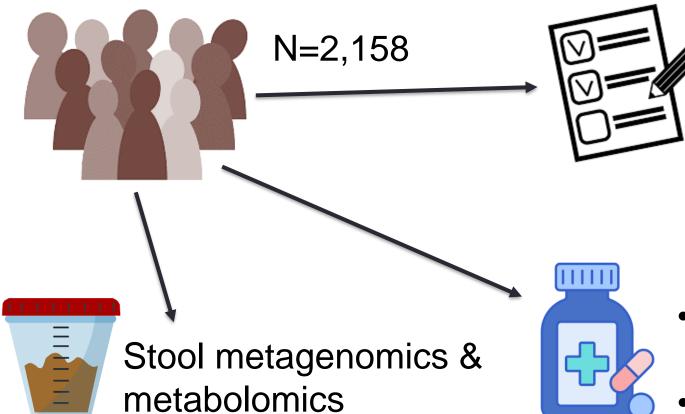


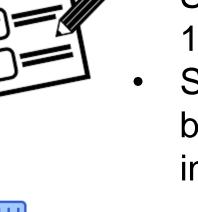
Gut Microbial Composition and Function Associated with Response to Antidepressant Medications: Evidence from a Community-based Cohort of Older Adults

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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)



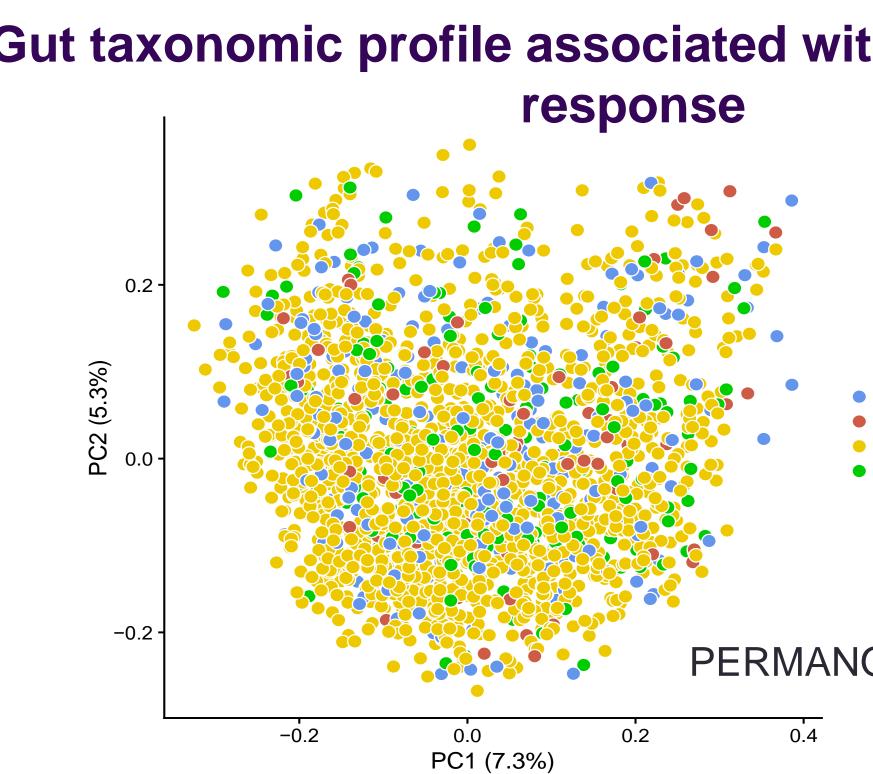


- Center of Epidemiologic Studies Depression Scale, 10-item version (CES-D-10) Sociodemographic,
- behavioral, and health information
- Medications recorded during clinical visits
- Antidepressants: ATC code N06
- An observational follow-up study after a randomized, blinded, placebocontrolled clinical 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.

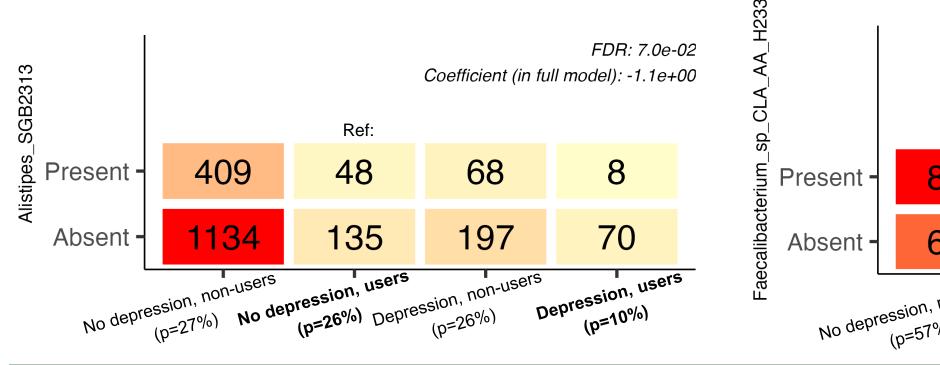
	-					
	Non	-users	Antidepressant users			
	No depression	n Depression	No depression	Depression		
Ν	1,596	279	199	84		
Age, year	82.3 (3.19)	82.5 (3.54)	81.9 (2.94)	81.3 (2.54)		
Female	742 (46.5%)	165 (59.1%)	123 (61.8%)	62 (73.8%)		
Education						
≤12 y	759 (47.6%)	151 (54.1%)	117 (58.8%)	44 (52.4%)		
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)		

