgrowth, and hippocampal dendritic spine density	Wang et al., *Journal of Molecular Neuroscience* (2005)
PWY-6121: 5-aminoimidazole ribonucleotide biosynthesis I	Lower abundance of 5-aminoimidazole ribonucleotide biosynthesis, along with UMP-related pathways, has been reported in the gut microbiome of individuals with mild cognitive impairment compared with controls	Wang et al., *Brain Research* (2007)
PWY-7185: UTP and CTP dephosphorylation I; PWY-7210: pyrimidine deoxyribonucleotide biosynthesis from CTP; PWY-7196: superpathway of pyrimidine ribonucleoside salvage	Involved in pyrimidine salvage and conversion among uridine/cytidine-derived nucleotide pools, including UMP, UDP, UTP, CTP, and deoxyribonucleotides	Chaudhari et al., *GeroScience* (2023)
PWY66-409: superpathway of purine nucleotide salvage	Salvages adenine, hypoxanthine, or guanine into AMP, IMP, and GMP	—
PWY-822: fructan biosynthesis	Fructans are typically synthesized from sucrose and are often found in oral-associated species; PWY-822 was reported to be enriched in a context involving oral-typical microbes moving into the gut during long-term PPI use	Bergeron and Burne, *Infection and Immunity* (2001)
PWY-6396: superpathway of 2,3-butanediol biosynthesis; P125-PWY: superpathway of (R,R)-butanediol biosynthesis	2,3-butanediol is a bacterial fermentation metabolite that can help neutralize pH and support bacterial survival under acidic conditions; related pathways have been enriched in contexts involving oral-typical microbes in the gut during long-term PPI use	Kim et al., *Gastroenterology* (2024)