Gut Microbial Composition and Function Associated with Response to Antidepressant Medications: Evidence from a Community-based Cohort of Older Adults

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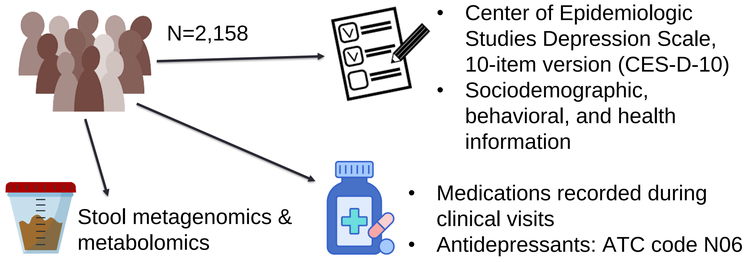
Accumulating evidence has suggested that depression and antidepressant use may alter the microbial composition. However, large population-based data on how gut microbiota can influence the efficacy of antidepressants are lacking. To address this research gap, we leveraged stool metagenomic and metabolomic data from the first batch of the ASPREE-XT Microbiome Sub-Study (n=2,158, age 81.6±3.2 years). The overall taxonomic composition moderately varied according to antidepressant use and depression status (PERMANOVA R2=0.3% P=0.001). A higher prevalence of *Faecalibacterium sp CLA AA H233* and a lower prevalence of *Alistipes SGB2313* was associated with worse response to antidepressants. In contrast, less responsiveness to antidepressants was associated with increased prevalence of biosynthesis pathways for 3-dehydroquinate and chorismite. Our metabolomics analysis also revealed interactions between antidepressant use and the metabolomics profiles. The positive correlation between antidepressants and CESD-10 score was attenuated among participants with a metabolomic profile enriched in amino acids. Additionally, lower prevalence of beneficial metabolites that interact with the gut microbiome and brain function, including cryptoxanthin, ectoine, LPC(18:1), beta-leucine, L-metanephrine, maslinic acid, and N-Acetylgalactosamine, were associated with less responsiveness to antidepressants.

ASPirin in Reducing Events in the Elderly - eXTension (ASPREE-XT)



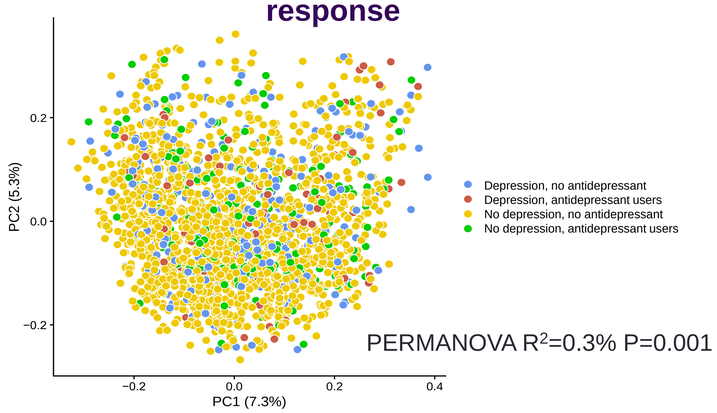
- Center of Epidemiologic Studies Depression Scale, 10-item version (CES-D-10)
- Sociodemographic, behavioral, and health information
- Medications recorded during clinical visits
- Antidepressants: ATC code N06

- An observational follow-up study after a randomized, blinded, placebo-controlled clinical trial of low-dose aspirin in healthy older adults.
- Depression: CESD-10≥8, or admission to hospital for greater than 24 hours, where depression was one of the primary reasons for admission.

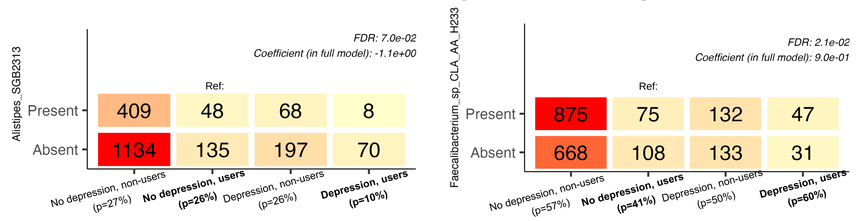
Participant characteristics

	Non-users		Antidepressant users	
	No depression	**Depression**	**No depression**	**Depression**
N	1,596	279	199	84
Age, year	82.3 (3.19)	82.5 (3.54)	81.9 (2.94)	81.3 (2.54)
Female	742 (46.5%)	165 (59.1%)	123 (61.8%)	62 (73.8%)
Education				
≤12 y	759 (47.6%)	151 (54.1%)	117 (58.8%)	44 (52.4%)
13-16 y	498 (30.6%)	69 (24.7%)	51 (25.7%)	27 (32.1%)
17-21 y	349 (21.9%)	59 (21.1%)	31 (15.6%)	13 (15.5%)
Ever smoke	678 (42.5%)	119 (42.7%)	75 (37.7%)	37 (44.0%)
Alcohol user	1418 (88.8%)	249 (89.2%)	172 (86.4%)	79 (94.0%)
BMI, kg/m²	27.4 (3.97)	27.9 (4.37)	27.8 (4.17)	28.2 (4.92)
CESD-10	2.76 (2.14)	10.7 (3.06)	3.47 (2.19)	11.7 (4.16)

