Supplemental Tables

Table S1 Basic information of studies participating in the Stage I analyses

Study (registry)	Study design	Race /ethnicity	Metabolites and incident diabetes analysis		GWAS of metabolites		Diet and metabolite analysis		Gut microbiota and metabolite analysis	
			N (cases/all)	Key data	N	Key data	N	Key data	N	Key data
HCHS/SOL (NCT02060344)	Prospective cohort	HA	367/2,821	11 fasting serum tryptophan metabolites at baseline; Incident T2D during ~6-year follow-up.	3,933	Genome-wide variants; 11 fasting serum tryptophan metabolites at baseline.	3,938	Dietary intakes of 10 major food groups and fiber at baseline; 11 fasting serum tryptophan metabolites at baseline.	759	4 fasting serum indole metabolites at baseline (2008-2011); 91 fecal bacterial genera at Visit 2 (2014-2017).
ARIC (NCT00005131)	Prospective cohort	EA	443/1,288	7 fasting serum tryptophan metabolites at baseline; Incident T2D during ~25-year follow-up.	1,509	Genome-wide variants; 7 fasting serum tryptophan metabolites at baseline.	NA	NA	NA	NA
		AA	593/1,443		1,772					
FHS (NCT00005136)	Prospective cohort	EA	218/1,424	8 fasting plasma tryptophan metabolites at baseline; Incident T2D during ~20-year follow-up.	2,076	Genome-wide variants; 8 fasting plasma tryptophan metabolites at baseline.	NA	NA	NA	NA
WHI (NCT00000611)	Prospective cohort	EA (78%), AA (12%), HA (3%), others (6%)	163/1,392	7 fasting plasma tryptophan metabolites at baseline; Incident T2D during ~17-year follow-up.	NA	NA	NA	NA	NA	NA
PREDIMED (ISRCTN35739639)	Prospective Case-cohort based on an intervention study	Spanish	248/885	5 fasting plasma tryptophan metabolites at baseline; Incident T2D during a median of 3.8 years of follow-up.	NA	NA	NA	NA	NA	NA

Abbreviations: HA, Hispanic Americans; EA, European American; AA, African American; HCHS/SOL, the Hispanic Community Health Study/Study of Latinos; ARIC, the Atherosclerosis Risk in Communities study; FHS, the Framingham Study; WHI, the Women's Health Initiative; PREDIMED, Prevención con Dieta Mediterránea.

Table S2 Regression models and covariates used in the analyses on the association between metabolites and incident type 2 diabetes

Cohort	Regression models	Covariates in Model 1	Covariates in Model 2	Covariates in Model 3	Covariates in Model 4	Covariates in Model 5
HCHS/SOL	Cox regressions	Age, sex, smoking, alcohol consumption, education, family income, fasting status, lipid-lowering medication use, anti-hypertensive medications, family history of diabetes, and study sampling weights.	Model 1 + BMI and WHR.	Model 1 + physical activity and AHEI-2010.	Model 1 + HDL-C, LDL-C and triglycerides.	Model 1 + SBP + DBP.
ARIC	Cox regressions	Age, sex, race/ethnicity, smoking, alcohol consumption, education, anti-hypertensive medications, family history of diabetes, and self-reported physician-diagnosed hypertension.	Model 1 + BMI and WHR.	Model 1 + physical activity and AHEI-2010.	Model 1 + HDL-C, LDL-C and triglycerides.	Model 1 + SBP + DBP.
WHI	Cox regressions	Age, smoking, alcohol consumption, education, family income, fasting status, lipid-lowering medication use, anti-hypertensive medications, family history of diabetes, self-reported physician-diagnosed hypertension, self-reported physician-diagnosed dyslipidemia, study arm, coronary heart disease case-control status, race.	Model 1 + BMI and WHR.	Model 1 + physical activity and HEI-2005.	Model 1 + HDL-C and total cholesterol.	Model 1 + SBP + DBP.
FHS	Cox regressions	Age, sex, smoking, alcohol consumption, education, lipid-lowering medication use, anti-hypertensive medications, family history of diabetes, self-reported physician-diagnosed hypertension, and self-reported physician-diagnosed dyslipidemia.	Model 1 + BMI and WHR.	Model 1 + physical activity and AHEI-2010.	Model 1 + HDL-C, LDL-C and triglycerides.	Model 1 + SBP + DBP.
PREDIMED	Weighted Cox regressions for case-cohort designs	Age, smoking, sex, lipid-lowering medication use, anti-hypertensive medications, self-reported physician-diagnosed hypertension, self-reported physician-diagnosed dyslipidemia, intervention arms, study center, and propensity scores.	Model 1 + BMI and waist circumference.	Not available.	Model 1 + HDL-C, LDL-C and triglycerides.	Model 1 + SBP + DBP.

Abbreviations: HCHS/SOL, the Hispanic Community Health Study/Study of Latinos; ARIC, the Atherosclerosis Risk in Communities study; FHS, the Framingham Study; WHI, the Women's Health Initiative; PREDIMED, Prevención con Dieta Mediterránea; BMI, body mass index; WHR, waist-hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; AHEI-2010, alternate healthy eating index 2010; HEI-2005, healthy eating index 2005; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Table S3 Basic information of studies participating in the Stage II analyses

Study	Study design	Race /ethnicity	Latent causal variable analysis		Fiber, gut microbiota and metabolite analysis		Milk-*LCT* interaction analysis on IPA		Milk-*LCT* interaction analysis on *Bifidobacterium*	
			N	**Key data**	**N**	**Key data**	**N**	**Key data**	**N**	**Key data**
HCHS/SOL	Prospective cohort	HA	NA	NA	2,759	Fiber intake at baseline (2008-2011); 21 IPA-associated fecal bacterial genera at Visit 2 (2014-2017).	3,899	*LCT* variant (SNP-rs4988235); Milk intake at baseline; Fasting serum IPA at baseline.	2,342	*LCT* variant (SNP-rs4988235); Milk intake at baseline; Fecal *Bifidobacterium* at Visit 2.
					752	Fiber intake at baseline; Fasting serum IPA at baseline; 21 IPA-associated fecal bacterial genera at Visit 2.				
ARIC	Prospective cohort	EA	NA	NA	NA	NA	1,504	Milk intake at baseline; *LCT* variant (SNP-rs4988235); Fasting serum IPA at baseline.	NA	NA
		AA					1,674			
HCHS/SOL ARIC FHS	Genome-wide meta-analysis	HA	3,933	GWAS summery statistics for 11 fasting circulating tryptophan metabolites	NA	NA	NA	NA	NA	NA
		EA	1,509							
		AA	1,772							
		EA	2,076							
DIAGRAM	Genome-wide meta-analysis	White	55,005 T2D cases/ 400,308 controls	Publicly available GWAS summery statistics for T2D	NA	NA	NA	NA	NA	NA

Abbreviations: HA, Hispanic Americans; EA, European American; AA, African American; IPA, indolepropionate; HCHS/SOL, the Hispanic Community Health Study/Study of Latinos; ARIC, the Atherosclerosis Risk in Communities study; FHS, the Framingham Study; DIAGRAM, Diabetes Genetics Replication and Meta-analysis Consortium.

Table S4 Characteristics of study participants free of diabetes at baseline

	HCHS/SOL	**ARIC**	**FHS**	**PREMED**	**WHI**
N	2821	2721	1,424	885	1,392
Age, years	45 (33-53)	52 (48- 58)	55 (9.5)	66 (62-71)	67.1 (6.9)
Women	1610 (57.1%)	1624 (59.7%)	741 (52.0%)	540 (61%)	1,392 (100%)
Race/ethnicity					
Hispanics/Latinos	2821 (100%)	NA	NA	NA	45 (3.2%)
Non-Hispanic whites	NA	1288 (47.3%)	1,424 (100%)	885 (100%)	1,088 (78.2%)
African American/Others	NA	1433 (52.7%)	NA	NA	259 (18.6%)
Education, less than high school	906 (32.2%)	286 (10.5%)	82 (5.8%)	NA	105 (7.5%)
Current smoking	606 (21.5%)	724 (26.6%)	248 (17.4%)	165 (18.6%)	146 (10.5%)
AHEI-2010 or HEI-2005	47.5 (42.5-53.1)	48.9 (41.2- 57.2)	42.2 (10.0)	NA	67.2 (11.2)*
Family history of diabetes	1132 (40.2%)	757 (27.8%)	247 (17.3%)	242 (27.3%)	437 (31.4%)
Self-reported dyslipidemia	NA	NA	NA	745 (84.2%)	237 (17.0%)
Self-reported hypertension	NA	1076 (39.5%)	NA	811 (91.6%)	733 (52.7%)
Lipid-lowering medication use	144 (5.2%)	NA	90 (6.3%)	32 (3.6%)	160 (11.5%)
Anti-hypertensive medication use	252 (9.1%)	765 (28.1%)	305 (21.4%)	427 (48.2%)	339 (24.4%)
BMI, kg/m^2	28.4 (25.1-32.0)	27.2 (24.5- 30.7)	27.3 (4.6)	29.7 (27.6-32.2)	27.92 (5.9)
Waist-to-Hip Ratio	0.9 (0.9-1.0)	0.9 (0.9- 1.0)	0.9 (0.1)	NA	0.8 (0.1)
HDL cholesterol, mg/dL	48.0 (41.0-57.0)	51.0 (41.4- 63.9)	48.0 (39.0-59.0)	51.0 (45.0-59.0)	51.0 (42.0-61.7)
LDL cholesterol, mg/dL	121.0 (98.0-144.0)	133.7 (108.8- 160.2)	126.2 (105.4-148.9)	137.0 (114.0-161.0)	NA
Triglycerides, mg/dL	108.0 (75.0-156.0)	100.0 (73.0- 142.0)	116.0 (83.0-169.5)	115.0 (91.0-156.0)	NA
Systolic blood pressure, mmHg	118.0 (109.0-129.0)	120.0 (109.0- 133.0)	124.0 (112.3-136.0)	147.5 (136.8-161.0)	130.5 (120.0-143.0)
Diastolic blood pressure, mmHg	72.0 (66.0-79.0)	75.0 (68.0- 83.0)	74.0 (68.0-81.0)	84.2 (78.0-90.5)	75.0 (69.0-82.0)

Data were presented as mean (standard deviation), median (25th-75th), or n (%).

