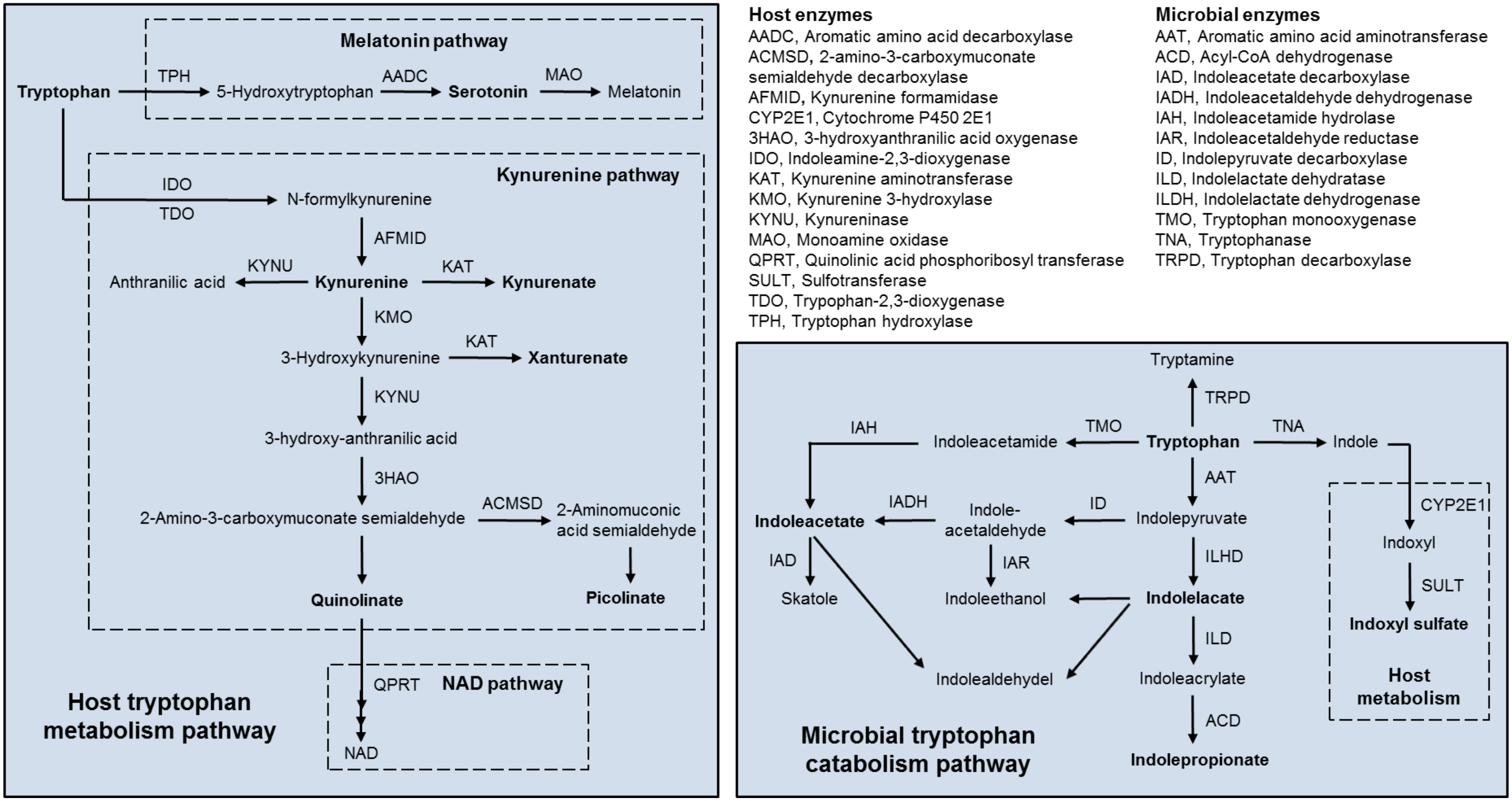
Supplemental Figures

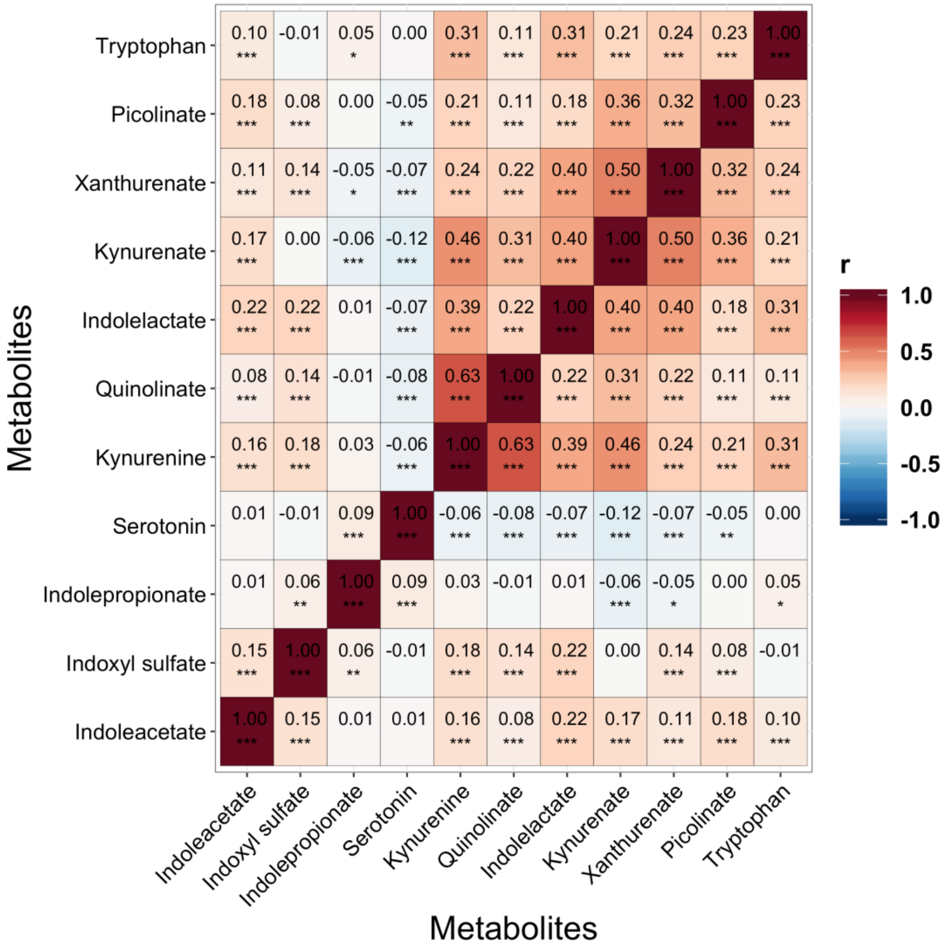
Figure S1 Host and microbial tryptophan metabolism pathways
A total of 11 tryptophan metabolites (in **Bold**) were measured in this study. This figure was adapted from Polyzos et al.[1], Badawy et al.[2], and Roager et al.[3].



Host enzymes
AADC, Aromatic amino acid decarboxylase
ACMSD, 2-amino-3-carboxymuconate semialdehyde decarboxylase
AFMID, Kynurenine formamidase
CYP2E1, Cytochrome P450 2E1
3HAO, 3-hydroxyanthranilic acid oxygenase
IDO, Indoleamine-2,3-dioxygenase
KAT, Kynurenine aminotransferase
KMO, Kynurenine 3-hydroxylase
KYNU, Kynureninase
MAO, Monoamine oxidase
QPRT, Quinolinic acid phosphoribosyl transferase
SULT, Sulfotransferase
TDO, Trypophan-2,3-dioxygenase
TPH, Tryptophan hydroxylase

Microbial enzymes
AAT, Aromatic amino acid aminotransferase
ACD, Acyl-CoA dehydrogenase
IAD, Indoleacetate decarboxylase
IADH, Indoleacetaldehyde dehydrogenase
IAH, Indoleacetamide hydrolase
IAR, Indoleacetaldehyde reductase
ID, Indolepyruvate decarboxylase
ILD, Indolelactate dehydratase
ILDH, Indolelactate dehydrogenase
TMO, Tryptophan monooxygenase
TNA, Tryptophanase
TRPD, Tryptophan decarboxylase

Figure S2 Correlation Heatmap among tryptophan metabolites
Data are partial Spearmen correlation coefficients (r) among tryptophan metabolites in 2821 SOL participants free of diabetes at baseline, adjusted for age, sex and field center. **P*<0.05; ***P*<0.01; ****P*<0.001.