Gut taxonomic profile associated with antidepressant response



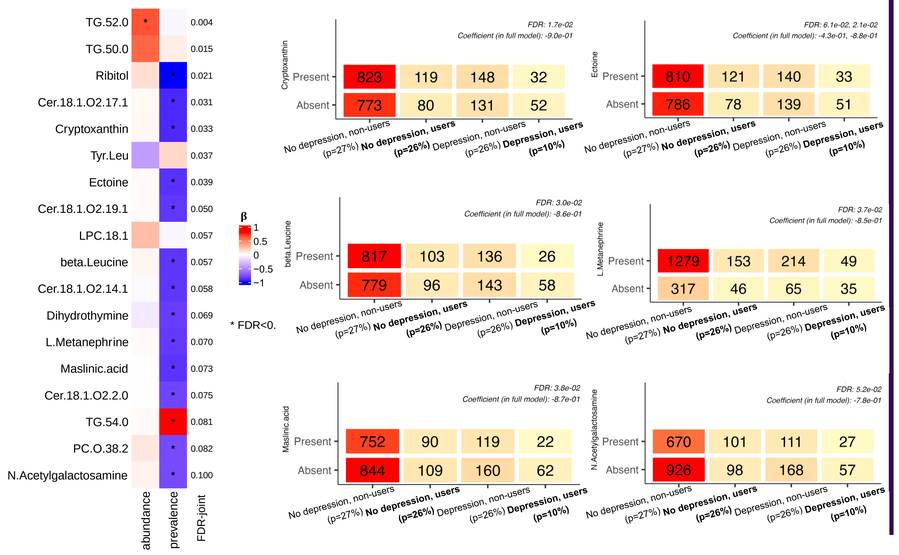
Prevalence of microbial taxa and pathways nominally associated with antidepressant response



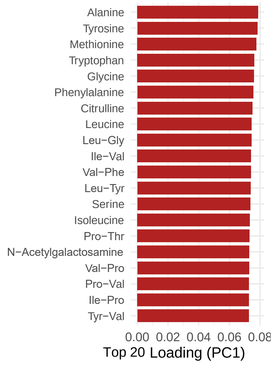
	Depression vs. no depression among antidepressant users			
Pathways	**Coef.**	**SE**	**P-value**	**FDR**
PWY.6160..3.dehydroquinate.biosynthesis.II..archaea	-0.67	0.28	0.017	0.273
PWY.6165..chorismate.biosynthesis.II..archaea	-0.67	0.28	0.017	0.273

Taxa with >1% relative abundance in >20% samples were examined (n=281).
Pathways with >0.01% relative abundance in >20% samples were examined (n=347).
Logistic regression adjusted for sex, age, education, number of concurrent drug intake, and batch using MaAsLin3.
FDR: p-value adjusted using the Benjamini-Hochberg method.

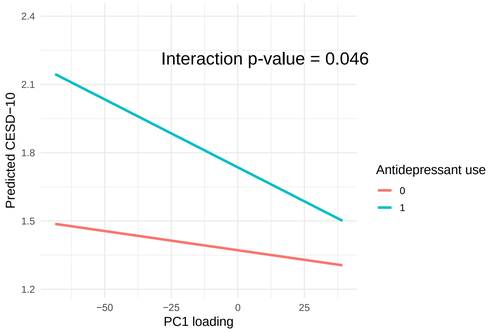
Gut metabolites associated with antidepressant response



Interactions of antidepressant use and gut metabolomic profile on depressive symptoms

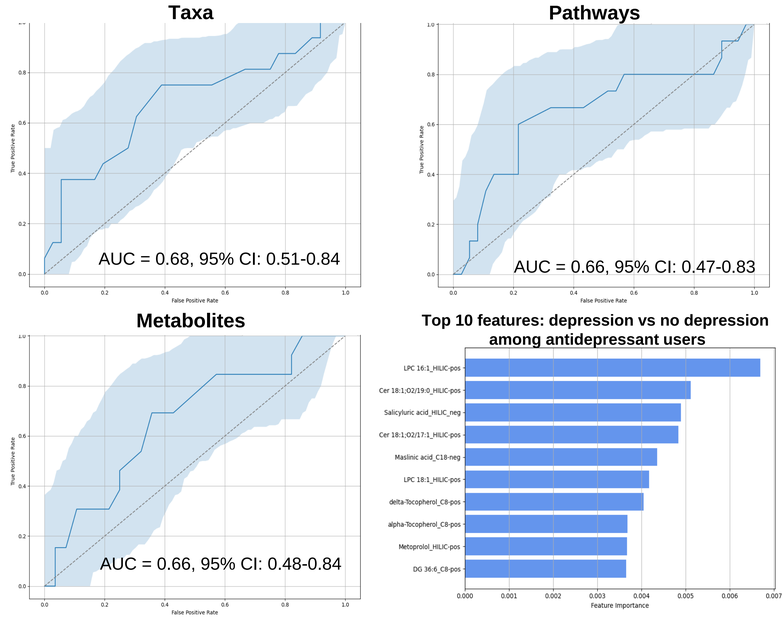


The first principal component explains 11.4% variance of the metabolomic profile.



Linear regression model predicting CESD-10 score while holding age, gender, and education constant.

Gut microbial profiles predicting antidepressant response based on Random Forest models



Conclusions & Implications

- Gut microbial features involved in inflammatory response, neurotransmitter synthesis, and brain functions may influence individual response to antidepressants.
- Our findings shed light on personalized microbiota-targeted therapies to optimize treatment efficacy.
- Future longitudinal and mechanistic studies are warranted to understand the causal mechanisms.

Acknowledgement

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