* WHI used HEI-2005.

Abbreviations: HCHS/SOL, the Hispanic Community Health Study/Study of Latinos; ARIC, the Atherosclerosis Risk in Communities study; FHS, the Framingham Study; WHI, the Women's Health Initiative; PREDIMED, Prevención con Dieta Mediterránea; AHEI-2010, Alternate Healthy Eating Index 2010; HEI-2005, Healthy Eating Index 2005; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table S5 Associations between the 11 tryptophan metabolites and risk of type 2 diabetes in HCHS/SOL, replication studies and all combined

	Cases/participants	Model 1			Model 2			Model 3			Model 4			Model 5		
		HR (95% CI)	***P***	***P-het***	**HR (95% CI)**	***P***	***P-het***	**HR (95% CI)**	***P***	***P-het***	**HR (95% CI)**	***P***	***P-het***	**HR (95% CI)**	***P***	***P-het***
Tryptophan																
HCHS/ SOL	367/2821	1.11 (0.97-1.26)	0.14		1.05 (0.92-1.20)	0.49		1.10 (0.97-1.26)	0.14		1.15 (1.02-1.28)	0.018		1.09 (0.96-1.25)	0.18	
FHS	218/1424	1.23 (1.08-1.39)	0.002		1.19 (1.05-1.35)	0.008		1.24 (1.09-1.41)	0.001		1.19 (1.05-1.36)	0.009		1.23 (1.08-1.40)	0.002	
PREDIMED	248/885	1.06 (0.87-1.29)	0.57		1.07 (0.88-1.30)	0.5		NA	NA		1.03 (0.84-1.26)	0.77		1.06 (0.87-1.28)	0.58	
WHI	163/1329	1.08 (0.91-1.27)	0.38		1.11 (0.94-1.31)	0.23		1.10 (0.93-1.29)	0.26		1.04 (0.88-1.23)	0.63		1.08 (0.91-1.27)	0.38	
ARIC	1036/2721	1.12 (1.05-1.20)	0.001		1.09 (1.02-1.17)	0.013		1.12 (1.05-1.20)	<0.001		1.08 (1.01-1.16)	0.03		1.12 (1.05-1.20)	<0.001	
Replication combined	1665/6359	1.13 (1.07-1.19)	<0.001	0.49	1.11 (1.05-1.17)	<0.001	0.67	1.14 (1.08-1.21)	<0.001	0.33	1.09 (1.03-1.15)	0.002	0.49	1.13 (1.07-1.19)	<0.001	0.46
All combined	2032/9180	1.12 (1.07-1.18)	<0.001	0.64	1.10 (1.05-1.16)	<0.001	0.71	1.13 (1.08-1.19)	<0.001	0.5	1.10 (1.05-1.16)	<0.001	0.55	1.12 (1.07-1.18)	<0.001	0.6
Serotonin																
HCHS/ SOL	367/2821	1.07 (0.94-1.21)	0.32		1.11 (0.97-1.26)	0.13		1.07 (0.94-1.21)	0.33		1.03 (0.92-1.16)	0.63		1.07 (0.94-1.21)	0.31	
FHS	218/1424	0.98 (0.87-1.10)	0.71		0.97 (0.86-1.11)	0.67		0.98 (0.87-1.11)	0.74		0.98 (0.87-1.11)	0.78		0.98 (0.87-1.11)	0.77	
WHI	163/1329	0.84 (0.72-0.98)	0.028		0.89 (0.76-1.04)	0.14		0.84 (0.72-0.98)	0.023		0.87 (0.74-1.02)	0.078		0.84 (0.72-0.98)	0.03	
ARIC	1036/2721	0.96 (0.90-1.02)	0.18		1.00 (0.93-1.06)	0.93		0.95 (0.90-1.02)	0.15		0.94 (0.85-1.01)	0.11		0.96 (0.90-1.02)	0.23	
Replication combined	1417/5474	0.95 (0.90-1.00)	0.043	0.26	0.98 (0.92-1.03)	0.45	0.41	0.94 (0.90-1.00)	0.033	0.24	0.94 (0.89-1.00)	0.039	0.47	0.95 (0.90-1.00)	0.063	0.25
All combined	1784/8295	0.96 (0.92-1.01)	0.13	0.14	1.00 (0.95-1.05)	0.92	0.2	0.96 (0.91-1.01)	0.11	0.12	0.96 (0.91-1.01)	0.095	0.36	0.97 (0.92-1.02)	0.18	0.14
Kynurenine																
HCHS/ SOL	367/2821	1.20 (1.06-1.36)	0.004		1.05 (0.92-1.20)	0.45		1.19 (1.05-1.35)	0.006		1.14 (1.01-1.29)	0.036		1.17 (1.03-1.33)	0.013	
FHS	218/1424	1.27 (1.10-1.45)	0.001		1.04 (0.91-1.20)	0.54		1.26 (1.09-1.45)	0.002		1.13 (0.98-1.31)	0.096		1.23 (1.06-1.42)	0.006	
PREDIMED	248/885	1.00 (0.84-1.18)	0.96		0.95 (0.79-1.13)	0.54		NA	NA		0.96 (0.80-1.14)	0.62		0.96 (0.81-1.14)	0.66	
WHI	163/1329	1.35 (1.13-1.39)	0.001		1.24 (1.03-1.49)	0.022		1.34 (1.12-1.60)	0.001		1.18 (0.98-1.41)	0.079		1.36 (1.14-1.62)	0.001	
ARIC	1036/2721	1.16 (1.09-1.24)	<0.001		1.07 (1.00-1.15)	0.056		1.17 (1.09-1.25)	<0.001		1.08 (1.01-1.16)	0.023		1.15 (1.07-1.23)	<0.001	
Replication combined	1665/6359	1.18 (1.11-1.24)	<0.001	0.06	1.07 (1.01-1.13)	0.022	0.22	1.20 (1.13-1.27)	<0.001	0.27	1.09 (1.03-1.15)	0.004	0.37	1.16 (1.10-1.22)	<0.001	0.04
All combined	2032/9180	1.18 (1.12-1.24)	<0.001	0.12	1.06 (1.01-1.12)	0.016	0.35	1.20 (1.14-1.26)	<0.001	0.46	1.09 (1.04-1.15)	0.001	0.46	1.16 (1.10-1.22)	<0.001	0.09
Kynurenate																
HCHS/ SOL	367/2821	1.22 (1.08-1.38)	0.002		1.10 (0.97-1.25)	0.15		1.21 (1.07-1.37)	0.002		1.11 (0.99-1.25)	0.062		1.19 (1.05-1.35)	0.006	
FHS	218/1424	1.11 (0.96-1.27)	0.15		0.99 (0.85-1.14)	0.84		1.11 (0.97-1.28)	0.13		1.07 (0.93-1.24)	0.34		1.07 (0.93-1.23)	0.35	