Participant characteristics

Alexander Chan,¹ Etienne Nzabarushimana,^{1,2} Curtis Huttenhower,^{3,4} Yiqing Wang^{1,2}



Interactions of antidepressant use and gut metabolomic profile on depressive symptoms Interaction p-value = 0.046 Depression, no antidepressa Depression, antidepressant user: No depression, no antidepressar No depression, antidepressant user Antidepressant use N-Acetylgalactosamine PERMANOVA R²=0.3% P=0.001 0.00 0.02 0.04 0.06 0.08 PC1 loading Top 20 Loading (PC1) The first principal component explains Linear regression model predicting CESD-10 score while holding age 11.4% variance of the metabolomic profile. gender, and education constant. **Prevalence of microbial taxa and pathways nominally** Gut microbial profiles predicting antidepressant associated with antidepressant response response based on Random Forest models FDR: 7.0e-0. Pathways Taxa FDR: 2.1e-02 Coefficient (in full model): -1.1e+00 Coefficient (in full model): 9 0e-01 68 8 47 Present -197 70 135 668 Absent -**Depression vs. no depression** among antidepressant users P-value FDR SE AUC = 0.68, 95% CI: 0.51-0.84 Coef. AUC = 0.66, 95% CI: 0.47-0.83 0.28 0.273 0.017 0.67 0.017 0.273 0.67 0.28 **Metabolites** Top 10 features: depression vs no depression among antidepressant users LPC 16:1 HILIC-pos Cer 18:1;02/19:0 HILIC-pos Salicyluric acid_HILIC_neg Cer 18:1;02/17:1 HILIC-pos Maslinic acid_C18-neg FDR: 6.1e-02, 2.1e-02 pefficient (in full model): -4.3e-01, -8.8e-01 LPC 18:1_HILIC-pos delta-Tocopherol_C8-pos 140 alpha-Tocopherol_C8-pos 139 Metoprolol_HILIC-pos AUC = 0.66, 95% CI: 0.48-0.84 -26%) Depression, non-users (p=26%) Depression, DG 36:6 C8-po **Conclusions & Implications** FDR: 3.7e-0 Coefficient (in full model): -8.5e-0 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



Path

athways	C
WY.61603.dehydroquinate.biosynthesis.IIarchaea	-0
WY.6165chorismate.biosynthesis.IIarchaea	-0

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). FDR: p-value adjusted using the Benjamini-Hochberg method.

Gut taxonomic profile associated with antidepressant Logistic regression adjusted for sex, age, education, number of concurrent drug intake, and batch using MaAsLin3. Gut metabolites associated with antidepressant response

FDR: 5.2e-02

Coefficient (in full model): -7.8e-0

TG.52.0	*		0.004					Coefficient (in fin	FDR: 1.7e-02 Il model): -9.0e-0	
TG.50.0			0.015		anthin			Coemcient (in fui	n model): -9.0e-0	1
Ribitol		*	0.021		Cryptoxanthin Cryptoxanthin A bresent -	823	119	148	32	
Cer.18.1.O2.17.1		*	0.031		Absent -	773	80	131	52	
Cryptoxanthin		*	0.033		u pressi	on, non-users 27%) No depre (f	ession, users (1)=26%) Depre	ession, non-user (p=26%) Dep	ers us	- ers
Tyr.Leu			0.037		No deprov	27%) No dor (r			(p=10%)	٢
Ectoine		*	0.039							
Cer.18.1.O2.19.1		*	0.050	β				Coefficient (in	FDR: 3.0e full model): -8.6e	
LPC.18.1			0.057	1 0.5	seta: Fencine Present					
beta.Leucine		*	0.057	0 	te Present	- 817	103	136	26	
Cer.18.1.O2.14.1		*	0.058		Absent		96	143	58	
Dihydrothymine		*	0.069	* FDR<0	. No depres	ssion, non-users (p=27%) No de l	pression, use	pression, non- (p=26%)	Depression, (p=10%	usei (6)
L.Metanephrine		*	0.070		110 -	(p=21 /0) (0	(p=2011)	(p=2077	(P ² -	٢
Maslinic.acid		*	0.073							
Cer.18.1.O2.2.0		*	0.075		7			Coefficient (in t	FDR: 3.8e- full model): -8.7e-	
TG.54.0		*	0.081		Wasilinic.acid Resent •					
PC.O.38.2		*	0.082		Resent ·	752	90	119	22	
.Acetylgalactosamine		*	0.100		Absent ·		109	160	62	
	abundance	prevalence	FDR-joint		No depress (p	ion, non-users =27%) No depr	ession, user (p=26%) Dep	s ession, non-u (p=26%) D	_{Sers} epression, us (p=10%)	5ers

the causal mechanisms.

Acknowledgement

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