	Indoleacetate	Indoxyl sulfate	Indolepropionate	Serotonin	Kynurenine	Quinolinate	Indolelactate	Kynurenate	Xanthurenate	Picolinate	Tryptophan
Tryptophan	0.10 ***	-0.01	0.05 *	0.00	0.31 ***	0.11 ***	0.31 ***	0.21 ***	0.24 ***	0.23 ***	1.00 ***
Picolinate	0.18 ***	0.08 ***	0.00	-0.05 **	0.21 ***	0.11 ***	0.18 ***	0.36 ***	0.32 ***	1.00 ***	0.23 ***
Xanthurenate	0.11 ***	0.14 ***	-0.05 *	-0.07 ***	0.24 ***	0.22 ***	0.40 ***	0.50 ***	1.00 ***	0.32 ***	0.24 ***
Kynurenate	0.17 ***	0.00	-0.06 ***	-0.12 ***	0.46 ***	0.31 ***	0.40 ***	1.00 ***	0.50 ***	0.36 ***	0.21 ***
Indolelactate	0.22 ***	0.22 ***	0.01	-0.07 ***	0.39 ***	0.22 ***	1.00 ***	0.40 ***	0.40 ***	0.18 ***	0.31 ***
Quinolinate	0.08 ***	0.14 ***	-0.01	-0.08 ***	0.63 ***	1.00 ***	0.22 ***	0.31 ***	0.22 ***	0.11 ***	0.11 ***
Kynurenine	0.16 ***	0.18 ***	0.03	-0.06 ***	1.00 ***	0.63 ***	0.39 ***	0.46 ***	0.24 ***	0.21 ***	0.31 ***
Serotonin	0.01	-0.01	0.09 ***	1.00 ***	-0.06 ***	-0.08 ***	-0.07 ***	-0.12 ***	-0.07 ***	-0.05 **	0.00
Indolepropionate	0.01	0.06 **	1.00 ***	0.09 ***	0.03	-0.01	0.01	-0.06 ***	-0.05 *	0.00	0.05 *
Indoxyl sulfate	0.15 ***	1.00 ***	0.06 **	-0.01	0.18 ***	0.14 ***	0.22 ***	0.00	0.14 ***	0.08 ***	-0.01
Indoleacetate	1.00 ***	0.15 ***	0.01	0.01	0.16 ***	0.08 ***	0.22 ***	0.17 ***	0.11 ***	0.18 ***	0.10 ***
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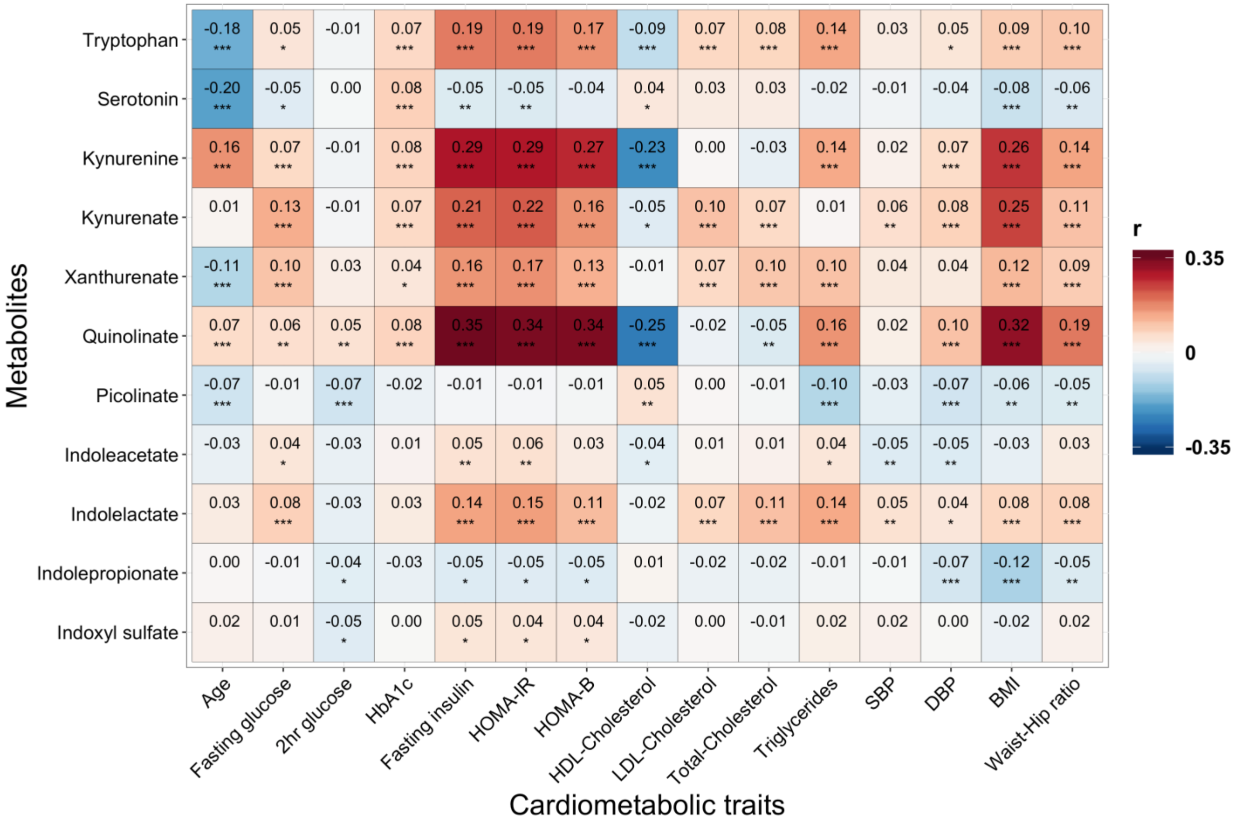
Figure S3 Correlation Heatmap between tryptophan metabolites and cardiometabolic traits