WHI	163/1329	1.31 (1.11-1.54)	0.002		1.22 (1.03-1.45)	0.019		1.29 (1.10-1.53)	0.002		1.23 (1.04-1.45)	0.018		1.30 (1.11-1.54)	0.002	
Replication combined	381/2753	1.18 (1.06-1.32)	0.002	0.13	1.08 (0.97-1.21)	0.17	0.06	1.19 (1.06-1.32)	0.002	0.18	1.14 (1.02-1.27)	0.023	0.25	1.16 (1.05-1.30)	0.006	0.08
All combined	748/5574	1.20 (1.11-1.30)	<0.001	0.31	1.09 (1.00-1.18)	0.046	0.16	1.20 (1.10-1.30)	<0.001	0.39	1.13 (1.04-1.22)	0.003	0.5	1.18(1.08-1.28)	<0.001	0.2
Xanthurenate																
HCHS/ SOL	367/2821	1.18 (1.05-1.33)	0.007		1.14 (1.00-1.28)	0.042		1.19 (1.05-1.34)	0.006		1.11 (0.99-1.23)	0.062		1.18 (1.04-1.33)	0.008	
FHS	218/1424	1.51 (1.30-1.77)	<0.001		1.38 (1.17-1.62)	<0.001		1.53 (1.31-1.78)	<0.001		1.49 (1.26-1.75)	<0.001		1.45 (1.24-1.69)	<0.001	
WHI	163/1329	1.12 (0.95-1.32)	0.19		1.06 (0.90-1.25)	0.5		1.10 (0.94-1.30)	0.24		1.06 (0.90-1.25)	0.5		1.12 (0.95-1.32)	0.19	
Replication combined	381/2753	1.31 (1.17-1.47)	<0.001	0.01	1.21 (1.08-1.36)	0.001	0.02	1.31 (1.17-1.47)	<0.001	0.01	1.26 (1.12-1.42)	<0.001	0.004	1.28 (1.15-1.44)	<0.001	0.02
All combined	748/5574	1.25 (1.15-1.36)	<0.001	0.01	1.18 (1.08-1.28)	<0.001	0.06	1.25 (1.15-1.36)	<0.001	0.01	1.17 (1.09-1.27)	<0.001	0.01	1.23 (1.14-1.34)	<0.001	0.05
Quinolinate																
HCHS/ SOL	367/2821	1.12 (0.99-1.26)	0.082		0.96 (0.84-1.10)	0.51		1.11 (0.98-1.25)	0.11		1.11 (0.99-1.25)	0.076		1.08 (0.96-1.22)	0.22	
FHS	218/1424	1.28 (1.12-1.46)	<0.001		1.07 (0.93-1.22)	0.36		1.26 (1.10-1.44)	0.001		1.14 (1.00-1.31)	0.051		1.27 (1.11-1.45)	<0.001	
PREDIMED	248/885	0.96 (0.81-1.13)	0.61		0.90 (0.75-1.06)	0.2		NA	NA		0.89 (0.75-1.06)	0.19		0.96 (0.81-1.13)	0.62	
Replication combined	466/2309	1.14 (1.03-1.27)	0.01	0.01	1.00 (0.90-1.11)	0.95	0.11	NA	NA	NA	1.04 (0.94-1.16)	0.47	0.03	1.14 (1.03-1.27)	0.012	0.01
All combined	833/5130	1.13 (1.05-1.23)	0.002	0.03	0.98 (0.90-1.07)	0.67	0.27	1.17 (1.07-1.29)	<0.001	0.15	1.07 (0.99-1.16)	0.084	0.06	1.12 (1.03-1.21)	0.006	0.03
Picolinate																
HCHS/ SOL	367/2821	1.02 (0.90-1.16)	0.75		1.03 (0.90-1.17)	0.68		1.03 (0.90-1.16)	0.69		1.06 (0.95-1.19)	0.31		1.04 (0.92-1.18)	0.54	
Indoleacetate																
HCHS/ SOL	367/2821	0.91 (0.81-1.03)	0.12		0.88 (0.78-0.99)	0.041		0.90 (0.80-1.02)	0.095		0.90 (0.81-1.01)	0.073		0.91 (0.81-1.03)	0.13	
ARIC	1036/2721	1.02 (0.96-1.09)	0.52		1.02 (0.96-1.09)	0.53		1.03 (0.97-1.10)	0.34		1.00 (0.94-1.06)	0.92		1.03 (0.96-1.09)	0.43	
Replication combined	1036/2721	1.02 (0.96-1.09)	0.52	NA	1.02 (0.96-1.09)	0.53	NA	1.03 (0.97-1.10)	0.34	NA	1.00 (0.94-1.06)	0.92	NA	1.03 (0.96-1.09)	0.43	NA
All combined	1403/5542	1.00 (0.94-1.06)	0.88	0.1	0.99 (0.94-1.05)	0.71	0.04	1.00 (0.95-1.06)	0.95	0.06	0.97 (0.92-1.03)	0.32	0.13	1.00 (0.95-1.06)	0.99	0.09
Indolelactate																
HCHS/ SOL	367/2821	1.30 (1.13-1.48)	<0.001		1.23 (1.08-1.41)	0.002		1.30 (1.14-1.48)	<0.001		1.18 (1.06-1.32)	0.003		1.29 (1.13-1.48)	<0.001	
ARIC	1036/2721	1.13 (1.05-1.21)	0.001		1.09 (1.01-1.17)	0.022		1.13 (1.06-1.22)	0.001		1.09 (1.02-1.18)	0.016		1.12 (1.04-1.20)	0.002	
Replication combined	1036/2721	1.13 (1.05-1.21)	0.001	NA	1.09 (1.01-1.17)	0.022	NA	1.13 (1.06-1.22)	0.001	NA	1.09 (1.02-1.18)	0.016	NA	1.12 (1.04-1.20)	0.002	NA
All combined	1403/5542	1.16 (1.09-1.24)	<0.001	0.07	1.12 (1.05-1.19)	0.001	0.11	1.17 (1.10-1.24)	<0.001	0.08	1.12 (1.05-1.19)	<0.001	0.25	1.15 (1.08-1.23)	<0.001	0.06
Indolepropionate																
HCHS/ SOL	367/2821	0.80 (0.71-0.90)	<0.001		0.86 (0.76-0.97)	0.018		0.81 (0.71-0.91)	<0.001		0.77 (0.69-0.87)	<0.001		0.81 (0.72-0.92)	0.001	

FHS	218/1424	0.87 (0.76-0.99)	0.035		0.94 (0.82-1.07)	0.35		0.88 (0.77-1.00)	0.053		0.87 (0.76-0.99)	0.034		0.86 (0.76-0.99)	0.03	
PREDIMED	248/885	0.86 (0.72-1.03)	0.11		0.93 (0.77-1.12)	0.44		NA	NA		0.84 (0.69-1.02)	0.073		0.86 (0.72-1.04)	0.12	
WHI	163/1329	0.80 (0.68-0.95)	0.011		0.91 (0.76-1.08)	0.28		0.83 (0.70-0.99)	0.038		0.83 (0.70-0.98)	0.031		0.80 (0.67-0.95)	0.01	
ARIC	1036/2721	0.92 (0.86-0.98)	0.009		0.96 (0.90-1.02)	0.2		0.93 (0.87-0.99)	0.025		0.93 (0.88-1.00)	0.038		0.92 (0.86-0.98)	0.008	
Replication combined	1665/6359	0.89 (0.85-0.94)	<0.001	0.44	0.95 (0.90-1.00)	0.049	0.94	0.91 (0.86-0.96)	0.001	0.42	0.91 (0.86-0.95)	<0.001	0.39	0.89 (0.85-0.94)	<0.001	0.44
All combined	2032/9180	0.88 (0.84-0.92)	<0.001	0.24	0.93 (0.89-0.98)	0.006	0.66	0.89 (0.85-0.94)	<0.001	0.2	0.88 (0.84-0.93)	<0.001	0.07	0.88 (0.84-0.92)	<0.001	0.35
Indoxyl sulfate																
HCHS/ SOL	367/2821	0.93 (0.83-1.04)	0.22		0.93 (0.82-1.04)	0.19		0.92 (0.82-1.03)	0.16		1.04 (0.92-1.17)	0.52		0.93 (0.83-1.05)	0.23	
FHS	218/1424	1.00 (0.88-1.13)	0.95		1.02 (0.89-1.16)	0.82		0.99 (0.87-1.12)	0.84		0.94 (0.82-1.07)	0.34		1.00 (0.88-1.13)	0.97	
PREDIMED	248/885	1.03 (0.87-1.21)	0.75		1.01 (0.85-1.20)	0.9		NA	NA		0.98 (0.82-1.16)	0.79		1.04 (0.88-1.24)	0.62	
WHI	163/1329	0.92 (0.79-1.08)	0.32		0.92 (0.78-1.08)	0.28		0.91 (0.78-1.07)	0.25		0.84 (0.72-0.99)	0.035		0.93 (0.79-1.08)	0.33	
ARIC	1036/2721	1.02 (0.96-1.09)	0.46		1.04 (0.98-1.11)	0.22		1.02 (0.96-1.09)	0.51		0.99 (0.93-1.05)	0.7		1.02 (0.96-1.09)	0.38	
Replication combined	1665/6359	1.01 (0.96-1.06)	0.73	0.68	1.02 (0.97-1.07)	0.43	0.55	1.00 (0.95-1.06)	0.94	0.41	0.96 (0.92-1.01)	0.15	0.32	1.01 (0.96-1.06)	0.69	0.67
All combined	2032/9180	1.00 (0.95-1.04)	0.86	0.53	1.00 (0.96-1.05)	0.85	0.36	0.99 (0.94-1.04)	0.61	0.32	0.97 (0.92-1.02)	0.29	0.3	1.00 (0.95-1.04)	0.91	0.53

Data are Hazard ratios (HRs) and 95% confidence intervals (85% CIs) of incident type 2 diabetes per SD increment of metabolite levels, after multivariate adjustment. Results were analyzed in each study and were combined using a fixed-effect meta-analysis.

Model 1: adjusted for age, sex, smoking, alcohol consumption, education, lipid-lowering medication use, anti-hypertensive medication use, family history of diabetes, self-reported physician-diagnosed hypertension, self-reported physician-diagnosed dyslipidemia, and other study-specific covariates as shown in Table S4.

Model 2: further adjusted for BMI and waist-to-hip ratio (in PREDIMED, waist circumference) based on Model 1.

Model 3: further adjusted for physical activity and AHEI-2010 (in WHI, HEI-2005) based on Model 1.

Model 4: further adjusted for HDL-C, LDL-C and triglycerides (in WHI, HDL-C and total cholesterol) based on Model 1.

Model 5: Further adjusted for systolic blood pressure and diastolic blood pressure based on Model 1.

Abbreviations: HCHS/SOL, the Hispanic Community Health Study/Study of Latinos; ARIC, the Atherosclerosis Risk in Communities study; FHS, the Framingham Study; WHI, the Women's Health Initiative; PREDIMED, Prevención con Dieta Mediterránea; BMI, body mass index; WHR, waist-hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; AHEI-2010, alternate healthy eating index 2010; HEI-2005, healthy eating index 2005; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Table S6 Genetic variants and loci associated with circulating tryptophan metabolites (*P*<5.0E-08)

