Table S6. The enriched metabolic sets of metabolites that have suggestive causal associations with each cognitive phenotype (IVW<0.05, all associations have been examined by sensitivity analysis).

All cognitive phenotypes			
Metabolite Set	**Total**	**Hit**	**P**
Alpha Linolenic Acid and Linoleic Acid Metabolism	17	3	0.00512
Phospholipid Biosynthesis	29	3	0.0232
Arginine and Proline Metabolism	52	4	0.0235
Urea Cycle	28	2	0.123
Aspartate Metabolism	35	2	0.177
Fatty Acid Biosynthesis	35	2	0.177
D-Arginine and D-Ornithine Metabolism	11	1	0.218
Phosphatidylethanolamine Biosynthesis	12	1	0.235
Ketone Body Metabolism	13	1	0.252
Phosphatidylcholine Biosynthesis	14	1	0.269
Beta Oxidation of Very Long Chain Fatty Acids	17	1	0.316
Glutathione Metabolism	20	1	0.361
Pantothenate and CoA Biosynthesis	21	1	0.376
Betaine Metabolism	21	1	0.376
Oxidation of Branched Chain Fatty Acids	26	1	0.443
Plasmalogen Synthesis	26	1	0.443
Mitochondrial Beta-Oxidation of Short Chain Saturated Fatty Acids	27	1	0.455
Mitochondrial Beta-Oxidation of Long Chain Saturated Fatty Acids	28	1	0.468
Ammonia Recycling	31	1	0.503
Beta-Alanine Metabolism	34	1	0.536
Methionine Metabolism	42	1	0.614
Steroidogenesis	43	1	0.623
Glycine and Serine Metabolism	59	1	0.741
Valine, Leucine and Isoleucine Degradation	59	1	0.741
Tryptophan Metabolism	59	1	0.741
Arachidonic Acid Metabolism	67	1	0.785
Purine Metabolism	73	1	0.814

Cognitive traits			
Metabolite Set	**Total**	**Hit**	**P**
Alpha Linolenic Acid and Linoleic Acid Metabolism	17	2	0.00715
Beta Oxidation of Very Long Chain Fatty Acids	17	1	0.128
Glutathione Metabolism	20	1	0.149
Pantothenate and CoA Biosynthesis	21	1	0.156

Oxidation of Branched Chain Fatty Acids	26	1	0.19
Mitochondrial Beta-Oxidation of Short Chain Saturated Fatty Acids	27	1	0.197
Beta-Alanine Metabolism	34	1	0.242
Fatty Acid Biosynthesis	35	1	0.248
Tryptophan Metabolism	59	1	0.386
Arachidonic Acid Metabolism	67	1	0.426

Non-Cognitive Traits

Metabolite Set	Total	Hit	P
Alpha Linolenic Acid and Linoleic Acid Metabolism	17	2	0.00542
Beta Oxidation of Very Long Chain Fatty Acids	17	1	0.113
Glutathione Metabolism	20	1	0.132
Oxidation of Branched Chain Fatty Acids	26	1	0.169
Urea Cycle	28	1	0.18
Phospholipid Biosynthesis	29	1	0.186
Aspartate Metabolism	35	1	0.221
Arginine and Proline Metabolism	52	1	0.312
Arachidonic Acid Metabolism	67	1	0.385
Purine Metabolism	73	1	0.412

Working Memory

Metabolite Set	Total	Hit	P
Phosphatidylethanolamine Biosynthesis	12	1	0.0355
Ketone Body Metabolism	13	1	0.0385
Phosphatidylcholine Biosynthesis	14	1	0.0414
Betaine Metabolism	21	1	0.0616
Plasmalogen Synthesis	26	1	0.0759
Mitochondrial Beta-Oxidation of Long Chain Saturated Fatty Acids	28	1	0.0816
Phospholipid Biosynthesis	29	1	0.0844
Fatty Acid Biosynthesis	35	1	0.101
Methionine Metabolism	42	1	0.121

Response Inhibition

Metabolite Set	Total	Hits	P value
Phospholipid Biosynthesis	29	1	0.111
Steroidogenesis	43	1	0.161
Arginine and Proline Metabolism	52	1	0.192
Valine, Leucine and Isoleucine Degradation	59	1	0.216