Data are partial Spearmen correlation coefficients (r) between tryptophan metabolites and cardiometabolic traits in 2821 SOL participants free of diabetes at baseline, adjusted for age, sex, field center, lipid-lowering medication use and anti-hypertensive medication use. Results were similar after excluding participants with lipid-lowering medication use or anti-hypertensive medication use (data not shown). *P<0.05; **P<0.01; ***P<0.001.

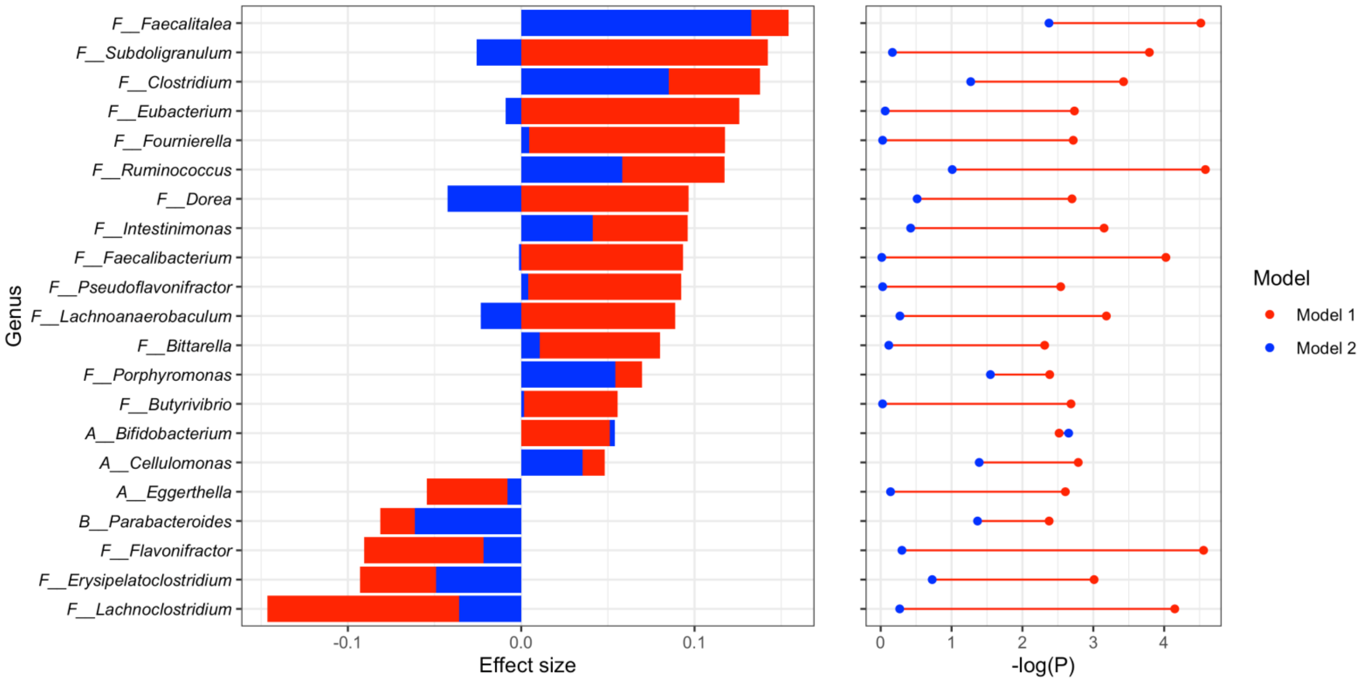


	Age	Fasting glucose	2hr glucose	HbA1c	Fasting insulin	HOMA-IR	HOMA-B	HDL-Cholesterol	LDL-Cholesterol	Total-Cholesterol	Triglycerides	SBP	DBP	BMI	Waist-Hip ratio
Tryptophan	-0.18 ***	0.05 *	-0.01	0.07 ***	0.19 ***	0.19 ***	0.17 ***	-0.09 ***	0.07 ***	0.08 ***	0.14 ***	0.03	0.05 *	0.09 ***	0.10 ***
Serotonin	-0.20 ***	-0.05 *	0.00	0.08 ***	-0.05 **	-0.05 **	-0.04	0.04 *	0.03	0.03	-0.02	-0.01	-0.04	-0.08 ***	-0.06 **
Kynurenine	0.16 ***	0.07 ***	-0.01	0.08 ***	0.29 ***	0.29 ***	0.27 ***	-0.23 ***	0.00	-0.03	0.14 ***	0.02	0.07 ***	0.26 ***	0.14 ***
Kynurenate	0.01	0.13 ***	-0.01	0.07 ***	0.21 ***	0.22 ***	0.16 ***	-0.05 *	0.10 ***	0.07 ***	0.01	0.06 **	0.08 ***	0.25 ***	0.11 ***
Xanthurenate	-0.11 ***	0.10 ***	0.03	0.04 *	0.16 ***	0.17 ***	0.13 ***	-0.01	0.07 ***	0.10 ***	0.10 ***	0.04	0.04	0.12 ***	0.09 ***
Quinolinate	0.07 ***	0.06 **	0.05 **	0.08 ***	0.35 ***	0.34 ***	0.34 ***	-0.25 ***	-0.02	-0.05 **	0.16 ***	0.02	0.10 ***	0.32 ***	0.19 ***