Metabolite	SNP	Locus	Chr	Position	A1	A2	EAF (min/max)	N	Effect	SE	*P*	Direction*	HetP	Known biological function in tryptophan metabolism or transportation of tryptophan metabolites	Previously reported GWAS loci associated with any tryptophan metabolites
Tryptophan															
	rs4691944	***TDO2***	**4**	**156753174**	**T**	**C**	**0.87/0.97**	**9016**	**0.16**	**0.02**	**1.3E-10**	**++++**	**1.8E-02**	*TDO2* encodes tryptophan 2,3-dioxygenase which catalyzes tryptophan to kynurenine	Tryptophan [Shin et al. Nature Genetics, 2014]
	rs12207199	*SLC16A10*	6	111525906	A	T	0.03/0.17	9016	0.12	0.02	4.7E-08	+-++	1.5E-01	*SLC16A10* encodes aromatic amino acid transporter 1 which transports tryptophan, tyrosine and phenylalanine	Tryptophan [Shin et al. Nature Genetics, 2014]
	rs402014	*SLC16A10*	6	111527696	T	C	0.50/0.57	9016	-0.08	0.01	1.2E-08	----	9.7E-01		
	rs186903200	*FSIP1*	15	40007123	C	G	0.01/0.01	1772	0.90	0.16	2.3E-08	?+??	NA		
Serotonin															
	rs7451008	*CDKAL1*	6	20673880	T	C	0.73/0.78	7214	0.10	0.02	2.2E-08	+++?	4.7E-01		Xanthurenate (gene level; P=5e-6; Rhee et al. Cell Metabolism, 2013]
	rs662138	***SLC22A1***	**6**	**160564476**	**C**	**G**	**0.79/0.93**	**9012**	**-0.16**	**0.02**	**1.6E-13**	**----**	**1.5E-01**	*SLC22A1* encodes organic cationic transporter 1 which plays a significant role in hepatic elimination of serotonin	
	rs4734879	*ZFPM2*	8	106583124	A	G	0.60/0.71	9012	0.09	0.02	4.8E-08	++++	2.6E-01		
	rs11213820	*C11orf53-COLCA1* ^{n}	11	111160491	T	C	0.24/0.36	7214	0.10	0.02	3.2E-08	+++?	7.9E-01		
Kynurenine															
	rs76506135	*IDO1-IDO2*	8	39770319	T	C	0.01/0.06	5705	-0.33	0.06	1.7E-08	--??	2.9E-01	*IDO1* and *IDO2* encode the two indoleamine 2,3-dioxygenase isozymes which both catalyze tryptophan to kynurenine	Hydroxytryptophan [Shin et al. Nature Genetics, 2014]
	rs2729456	***IDO1-IDO2***	**8**	**39819808**	**T**	**G**	**0.59/0.71**	**8669**	**0.12**	**0.02**	**1.8E-15**	**++++**	**4.9E-01**		
	rs3184504	*SH2B3*	12	111884608	T	C	0.10/0.50	8669	0.10	0.02	4.5E-08	++++	9.8E-01		Kynurenine [Shin et al. Nature Genetics, 2014]
	rs4419070	*SLC7A5*	16	87863267	T	C	0.04/0.15	8669	0.18	0.03	7.1E-12	++++	4.3E-01	*SLC7A5* encodes L-type amino acid transporter 1 (LAT1) which mediates tryptophan/kynurenine exchange	Kynurenine [Shin et al. Nature Genetics, 2014]; Kynurenine [Long et al. Nature Genetics, 2017]
	rs8063871	*SLC7A5*	16	87863500	A	C	0.60/0.74	8669	0.12	0.02	4.4E-13	++++	5.1E-02		
	rs8050771	***SLC7A5***	**16**	**87878570**	**A**	**G**	**0.26/0.43**	**8669**	**0.19**	**0.02**	**2.2E-30**	**++++**	**1.4E-01**		
Kynurenate															
	rs4648727	*GNB1*	1	1776269	A	C	0.35/0.45	5735	0.11	0.02	1.9E-08	+??+	4.3E-01		

	rs61825638	***KMO***	**1**	**241713402**	**T**	**C**	**0.19/0.19**	**3933**	**0.37**	**0.03**	**1.2E-37**	**+???**	**NA**	*KMO* encodes Kynurenine 3-monooxygenase which catalyzes Kynurenine to hydroxykynurenine	Kynurenate [Long et al. Nature Genetics, 2017]
	rs6429281	*KMO*	1	241749007	T	C	0.16/0.16	3933	0.18	0.03	2.7E-09	+???	NA		
	rs11733850	***AADAT***	**4**	**171023301**	**T**	**C**	**0.06/0.11**	**5735**	**0.22**	**0.04**	**1.2E-09**	**+??+**	**1.1E-01**	*AADAT* encodes kynurenine/alpha-aminoadipate aminotransferase	
Xanthurenate															
	rs887829	***UGT1A***	**2**	**234668570**	**T**	**C**	**0.31/0.33**	**5386**	**0.17**	**0.02**	**1.5E-19**	**+??+**	**7.7E-02**		Xanthurenate [Rhee et al. Cell Metabolism, 2013]
	rs10145643	*SLC10A1*	14	70252470	A	G	0.72/0.72	3933	-0.13	0.02	6.9E-09	-???	NA		
Quinolinate															
	rs10496731	***ACMSD***	**2**	**135597628**	**T**	**G**	**0.38/0.51**	**5388**	**0.12**	**0.02**	**3.6E-10**	**+??+**	**6.0E-01**	*ACMSD* encodes aminocarboxymuconate-semialdehyde decarboxylase which limits and regulates the formation of quinolinate	N1-methyl-3-pyridone-4-carboxamide, an endproduct of NAD degradation [Shin et al. Nature Genetics, 2014]
	rs62513117	***IDO1-IDO2***	**8**	**39812141**	**A**	**G**	**0.74/0.74**	**3933**	**0.16**	**0.03**	**7.3E-10**	**+???**	**NA**	This SNP is in LD (r=0.37 in CEU, 0.21 in AA, and 0.61 in HA) with the kynurenine-associated SNP rs2729456 at the *IDO1-IDO2* locus (see biological function above)	Hydroxytryptophan [Shin et al. Nature Genetics, 2014]
Picolinate															
	rs80093546	*CUL1*	7	148433716	G	T	0.99	3933	0.64	0.12	3.7E-08	+???	NA		
	rs7499271	***ACSM1-ACSM2B***	**16**	**20555259**	**T**	**A**	**0.09**	**3933**	**0.53**	**0.04**	**2.2E-46**	**+???**	**NA**		
	rs200661965	*ACSM1-ACSM2B*	16	20585003	C	T	0.12	3933	-0.19	0.03	1.2E-09	-???	NA		
	rs368315271	*ACSM1-ACSM2B*	16	20587526	T	C	0.03	3933	0.43	0.06	1.8E-11	+???	NA		
	rs4105168	*ACSM1-ACSM2B*	16	20633414	G	C	0.12	3933	0.34	0.04	9.0E-21	+???	NA		
	rs55689267	*ACSM1-ACSM2B*	16	20681700	T	C	0.99	3933	-0.74	0.10	4.7E-13	-???	NA		
	rs9924430	*SCNN1B*	16	23387698	C	T	0.05	3933	0.29	0.05	3.0E-08	+???	NA		
	rs11641469	***CDK10***	**16**	**89745421**	**A**	**G**	**0.59**	**3933**	**0.15**	**0.02**	**7.6E-12**	**+???**	**NA**		
Indoleacetate															
	rs191814634	*SEPHS2P1*	5	14957733	C	G	0.91/0.99	7214	-0.26	0.04	1.1E-08	---?	6.7E-01		
	rs11575302	*DDC*	7	50607694	A	G	0.02/0.15	7214	-0.21	0.04	1.7E-08	---?	2.2E-01	*DDC* encodes dopa decarboxylase which converts tryptophan to tryptamine, and tryptamine can be further	Indoleacetate [Shin et al. Nature Genetics, 2014]

														metabolized to indoleacetate	
Indolelactate															
	rs148756272	*PKN3*	9	131480262	T	C	0.01/0.07	5705	0.32	0.06	2.3E-08	++??	1.5E-01		
	rs7875300	***KYAT1***	**9**	**131573261**	**A**	**G**	**0.25/0.45**	**7214**	**-0.15**	**0.02**	**1.9E-16**	**---?**	**5.9E-01**	*KYAT1* encodes kynurenine aminotransferase 1 which converts tryptophan to indolepyruvate, and indolepyruvate is then converted to indolelactate.	Indolelactate [Shin et al. Nature Genetics, 2014]; Indolelactate [Yu et al. Genome Biology, 2016]
Indolepropionate															
	rs7570971	***LCT***	**2**	**135837906**	**A**	**C**	**0.34/0.88**	**7214**	**0.18**	**0.02**	**2.9E-18**	**+++?**	**7.4E-01**		
	rs72847650	*HNRNPKP2-UBBP1*	2	137051974	A	C	0.09/0.43	7214	-0.13	0.02	1.6E-08	---?	4.2E-01		Indolepropionate [Shin et al. Nature Genetics, 2014]
	rs149241657	*ACSM5*	16	20448142	A	G	0.91/0.97	7214	0.26	0.04	4.3E-09	+++?	7.2E-01		
	rs59261767	*ACSM2A*	16	20477004	T	C	0.01/0.03	5705	0.45	0.07	9.2E-12	++??	6.5E-02		
	rs6497490	*ACSM2A*	16	20477474	T	G	0.87/0.96	8652	-0.22	0.03	1.6E-15	----	7.5E-01		
	rs1505100	***ACSM2A***	**16**	**20481672**	**A**	**T**	**0.48/0.71**	**8652**	**0.15**	**0.02**	**5.6E-22**	**++++**	**2.4E-01**		
Indoxylsulfate															
	rs80303567	*LINC01082*	16	86194834	C	G	0.01/0.04	5705	-0.404	0.07	8.9E-09	--??	5.6E-01		

Lead SNPs at each locus at genome-wide significance (*P*<4.5E-9) are highlighted in bold.

*Direction indicates association directions for HCHS/ SOL Hispanics/Latinos, ARIC African Americans, ARIC Whites, and FHS Whites, orderly. +, positive association, -, inverse association, ?, data not available.

Abbreviations: Chr, chromosome; A1, effect allele; A2, reference allele; EAF, effect allele frequency; HetP, P for heterogeneity.