Emotion Response

Metabolite Set	Total	Hits	P value

Arginine and Proline Metabolism	52	2	0.00767
D-Arginine and D-Ornithine Metabolism	11	1	0.0326
Urea Cycle	28	1	0.0816
Ammonia Recycling	31	1	0.0901
Aspartate Metabolism	35	1	0.101
Glycine and Serine Metabolism	59	1	0.167
Glycine and Serine Metabolism	59	1	0.167

Table S7. Identified Serum Metabolites in enriched significant metabolic pathways for different cognitive phenotypes

Metabolic Pathway	All	Cognitive traits	Non-Cognitive traits	Emotion Recognition	Response Inhibition	Working Memory
Alpha Linolenic Acid and Linoleic Acid Metabolism	Arachidonic acid; Dihomo-gamma-linolenic acid; Docosapentaenoic acid	Arachidonic acid; Dihomo-gamma-linolenic acid	Arachidonic acid; Docosapentaenoic acid	/	/	/
Phospholipid Biosynthesis	1-palmitoylglycerophosphocholine; 1-palmitoylglycerophosphoethanolamine; Choline	/	1-palmitoylglycerophosphocholine	/	1-palmitoylglycerophosphoethanolamine	Choline
Arginine and Proline Metabolism	Creatine; Urea; Citrulline; 4-Hydroxyproline	/	Citrulline	Urea; Creatine	4-Hydroxyproline	/
D-Arginine and D-Ornithine Metabolism	Urea	/	Citrulline	Urea	/	/
Phosphatidylethanolamine Biosynthesis	Choline	/	/	/	/	Choline
Ketone Body Metabolism	3-Hydroxybutyric acid	/	/	/	/	3-Hydroxybutyric acid
Phosphatidylcholine Biosynthesis	Choline	/	/	/	/	Choline

Table S8. The mediation effect of serum metabolites in the causal association between gut microbiome and cognitive phenotypes (based on MR IVW estimates).

Gut Microbiota	Metabolites	Cognitive phenotypes	Direct Effect		Indirect Effect		
			β (95% CI)	P-value	β (95% CI)	P-value	Proportion mediated
class Clostridia id.1859	Myristate	Cognitive traits	0.112 (0.039, 0.185)	2.61E-03	0.009 (-0.000, 0.022)	0.058	7.8%
genus Escherichia Shigella id.3504	7-HOCA	Response Inhibition	-0.289 (-0.550, -0.029)	2.94E-02	-0.066 (-0.168, 0.003)	0.070	22.7%
genus Methanobrevibacter id.123	Acetylcarnitine	Non-Cognitive traits	0.077 (0.016, 0.138)	1.36E-02	0.008 (0.001, 0.022)	4.40E-02	11.0%
genus Turicibacter id.2162	Homostachydrine	Emotion Recognition	0.268 (0.029, 0.507)	2.81E-02	0.105 (0.006, 0.259)	2.60E-02	39.1%

* P-values presented in scientific notation indicate statistical significance (<0.05).

Table S9. The mediation effect of serum metabolites in the causal association between gut microbiome and cognitive phenotypes (based on MR cML-MR estimates)

Gut Microbiota	Metabolites	Cognitive phenotypes	Direct Effect		Indirect Effect		
			β (95% CI)	P-value	β (95% CI)	P-value	Proportion mediated
class Clostridia id.1859	Myristate	Cognitive traits	0.118 (0.046, 0.190)	1.237E-03	0.009 (-0.000, 0.024)	0.058	7.8%
genus Escherichia Shigella id.3504	7-HOCA	Response Inhibition	-0.297 (-0.563, -0.031)	2.851E-02	-0.070 (-0.181, 0.004)	0.072	23.7%
genus Methanobrevibacter id.123	Acetylcarnitine	Non-Cognitive traits	0.079 (0.015, 0.142)	1.501E-02	0.009 (0.001, 0.023)	2.40E-02	11.3%
genus Turicibacter id.2162	Homostachydrine	Emotion Recognition	0.277 (0.031, 0.522)	2.714E-02	0.111 (0.009, 0.269)	1.80E-02	40.3%

* P-values presented in scientific notation indicate statistical significance (<0.05).

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