Picolinate	-0.07 ***	-0.01	-0.07 ***	-0.02	-0.01	-0.01	-0.01	0.05 **	0.00	-0.01	-0.10 ***	-0.03	-0.07 ***	-0.06 **	-0.05 **
Indoleacetate	-0.03	0.04 *	-0.03	0.01	0.05 **	0.06 **	0.03	-0.04 *	0.01	0.01	0.04 *	-0.05 **	-0.05 **	-0.03	0.03
Indolelactate	0.03	0.08 ***	-0.03	0.03	0.14 ***	0.15 ***	0.11 ***	-0.02	0.07 ***	0.11 ***	0.14 ***	0.05 **	0.04 *	0.08 ***	0.08 ***
Indolepropionate	0.00	-0.01	-0.04 *	-0.03	-0.05 *	-0.05 *	-0.05 *	0.01	-0.02	-0.02	-0.01	-0.01	-0.07 ***	-0.12 ***	-0.05 **
Indoxyl sulfate	0.02	0.01	-0.05 *	0.00	0.05 *	0.04 *	0.04 *	-0.02	0.00	-0.01	0.02	0.02	0.00	-0.02	0.02

Figure S4 Associations of 22 gut bacterial genera and serum indolepropionate before and after mutual adjustment.

Model 1: adjusting for age, sex, study center, smoking, education, family income, physical activity, AHEI-2010, use of antibiotics, and use of probiotics;

Model 2 (mutual adjustment): further adjusting for other 21bacterial genera based on Model 1 (all 22 bacterial genera were included in the model simultaneously).



References

1. Polyzos KA, Ketelhuth DF. The role of the kynurenine pathway of tryptophan metabolism in cardiovascular disease. An emerging field. Hamostaseologie 2015;35:128-36.
2. Badawy AA. Kynurenine Pathway of Tryptophan Metabolism: Regulatory and Functional Aspects. Int J Tryptophan Res 2017;10:1178646917691938.
3. Roager HM, Licht TR. Microbial tryptophan catabolites in health and disease. Nat Commun 2018;9:3294.