Table S7 Estimated genetic heritability, genetic correlation with type 2 diabetes, and potential causal relationship with type 2 diabetes, for each tryptophan metabolite

Metabolites	**Current study**			**Shin et al. Nature Genetics, 2014**		**Long et al. Nature Genetics, 2017**			**LCV models†**						
	SNP-based genetic heritability*			Heritability estimated by the classical twin model	Explained heritability by GWAS variants	Heritability estimated by the classical twin model	Explained heritability by GWAS variants		Causal relationship					h^2 Z-score	
	h^2	SE	P						r_g	GCP	SE	P		Metabolite	T2D
Tryptophan	0.019	0.041	0.64	0.387	0.023	0.31	NA		NA	NA	NA	NA		1.4	107.2
Serotonin	0.130	0.049	0.008	0.331	NA	NA	NA		-0.062	0.057	0.287	0.51		14.6	107.1
Kynurenine	0.074	0.048	0.12	0.433	0.065	0.60	0.025		0.006	0.365	0.378	0.62		7.1	107.2
Kynurenate	0.000	0.073	0.81	NA	NA	0.62	0.034		NA	NA	NA	NA		NA	NA
Xanthurenate	0.070	0.080	0.39	NA	NA	0.46	NA		NA	NA	NA	NA		4.6	105.7
Quinolinate	0.000	0.084	0.87	NA	NA	0.25	NA		NA	NA	NA	NA		NA	NA
Picolinate	0.064	0.116	0.58	NA	NA	NA	NA		NA	NA	NA	NA		2.3	105.7
Indoleacetate	0.019	0.058	0.74	0.235	NA	NA	NA		NA	NA	NA	NA		1.6	106.1
Indolelactate	0.000	0.048	0.21	0.306	0.016	0.63	NA		NA	NA	NA	NA		NA	NA
Indolepropionate	0.107	0.058	0.06	0.302	0.043	0.46	0.019		-0.207	0.757	0.153	1.6E-24		8.0	107.2
Indoxyl sulfate	0.039	0.042	0.36	0.248	NA	0.30	NA		NA	NA	NA	NA		3.7	107.2

*SNP-based genetic heritability (h^2) and genetic correlations (rg) were estimated using linkage disequilibrium score regression.

†Causal relationship was estimated using latent causal variable (LCV) models that estimate causality while accounting for horizonal pleiotropy. Genetic causality proportion (GCP) >0.6 suggests nearly full genetic causality. LCV were applied when the h^2 Z-score of exposure and outcome both ≥7, otherwise the causal relationship will be overestimated. As such, causal relationship was tested for serotonin, kynurenine, and indolepropionate with T2D. The 3 metabolites with h^2=0 (kynurenate, quinolinate, and indolelactate) and the other 5 metabolites with h^2 Z-score <7 from LCV (tryptophan, xanthurenate, picolinate, indoleacetate, indoxyl sulfate) were not tested for their causal relationships with T2D.

Table S8 Associations of 10 major food groups with serum tryptophan metabolites

	Tryptophan			**Serotonin**			**Kynurenine**			**Kynurenate**			**Xanthurenate**			**Quinolinate**		
	Beta	SE	*P*	Beta	SE	*P*	Beta	SE	*P*	Beta	SE	*P*	Beta	SE	*P*	Beta	SE	*P*
Model 1																		
Vegetable	0.00	0.02	8.7E-01	0.08	0.02	**1.3E-03**	-0.06	0.02	**5.8E-03**	0.02	0.02	5.1E-01	0.00	0.02	9.3E-01	-0.11	0.02	**4.6E-06**
Fruit	0.01	0.02	6.0E-01	0.08	0.02	**5.7E-04**	-0.07	0.02	**2.6E-03**	-0.11	0.02	**8.6E-06**	-0.08	0.02	**3.6E-04**	-0.09	0.02	**5.5E-04**
Nut and legume	0.00	0.05	9.7E-01	0.17	0.06	**2.4E-03**	-0.12	0.06	3.1E-02	-0.14	0.06	**1.1E-02**	-0.08	0.05	1.4E-01	-0.28	0.06	**1.0E-06**
Whole grain	0.01	0.02	4.7E-01	0.06	0.02	**4.4E-04**	-0.05	0.02	**2.5E-03**	-0.05	0.02	**2.5E-03**	-0.01	0.02	3.4E-01	-0.04	0.02	**1.4E-02**
Refined grain	-0.01	0.02	6.1E-01	-0.05	0.02	**3.8E-03**	0.03	0.02	6.9E-02	0.03	0.02	1.6E-01	-0.01	0.02	6.6E-01	0.07	0.02	**4.9E-05**
Red meat	0.03	0.06	5.9E-01	-0.14	0.07	3.5E-02	0.17	0.07	**1.0E-02**	0.35	0.07	**9.9E-08**	0.17	0.06	**6.7E-03**	0.16	0.07	**1.8E-02**
Poultry	0.000	0.002	8.1E-01	0.000	0.002	8.6E-01	-0.004	0.002	3.6E-02	0.000	0.002	8.2E-01	0.003	0.002	7.3E-02	-0.006	0.002	**6.6E-03**
Fish	-0.11	0.12	3.7E-01	0.16	0.13	2.1E-01	-0.25	0.13	4.8E-02	0.01	0.13	9.2E-01	-0.02	0.12	8.6E-01	-0.27	0.13	4.4E-02
Egg	-0.03	0.02	7.7E-02	0.01	0.02	4.8E-01	-0.02	0.02	3.5E-01	0.01	0.02	4.4E-01	0.01	0.02	3.9E-01	0.03	0.02	1.2E-01
Dairy	0.08	0.03	**8.5E-03**	0.00	0.03	9.7E-01	0.05	0.03	1.3E-01	-0.01	0.03	7.6E-01	0.04	0.03	2.4E-01	0.12	0.03	**3.2E-04**
Model 2																		
Vegetable	0.02	0.03	4.4E-01	0.06	0.03	5.6E-02	-0.04	0.03	1.6E-01	0.08	0.03	7.3E-03	0.05	0.03	6.2E-02	-0.09	0.03	7.3E-03
Fruit	0.01	0.02	7.0E-01	0.06	0.03	2.6E-02	-0.05	0.03	6.2E-02	-0.10	0.03	1.0E-04	-0.10	0.02	1.2E-04	-0.03	0.03	2.7E-01
Nut and legume	0.01	0.06	7.9E-01	0.12	0.06	3.8E-02	-0.08	0.06	2.0E-01	-0.07	0.06	2.1E-01	-0.03	0.06	5.4E-01	-0.22	0.06	3.3E-04
Whole grain	0.01	0.02	6.7E-01	0.04	0.02	8.4E-02	-0.04	0.02	3.3E-02	-0.04	0.02	5.0E-02	-0.02	0.02	3.6E-01	0.01	0.02	8.0E-01
Refined grain	0.00	0.02	9.3E-01	0.00	0.02	9.9E-01	-0.02	0.02	4.4E-01	-0.03	0.02	1.7E-01	-0.04	0.02	3.8E-02	0.05	0.02	3.9E-02
Red meat	0.06	0.07	3.7E-01	-0.04	0.07	5.7E-01	0.06	0.07	4.1E-01	0.29	0.07	8.1E-05	0.18	0.07	8.6E-03	0.04	0.07	5.7E-01
Poultry	0.001	0.002	8.0E-01	-0.001	0.002	8.0E-01	-0.003	0.002	1.7E-01	0.002	0.002	3.8E-01	0.006	0.002	6.1E-03	-0.004	0.002	5.8E-02
Fish	-0.08	0.12	5.1E-01	0.09	0.13	5.1E-01	-0.17	0.13	2.0E-01	0.08	0.13	5.4E-01	0.04	0.12	7.6E-01	-0.15	0.13	2.6E-01
Egg	-0.02	0.02	1.2E-01	0.02	0.02	3.5E-01	-0.02	0.02	3.1E-01	0.01	0.02	5.8E-01	0.01	0.02	5.6E-01	0.03	0.02	1.0E-01
Dairy	0.08	0.03	1.0E-02	0.01	0.03	7.8E-01	0.04	0.03	2.5E-01	0.00	0.03	9.4E-01	0.05	0.03	1.1E-01	0.10	0.03	4.1E-03

Data are differences (beta) and standard error (SE) in metabolites associated with one serving/day intake of food groups.

Model 1, adjusted for age, gender, center, smoking, physical activity, education, income, and total energy intake. P-values remained significant after FDR correction are highlight in bold.

Model 2, further adjusted for other food groups based on Model 1 (all 10 food groups were included in the model simultaneously). FDR correction was not applied in this model.

Table S8 Associations of 10 major food groups with serum tryptophan metabolites (continued)

	Quinolinate			Picolinate			Indoleacetate			indolelactate			indolepropionate			Indoxyl sulfate		
	Beta	SE	*P*	Beta	SE	*P*	Beta	SE	*P*	Beta	SE	*P*	Beta	SE	*P*	Beta	SE	*P*
Model 1																		
Vegetable	-0.11	0.02	**4.6E-06**	0.00	0.02	9.9E-01	-0.03	0.02	2.0E-01	-0.01	0.02	6.5E-01	0.17	0.02	**3.3E-13**	-0.11	0.02	**9.1E-06**
Fruit	-0.09	0.02	**5.5E-04**	-0.02	0.02	3.3E-01	-0.09	0.02	**4.4E-04**	-0.06	0.02	**1.3E-02**	0.31	0.02	**6.1E-39**	-0.12	0.02	**6.9E-07**
Nut and legume	-0.28	0.06	**1.0E-06**	-0.11	0.05	4.9E-02	-0.02	0.06	7.3E-01	-0.01	0.05	8.5E-01	0.47	0.06	**6.7E-17**	-0.30	0.06	**2.8E-07**
Whole grain	-0.04	0.02	**1.4E-02**	-0.02	0.02	3.2E-01	0.04	0.02	**1.8E-02**	-0.06	0.02	**2.7E-04**	0.16	0.02	**2.0E-22**	-0.07	0.02	**1.1E-04**
Refined grain	0.07	0.02	**4.9E-05**	-0.01	0.02	6.1E-01	-0.01	0.02	7.0E-01	0.01	0.02	3.7E-01	-0.12	0.02	**5.8E-11**	0.03	0.02	6.7E-02
Red meat	0.16	0.07	**1.8E-02**	0.16	0.06	**9.1E-03**	-0.03	0.07	7.0E-01	0.09	0.06	1.2E-01	-0.64	0.07	**1.5E-22**	0.12	0.07	6.8E-02
Poultry	-0.006	0.002	**6.6E-03**	0.005	0.002	**1.4E-02**	0.001	0.002	6.8E-01	0.002	0.002	2.7E-01	-0.001	0.002	**7.1E-01**	0.010	0.002	**5.8E-06**
Fish	-0.27	0.13	4.4E-02	0.04	0.12	7.6E-01	0.07	0.13	6.2E-01	-0.08	0.12	5.2E-01	0.28	0.13	2.8E-02	0.21	0.13	1.1E-01
Egg	0.03	0.02	1.2E-01	0.01	0.02	5.0E-01	0.02	0.02	2.7E-01	0.01	0.02	6.9E-01	-0.02	0.02	3.7E-01	0.02	0.02	3.2E-01
Dairy	0.12	0.03	**3.2E-04**	0.05	0.03	1.0E-01	0.01	0.03	7.0E-01	-0.06	0.03	3.7E-02	0.04	0.03	1.8E-01	-0.03	0.03	3.2E-01
Model 2																		
Vegetable	-0.09	0.03	7.3E-03	0.06	0.03	3.8E-02	-0.01	0.03	7.2E-01	0.01	0.03	6.9E-01	0.10	0.03	1.4E-03	-0.11	0.03	5.5E-04
Fruit	-0.03	0.03	2.7E-01	-0.03	0.03	2.1E-01	-0.10	0.03	1.8E-04	-0.06	0.02	1.7E-02	0.26	0.03	1.7E-24	-0.12	0.03	5.7E-06
Nut and legume	-0.22	0.06	3.3E-04	-0.06	0.06	2.9E-01	-0.03	0.06	6.2E-01	0.02	0.05	6.7E-01	0.31	0.06	9.3E-08	-0.24	0.06	8.6E-05
Whole grain	0.01	0.02	8.0E-01	-0.02	0.02	4.2E-01	0.05	0.02	1.0E-02	-0.07	0.02	4.0E-04	0.10	0.02	2.0E-07	-0.04	0.02	7.0E-02
Refined grain	0.05	0.02	3.9E-02	-0.03	0.02	1.3E-01	0.00	0.02	9.9E-01	-0.04	0.02	7.4E-02	0.05	0.02	1.5E-02	-0.05	0.02	3.2E-02
Red meat	0.04	0.07	5.7E-01	0.22	0.07	1.8E-03	-0.01	0.07	8.9E-01	0.03	0.07	6.4E-01	-0.41	0.07	8.6E-09	0.12	0.07	1.2E-01
Poultry	-0.004	0.002	5.8E-02	0.007	0.002	1.4E-03	0.002	0.002	3.3E-01	0.002	0.002	2.9E-01	-0.006	0.002	4.3E-03	0.012	0.002	2.5E-07
Fish	-0.15	0.13	2.6E-01	0.07	0.13	5.9E-01	0.13	0.13	3.4E-01	-0.08	0.12	5.3E-01	0.02	0.13	8.6E-01	0.32	0.13	1.6E-02
Egg	0.03	0.02	1.0E-01	0.01	0.02	5.4E-01	0.01	0.02	4.4E-01	0.00	0.02	9.0E-01	0.00	0.02	9.3E-01	0.00	0.02	8.6E-01
Dairy	0.10	0.03	4.1E-03	0.07	0.03	3.4E-02	0.01	0.03	7.5E-01	-0.05	0.03	8.0E-02	0.04	0.03	2.1E-01	-0.02	0.03	4.9E-01

Data are differences (beta) and standard error (SE) in metabolites associated with one serving/day intake of food groups.

Model 1, adjusted for age, gender, center, smoking, physical activity, education, income, and total energy intake. P-values remained significant after FDR correction are highlight in bold.

Model 2, further adjusted for other food groups based on Model 1 (all 10 food groups were included in the model simultaneously). FDR correction was not applied in this model.

Table S9 Associations of dietary intakes of macronutrients, fiber and tryptophan with serum tryptophan metabolites

	Tryptophan			**Serotonin**			**Kynurenine**			**Kynurenate**			**Xanthurenate**			**Quinolinate**		
	Beta	SE	*P-value*	Beta	SE	*P-value*	Beta	SE	*P-value*	Beta	SE	*P-value*	Beta	SE	*P-value*	Beta	SE	*P-value*
Model 1																		
Carbohydrate	0.002	0.001	5.8E-02	0.002	0.001	6.7E-02	0.001	0.001	6.4E-01	-0.010	0.001	1.3E-14	-0.009	0.001	8.0E-12	0.000	0.001	8.7E-01
Protein	0.006	0.003	8.3E-02	-0.002	0.004	5.3E-01	-0.004	0.004	3.4E-01	0.022	0.004	2.6E-09	0.024	0.003	1.2E-12	-0.004	0.004	2.9E-01
Fat	-0.008	0.004	4.3E-02	-0.007	0.004	9.7E-02	0.004	0.004	3.1E-01	0.022	0.004	9.5E-07	0.009	0.004	3.2E-02	0.009	0.004	4.4E-02
Fiber	0.005	0.007	4.8E-01	0.046	0.008	2.5E-09	-0.037	0.008	1.2E-06	-0.036	0.008	3.1E-06	-0.021	0.007	4.4E-03	-0.043	0.008	5.2E-08
Tryptophan	0.706	0.291	1.5E-02	-0.424	0.308	1.7E-01	-0.092	0.309	7.7E-01	1.684	0.310	5.7E-08	1.803	0.290	5.3E-10	-0.052	0.316	8.7E-01
Model 2																		
Carbohydrate	0.006	0.002	1.1E-02	-0.004	0.002	1.1E-01	0.009	0.003	3.3E-04	-0.008	0.003	2.1E-03	-0.012	0.002	8.7E-07	0.012	0.003	5.6E-06
Fat	0.003	0.007	6.7E-01	-0.005	0.007	5.0E-01	0.015	0.007	3.2E-02	-0.004	0.007	6.1E-01	-0.023	0.007	5.4E-04	0.025	0.007	6.4E-04
Fiber	-0.009	0.008	2.7E-01	0.053	0.009	7.6E-10	-0.049	0.009	1.5E-08	-0.023	0.009	7.4E-03	-0.011	0.008	1.6E-01	-0.055	0.009	6.1E-10
Tryptophan	1.299	0.357	2.8E-04	-0.948	0.377	1.2E-02	0.835	0.378	2.7E-02	1.037	0.379	6.3E-03	0.875	0.355	1.4E-02	1.086	0.387	5.0E-03

Table S9 (continued)

	Picolinate			**Indoleacetate**			**indolelactate**			**indolepropionate**			**Indoxyl sulfate**		
	Beta	SE	*P-value*	Beta	SE	*P-value*	Beta	SE	*P-value*	Beta	SE	*P-value*	Beta	SE	*P-value*
Model 1															
Carbohydrate	-0.007	0.001	7.7E-09	-0.005	0.001	7.8E-04	-0.004	0.001	3.8E-03	0.014	0.001	4.3E-24	-0.005	0.001	9.3E-04
Protein	0.025	0.003	6.7E-13	0.011	0.004	2.1E-03	0.005	0.003	1.4E-01	-0.008	0.004	3.6E-02	0.012	0.004	1.1E-03
Fat	0.009	0.004	2.9E-02	0.009	0.004	4.3E-02	0.001	0.004	8.8E-01	-0.039	0.004	7.0E-19	0.008	0.005	8.9E-02
Fiber	-0.010	0.007	1.8E-01	-0.001	0.008	9.1E-01	-0.022	0.007	2.2E-03	0.124	0.007	7.2E-60	-0.057	0.008	5.2E-13
Tryptophan	1.853	0.295	4.0E-10	0.996	0.314	1.5E-03	0.515	0.282	6.8E-02	-0.593	0.310	5.6E-02	0.874	0.317	5.9E-03
Model 2															
Carbohydrate	-0.008	0.002	7.8E-04	-0.004	0.003	1.1E-01	-0.007	0.002	3.4E-03	0.003	0.002	1.8E-01	0.001	0.003	8.1E-01
Fat	-0.013	0.007	6.2E-02	0.000	0.007	9.6E-01	-0.020	0.007	2.2E-03	-0.007	0.007	3.4E-01	-0.006	0.007	4.4E-01
Fiber	-0.002	0.008	7.8E-01	0.007	0.009	4.5E-01	-0.019	0.008	1.4E-02	0.114	0.008	1.8E-40	-0.064	0.009	6.0E-13
Tryptophan	1.164	0.363	1.4E-03	0.584	0.387	1.3E-01	0.061	0.346	8.6E-01	-0.601	0.368	1.0E-01	1.179	0.387	2.3E-03

Data are differences (beta) and standard error (SE) in metabolites associated with g/day intake of nutrients/1000 kcal energy.

Model 1, adjusted for age, gender, center, smoking, physical activity, education, income, and total energy intake.

Model 2, further adjusted for other nutrients based on Model 1 (Dietary carbohydrate, fat, fiber and tryptophan were included in the model simultaneously). As dietary protein intake was highly correlated with dietary tryptophan intake (r=0.9), it was not included in this model.

Table S10 Associations of gut bacterial taxa with serum levels of 4 indole metabolites

Phylum	Genus	Prevalence	Relative abundance (%)	Indolepropionate			indolelactate			indoleacetate			Indoxyl sulfate		
				Beta	SE	*P*	Beta	SE	*P*	Beta	SE	*P*	Beta	SE	*P*
Firmicutes	Ruminococcus	1.000	1.876	0.117	0.028	**2.6E-05**	0.018	0.026	5.0E-01	0.026	0.030	3.9E-01	0.041	0.030	1.6E-01
Firmicutes	Flavonifractor	1.000	0.310	-0.091	0.021	**2.8E-05**	0.019	0.020	3.5E-01	-0.043	0.023	6.6E-02	0.034	0.023	1.4E-01
Firmicutes	Faecalitalea	1.000	0.065	0.154	0.037	**3.0E-05**	-0.004	0.035	9.0E-01	0.052	0.040	1.9E-01	0.113	0.039	**4.0E-03**
Firmicutes	Lachnoclostridium	1.000	0.571	-0.146	0.037	**7.1E-05**	0.043	0.035	2.1E-01	0.018	0.039	6.4E-01	0.073	0.039	6.3E-02
Firmicutes	Faecalibacterium	1.000	1.930	0.093	0.024	**9.5E-05**	-0.038	0.022	9.3E-02	-0.005	0.026	8.5E-01	0.016	0.025	5.3E-01
Firmicutes	Subdoligranulum	1.000	0.038	0.142	0.038	**1.6E-04**	-0.052	0.035	1.4E-01	0.081	0.040	4.5E-02	0.044	0.040	2.8E-01
Firmicutes	Clostridium	1.000	0.916	0.138	0.039	**3.7E-04**	0.010	0.036	7.8E-01	0.027	0.041	5.1E-01	0.032	0.041	4.4E-01
Firmicutes	Lachnoanaerobaculum	0.988	0.010	0.089	0.026	**6.5E-04**	-0.034	0.024	1.7E-01	0.028	0.028	3.1E-01	0.051	0.028	6.5E-02
Firmicutes	Intestinimonas	1.000	0.171	0.096	0.028	**7.0E-04**	-0.030	0.027	2.6E-01	0.065	0.030	3.3E-02	0.084	0.030	5.4E-03
Firmicutes	Erysipelatoclostridium	1.000	0.180	-0.093	0.028	**9.8E-04**	0.014	0.026	5.8E-01	0.012	0.030	6.9E-01	-0.020	0.030	5.1E-01
Actinobacteria	Cellulomonas	0.994	0.259	0.048	0.015	**1.6E-03**	0.004	0.014	8.0E-01	0.047	0.016	**3.6E-03**	0.019	0.016	2.5E-01
Firmicutes	Eubacterium	1.000	1.707	0.126	0.040	**1.8E-03**	-0.009	0.038	8.1E-01	-0.020	0.043	6.5E-01	0.037	0.043	3.9E-01
Firmicutes	Fournierella	1.000	0.040	0.118	0.038	**1.9E-03**	-0.006	0.036	8.6E-01	0.113	0.040	**5.3E-03**	0.047	0.040	2.4E-01
Firmicutes	Dorea	1.000	1.083	0.097	0.031	**2.0E-03**	-0.026	0.029	3.7E-01	-0.014	0.033	6.7E-01	0.024	0.033	4.8E-01
Firmicutes	Butyrivibrio	0.999	1.090	0.056	0.018	**2.1E-03**	-0.007	0.017	6.8E-01	0.018	0.019	3.5E-01	-0.018	0.019	3.4E-01
Actinobacteria	Eggerthella	0.994	0.094	-0.055	0.018	**2.5E-03**	0.033	0.017	5.1E-02	-0.024	0.019	2.2E-01	0.029	0.019	1.3E-01
Firmicutes	Pseudoflavonifractor	0.999	0.035	0.092	0.031	**2.9E-03**	-0.010	0.029	7.2E-01	0.078	0.033	1.8E-02	0.102	0.033	**1.8E-03**
Actinobacteria	Bifidobacterium	1.000	1.853	0.051	0.017	**3.0E-03**	-0.006	0.016	7.3E-01	-0.033	0.018	7.1E-02	-0.040	0.018	2.7E-02
Bacteroidetes	Porphyromonas	0.994	0.067	0.070	0.024	**4.1E-03**	-0.006	0.023	8.0E-01	0.041	0.026	1.1E-01	0.069	0.026	7.6E-03
Bacteroidetes	Parabacteroides	1.000	2.391	-0.081	0.028	**4.2E-03**	0.010	0.027	7.1E-01	-0.057	0.030	6.2E-02	0.103	0.030	**5.9E-04**
Firmicutes	Bittarella	0.994	0.012	0.080	0.028	**4.9E-03**	-0.004	0.027	8.8E-01	0.059	0.030	5.1E-02	0.075	0.030	1.3E-02
Actinobacteria	Adlercreutzia	0.878	0.019	0.034	0.012	6.1E-03	-0.006	0.011	6.0E-01	0.011	0.013	3.9E-01	0.011	0.013	3.8E-01
Firmicutes	Unclassfied	1.000	0.156	0.106	0.039	6.4E-03	-0.061	0.036	9.1E-02	-0.001	0.041	9.8E-01	0.097	0.041	1.9E-02
Firmicutes	Holdemania	0.994	0.024	0.064	0.024	7.0E-03	-0.024	0.022	2.7E-01	0.022	0.025	3.8E-01	0.051	0.025	4.3E-02
Firmicutes	Unclassfied	1.000	0.120	0.099	0.038	8.6E-03	-0.087	0.035	1.3E-02	0.046	0.040	2.6E-01	0.067	0.040	9.4E-02
Firmicutes	Blautia	1.000	4.058	-0.143	0.054	8.6E-03	0.045	0.051	3.8E-01	-0.005	0.058	9.3E-01	-0.011	0.058	8.5E-01
Firmicutes	Marvinbryantia	0.997	0.011	0.084	0.032	9.1E-03	-0.001	0.030	9.8E-01	-0.012	0.034	7.3E-01	0.026	0.034	4.4E-01
Fusobacteria	Fusobacterium	0.729	0.080	-0.030	0.011	9.7E-03	0.007	0.011	5.3E-01	-0.011	0.012	3.8E-01	-0.012	0.012	3.2E-01
Firmicutes	Unclassfied	1.000	0.171	0.114	0.044	1.0E-02	-0.040	0.042	3.3E-01	0.021	0.047	6.6E-01	-0.037	0.047	4.3E-01
Bacteroidetes	Barnesiella	0.999	0.828	0.038	0.015	1.2E-02	-0.018	0.014	1.9E-01	0.004	0.016	8.0E-01	0.025	0.016	1.2E-01
Firmicutes	Oscillibacter	1.000	1.513	0.074	0.030	1.2E-02	-0.029	0.028	3.0E-01	0.027	0.032	3.9E-01	0.073	0.031	2.0E-02

Bacteroidetes	Alistipes	1.000	5.422	0.061	0.024	1.3E-02	-0.024	0.023	2.9E-01	-0.011	0.026	6.7E-01	0.077	0.026	**2.9E-03**
Bacteroidetes	Bacteroides	1.000	35.801	-0.086	0.037	2.1E-02	0.034	0.035	3.3E-01	-0.093	0.040	1.9E-02	0.035	0.040	3.8E-01
Firmicutes	Roseburia	1.000	5.051	0.070	0.031	2.3E-02	-0.001	0.029	9.6E-01	0.021	0.033	5.2E-01	-0.031	0.033	3.4E-01
Bacteroidetes	Prevotella	1.000	12.663	0.034	0.015	2.4E-02	0.001	0.014	9.2E-01	0.044	0.016	6.0E-03	0.021	0.016	1.9E-01
Firmicutes	Holdemanella	1.000	0.163	0.051	0.023	2.5E-02	-0.034	0.021	1.1E-01	0.024	0.024	3.2E-01	-0.020	0.024	4.1E-01
Verrucomicrobia	Akkermansia	0.968	0.766	0.023	0.010	2.8E-02	-0.003	0.010	7.3E-01	0.012	0.011	2.8E-01	0.039	0.011	**4.2E-04**
Firmicutes	Unclassfied	1.000	4.705	0.050	0.023	2.9E-02	-0.019	0.022	3.8E-01	-0.044	0.024	7.1E-02	-0.041	0.024	9.3E-02
Firmicutes	Streptococcus	1.000	0.322	-0.049	0.023	3.4E-02	-0.005	0.022	8.3E-01	-0.004	0.025	8.7E-01	0.005	0.025	8.5E-01
Spirochaetes	Treponema	0.907	0.024	0.043	0.020	3.5E-02	-0.023	0.019	2.2E-01	0.053	0.022	1.4E-02	0.008	0.021	7.2E-01
Proteobacteria	Escherichia	0.994	1.973	-0.027	0.013	3.6E-02	-0.004	0.012	7.7E-01	0.002	0.014	8.8E-01	0.022	0.014	1.1E-01
Proteobacteria	Shigella	0.785	0.592	-0.016	0.008	5.0E-02	-0.005	0.008	4.7E-01	0.004	0.009	6.4E-01	0.012	0.008	1.5E-01
Firmicutes	Tyzzerella	1.000	0.253	-0.073	0.040	6.4E-02	0.018	0.037	6.3E-01	-0.016	0.042	7.0E-01	-0.047	0.042	2.7E-01
Firmicutes	Coprococcus	1.000	0.977	0.057	0.031	7.1E-02	-0.027	0.029	3.5E-01	-0.017	0.034	6.2E-01	-0.066	0.033	4.6E-02
Euryarchaeota	Methanobrevibacter	0.717	0.080	0.015	0.009	1.0E-01	0.007	0.009	4.4E-01	0.045	0.010	**2.3E-06**	-0.007	0.010	4.4E-01
Firmicutes	Faecalicatena	1.000	0.041	0.076	0.046	1.0E-01	0.047	0.043	2.8E-01	0.048	0.049	3.3E-01	0.137	0.049	**5.0E-03**
Firmicutes	Ruminiclostridium	1.000	0.924	0.029	0.018	1.1E-01	-0.022	0.017	1.8E-01	0.048	0.019	1.2E-02	0.036	0.019	5.6E-02
Firmicutes	Hungatella	1.000	0.132	-0.051	0.032	1.1E-01	-0.012	0.030	6.9E-01	0.022	0.034	5.2E-01	0.065	0.034	5.6E-02
Firmicutes	Acidaminococcus	0.936	0.361	-0.016	0.010	1.2E-01	0.002	0.010	8.2E-01	0.012	0.011	2.7E-01	0.010	0.011	3.8E-01
Actinobacteria	Collinsella	0.999	0.368	0.030	0.019	1.2E-01	0.011	0.018	5.6E-01	0.009	0.021	6.5E-01	0.044	0.020	3.1E-02
Firmicutes	Acetivibrio	0.999	0.032	0.039	0.026	1.3E-01	0.021	0.024	3.9E-01	0.045	0.027	9.9E-02	0.049	0.027	7.1E-02
Firmicutes	Dialister	0.931	0.318	0.015	0.010	1.3E-01	-0.005	0.009	6.2E-01	0.001	0.011	9.4E-01	0.001	0.011	9.1E-01
Firmicutes	Butyricicoccus	1.000	0.037	0.048	0.034	1.5E-01	-0.020	0.031	5.2E-01	0.052	0.036	1.5E-01	-0.002	0.036	9.6E-01
Actinobacteria	Actinomyces	0.997	0.015	-0.046	0.032	1.5E-01	-0.049	0.030	1.1E-01	0.012	0.034	7.2E-01	-0.021	0.034	5.4E-01
Firmicutes	Phascolarctobacterium	0.979	0.276	0.017	0.012	1.5E-01	0.016	0.011	1.6E-01	0.020	0.013	1.1E-01	-0.014	0.013	2.7E-01
Firmicutes	Lactococcus	0.767	0.011	-0.016	0.011	1.6E-01	-0.007	0.011	5.2E-01	0.006	0.012	6.2E-01	-0.016	0.012	1.9E-01
Proteobacteria	Proteus	0.094	0.026	-0.026	0.019	1.6E-01	0.009	0.017	5.9E-01	-0.014	0.020	4.7E-01	-0.006	0.020	7.4E-01
Firmicutes	Megamonas	0.719	0.255	0.014	0.010	1.8E-01	0.008	0.010	3.9E-01	-0.015	0.011	1.8E-01	-0.006	0.011	6.0E-01
Firmicutes	Dielma	0.976	0.016	-0.025	0.019	1.9E-01	-0.016	0.018	3.7E-01	-0.008	0.020	7.0E-01	0.001	0.020	9.8E-01
Firmicutes	Veillonella	0.976	0.046	-0.021	0.016	2.0E-01	-0.019	0.015	2.1E-01	0.021	0.017	2.2E-01	-0.045	0.017	8.5E-03
Firmicutes	Anaerostipes	1.000	0.915	-0.033	0.026	2.0E-01	-0.014	0.024	5.6E-01	-0.079	0.028	**4.7E-03**	-0.009	0.028	7.3E-01
Firmicutes	Intestinibacter	0.988	0.086	0.020	0.016	2.2E-01	-0.032	0.015	3.5E-02	-0.025	0.017	1.5E-01	-0.081	0.017	**2.9E-06**
Bacteroidetes	Odoribacter	1.000	0.931	0.032	0.026	2.2E-01	0.007	0.024	7.8E-01	0.037	0.028	1.8E-01	0.085	0.027	**2.0E-03**
Actinobacteria	Gordonibacter	0.987	0.028	0.025	0.022	2.6E-01	0.022	0.021	3.0E-01	-0.008	0.023	7.5E-01	0.079	0.023	**6.6E-04**
Actinobacteria	Senegalimassilia	0.946	0.032	0.016	0.014	2.8E-01	-0.002	0.014	9.1E-01	0.001	0.015	9.3E-01	0.028	0.015	7.0E-02

Firmicutes	Megasphaera	0.935	0.076	0.014	0.013	2.9E-01	0.015	0.012	2.2E-01	-0.007	0.014	5.9E-01	0.004	0.014	7.5E-01
Firmicutes	Enterococcus	0.983	0.062	0.019	0.019	3.3E-01	-0.002	0.018	9.3E-01	0.000	0.020	9.9E-01	-0.006	0.020	7.5E-01
Firmicutes	Catenibacterium	0.968	0.324	0.010	0.011	3.3E-01	-0.003	0.010	7.7E-01	0.035	0.011	**2.5E-03**	0.002	0.011	8.8E-01
Firmicutes	Unclassfied	1.000	0.025	-0.038	0.039	3.4E-01	-0.045	0.037	2.2E-01	-0.021	0.042	6.2E-01	0.038	0.041	3.6E-01
Proteobacteria	Parasutterella	0.910	0.209	-0.009	0.010	3.9E-01	-0.008	0.009	4.0E-01	-0.010	0.011	3.5E-01	0.001	0.010	9.3E-01
Proteobacteria	Sutterella	0.967	0.658	0.008	0.010	3.9E-01	-0.014	0.009	1.2E-01	-0.006	0.011	5.4E-01	0.001	0.010	9.0E-01
Bacteroidetes	Paraprevotella	1.000	0.310	0.016	0.019	3.9E-01	0.021	0.018	2.4E-01	0.045	0.020	2.4E-02	0.048	0.020	1.7E-02
Bacteroidetes	Sanguibacteroides	0.830	0.011	0.011	0.013	4.1E-01	-0.002	0.012	8.9E-01	0.011	0.014	4.3E-01	0.048	0.013	**4.4E-04**
Proteobacteria	Klebsiella	0.946	0.739	-0.008	0.010	4.3E-01	-0.006	0.010	5.7E-01	-0.005	0.011	6.5E-01	-0.003	0.011	7.7E-01
Firmicutes	Mitsuokella	0.334	0.048	0.008	0.010	4.3E-01	-0.005	0.010	6.2E-01	0.012	0.011	2.6E-01	0.002	0.011	8.4E-01
Proteobacteria	Dakarella	0.369	0.028	-0.007	0.010	4.5E-01	0.000	0.009	9.9E-01	0.004	0.010	7.1E-01	0.003	0.010	7.5E-01
Proteobacteria	Comamonas	0.139	0.011	0.011	0.016	4.8E-01	0.007	0.015	6.2E-01	0.012	0.017	4.7E-01	-0.012	0.017	4.8E-01
Bacteroidetes	Butyricimonas	0.996	0.216	0.013	0.018	4.8E-01	-0.017	0.017	3.0E-01	0.010	0.019	5.9E-01	0.045	0.019	1.6E-02
Proteobacteria	Pseudomonas	0.450	0.024	0.008	0.012	5.2E-01	-0.001	0.011	9.0E-01	0.006	0.013	6.3E-01	-0.005	0.013	7.2E-01
Proteobacteria	Kluyvera	0.582	0.015	0.007	0.011	5.4E-01	-0.003	0.010	7.7E-01	-0.003	0.012	8.3E-01	0.004	0.012	7.3E-01
Firmicutes	Anaerotruncus	1.000	0.127	0.017	0.031	5.8E-01	0.005	0.029	8.7E-01	0.008	0.033	8.1E-01	0.120	0.032	**2.1E-04**
Firmicutes	Lactobacillus	0.985	0.160	-0.008	0.014	5.8E-01	-0.015	0.013	2.5E-01	0.011	0.015	4.7E-01	0.010	0.015	5.1E-01
Firmicutes	Coprobacillus	1.000	0.086	0.014	0.030	6.5E-01	-0.046	0.028	1.0E-01	0.017	0.032	6.0E-01	0.059	0.032	6.4E-02
Firmicutes	Phocea	0.994	0.025	-0.011	0.024	6.6E-01	-0.004	0.023	8.5E-01	0.019	0.026	4.6E-01	0.058	0.025	2.3E-02
Firmicutes	Eisenbergiella	0.994	0.111	0.008	0.019	6.6E-01	0.012	0.018	5.1E-01	0.003	0.020	8.9E-01	0.042	0.020	3.6E-02
Proteobacteria	Bilophila	0.970	0.315	0.005	0.013	7.2E-01	-0.011	0.012	3.7E-01	-0.010	0.014	4.8E-01	0.017	0.013	2.2E-01
Firmicutes	Ruthenibacterium	1.000	0.372	0.009	0.026	7.3E-01	-0.015	0.025	5.5E-01	0.030	0.028	2.9E-01	0.077	0.028	5.6E-03
Proteobacteria	Desulfovibrio	0.779	0.041	-0.003	0.010	7.5E-01	-0.011	0.009	2.5E-01	-0.002	0.011	8.6E-01	0.022	0.011	4.0E-02
Synergistetes	Pyramidobacter	0.275	0.017	-0.004	0.012	7.7E-01	0.005	0.012	6.7E-01	0.026	0.013	4.5E-02	0.035	0.013	7.9E-03
Bacteroidetes	Coprobacter	0.997	0.096	0.005	0.023	8.2E-01	-0.016	0.021	4.5E-01	-0.033	0.024	1.7E-01	0.053	0.024	3.0E-02
Firmicutes	Sellimonas	0.988	0.028	-0.001	0.019	9.7E-01	0.032	0.017	6.7E-02	0.045	0.020	2.4E-02	0.024	0.020	2.2E-01
Synergistetes	Cloacibacillus	0.349	0.016	0.000	0.011	9.9E-01	0.009	0.011	4.2E-01	0.030	0.012	1.1E-02	0.021	0.012	8.0E-02

Data are differences (beta) and standard error (SE) in metabolites per SD increment of gut bacterial taxa (central-log transformed), adjusted for age, sex, study center, smoking, education, family income, physical activity, dietary quality, use of antibiotics, and use of probiotics.

P-values remained significant after FDR correction are highlighted in bold.